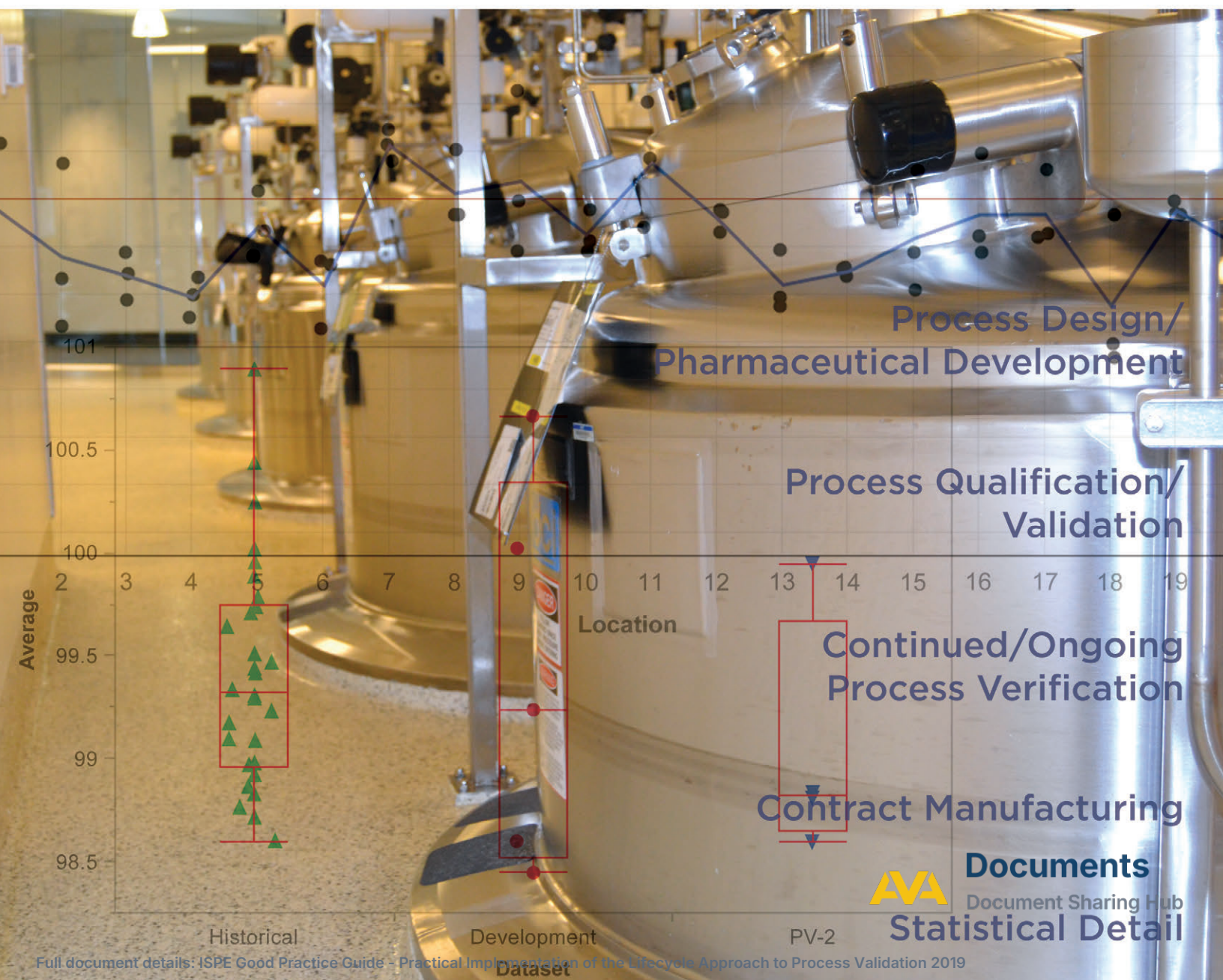


Practical Implementation of the Lifecycle Approach to Process Validation





GOOD PRACTICE GUIDE:

Practical Implementation of the Lifecycle Approach to Process Validation

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Foreword

During my tenure at the FDA, I presented at many industry conferences on various topics, but few represented such significant change and improvement as those which culminated in the lifecycle approach to Process Validation (PV). In 2002, FDA launched the Pharmaceutical Quality for the 21st Century initiative aimed at modernizing pharmaceutical manufacturing using sound science and risk-based approaches. ICH shortly thereafter also embarked on its vision for pharmaceutical quality and set forth ICH Q8, Q9, Q10, and Q11.

- Q8 Pharmaceutical Development (August 2009)
- Q9 Quality Risk Management (November 2009)
- Q10 Pharmaceutical Quality System (June 2008)
- Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) (May 2012)

A fundamental principle to ensure product quality is PV. In the past, interpretation of FDA's Compliance Policy Guide (<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074411.htm>), which addressed process validation and the subject of guidance from FDA over multiple versions, there had been the impression that three commercial PV batches were almost always enough to ensure a robust and consistent process. This guide was updated in 2004 to facilitate understanding of requirements to bring products to market, especially when extensive process development efforts and large numbers of PV batches are not practical, e.g., orphan drugs.

Over time in FDA and in other international guidances, three batches had become the standard to demonstrate a validated process. With the lifecycle approach, efforts were made to bring PV into the 21st Century - to provide scientific evidence to justify going from development to commercial manufacturing while maintaining the desired process control over the product's lifecycle. The intent was also to capture modern manufacturing methods using enhanced approaches, e.g., continuous manufacturing.

In 2011, the 1987 Guideline on General Principles of Process Validation was replaced, reflecting the modernization efforts for pharmaceutical quality initiated by FDA and in the international arena. Of the regulatory guidances issued to date, the FDA Guidance for Industry: Process Validation: General Principles and Practices of January 2011 contains the most detail in regard to expectations for the three stages of the lifecycle approach to PV, but was followed internationally by several other impactful guidances and regulations, outlined below.

In February 2014, EMA published its "Guideline on process validation for finished products – information and data to be provided in regulatory submissions." The scope of this document covered:

- Human medicinal products
- Veterinary medicinal products
- Biological products

A companion guideline "Guideline on process validation for the manufacture of biotechnology-derived active substances and data for inclusion in the regulatory submission" was published in April 2014.

These documents introduced the concepts of science and risk-based validation to Europe via:

- Process evaluation (Stages 1 and 2)
- Process verification (Stage 3)

The EU PV guidance sets out three approaches for PV:

- Traditional (three batches)
- Continuous process verification
- Hybrid (three batches or Continuous in different steps of the process)

Additionally, these guidance documents refer to GMP requirements for PV in Annex 15: Qualification and Validation to the EudraLex Volume 4 (Good Manufacturing Practice Medicinal Products for Human and Veterinary Use). This guidance was published for comment in March 2015 and became operational in October of the same year concurrent with its publication by PIC/S. Unlike the FDA guidance; Annex 15 also contains specific validation approaches to:

- Transport verification
- Packaging qualification
- Utilities qualification
- Test method validation
- Cleaning validation

The EMA guideline on PV for finished products underwent a minor update in November 2016.

With these modern approaches to pharmaceutical development and manufacturing and the advancement of the concept of PV to a lifecycle approach, ISPE's Product Quality Lifecycle Initiative (PQLI®) has been providing the technical underpinnings to develop the necessary education, training, and discussion papers to pharmaceutical professionals engaged in all facets of pharmaceutical development, commercialization, and manufacturing. This *Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* brings together an excellent reference providing the technical and scientific detail needed to lead PV through scientifically sound development to robust reliable processes, ensuring the continued supply of quality medicines to patients.

An expert group of volunteers with manufacturing, quality, technical development, and statistician backgrounds has brought this effort to the point of providing this Guide to our ISPE members. It covers a wide variety of manufacturing types including small and large molecule, active pharmaceutical ingredients (including intermediate steps), solid oral dosage forms, sterile drug product, etc.

This Guide will be an invaluable reference bringing together many of the efforts to date for use in your daily activities and as an underpinning to ISPE's ongoing education and training in this area.

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1 Introduction

Between 2004 and 2009, ICH published guidance documents Q8 (Quality by Design – Pharmaceutical Development) [1], and Q9 (Quality Risk Management) [2], which describe the science and risk-based approach to the development of pharmaceutical products. These guidances represented a paradigm shift in development, commercialization, transfer, and management throughout the product lifecycle.

The science and risk-based approach to Process Validation (PV) leverages information and knowledge from product development activities to make certain patient requirements are translated into product attributes. This requires that suitable manufacturing processes are defined with a control strategy that reliably ensures these attributes are met. Regulatory authorities worldwide have published revised guidances for science and risk-based approaches to be applied to PV, which presents a significant change to the way validation had been conducted.

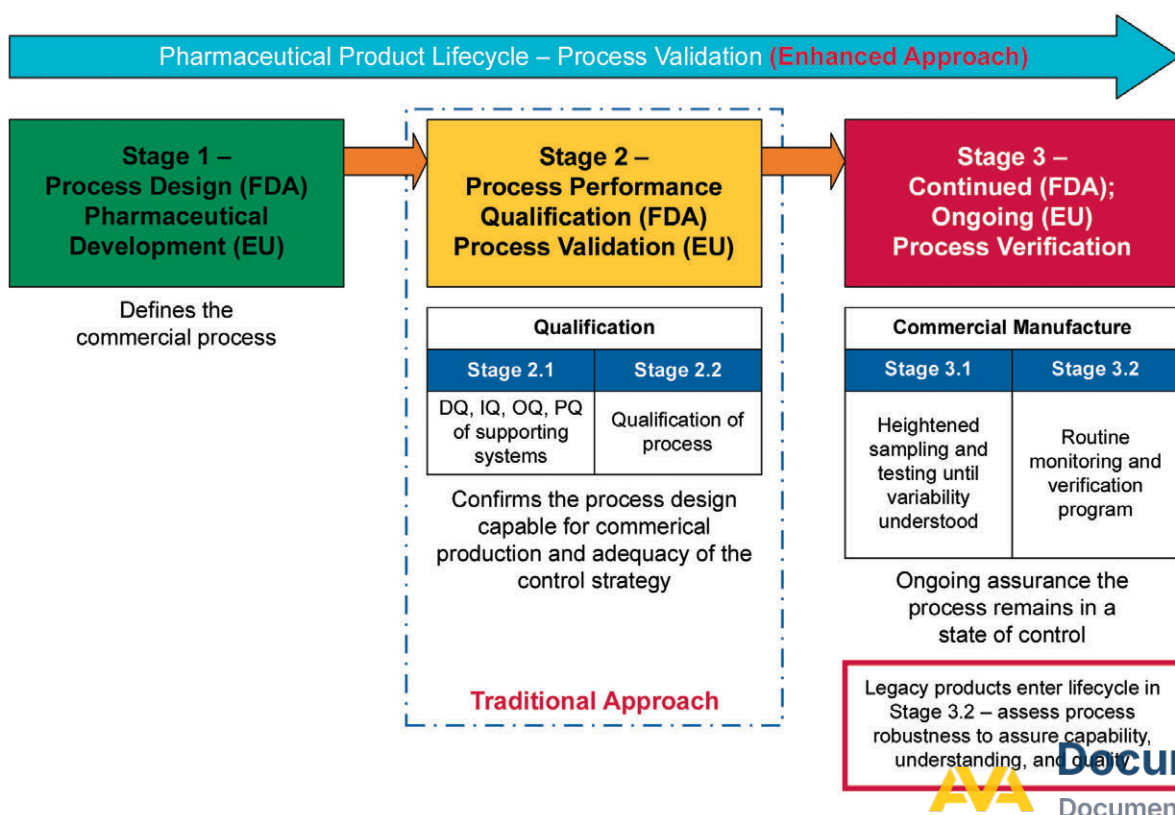
PV demonstrates manufacturing control strategy adequacy and robustness and provides ongoing assurance that the process remains in control. It is defined in the 2011 FDA PV Guidance as [3]:

“...the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.”

Other regulatory authorities have similar definitions for PV although terminology may differ.

This new (enhanced) approach to PV encompasses three stages, illustrated in Figure 1.1, as compared to the traditional or historic approach. The science and risk-based approach combines product development knowledge with a structured process performance and product quality monitoring system to provide for validation throughout the product lifecycle.

Figure 1.1: Process Validation Overview – Process Validation Lifecycle – the Enhanced Approach



The science and risk-based approach to PV brings an expectation for an improved understanding of process control and robustness via clearer focus of Critical Quality Attributes (CQAs) and the impact of Material CQA and Critical Process Parameter (CPP) variability on these product CQAs. PV is no longer considered a one-time event; a lifecycle approach is expected by most global markets. PV success relies on establishing a comprehensive science-based process design that focuses on understanding sources of variability to achieve product realization.

The intent of this Guide is to cover the following:

- Present information to assist companies, globally or locally, in understanding the application of validation requirements for US, EU, and elsewhere, and explain the role in assuring reliable supply
- Demonstrate that process understanding and a well-designed control strategy are the keys to reliable supply and validation success
- Show how qualification is an essential element supporting PV
- Assist in clarifying and aligning the different terminology used by regulators and demonstrating similarities in the underlying fundamental principles
- Provide details of how each of the three validation stages may be implemented and how the stages are linked
- Illustrate application of the three-stage approach using case studies for both large and small molecule products
- Provide practical implementation advice, including leveraging some of the formerly issued ISPE PV Team discussion papers [4]
- Offer guidance on the way science and risk-based approaches support validation
- Reinforce that the principle of lifecycle PV is to help assure the adequacy of the development and manufacture of pharmaceutical products – to both industry and regulators
- Provide information for determining the number of batches for PV Stage 2
- Provide statistical rationale and information that may be applied at different stages of the lifecycle
- Illustrate ways for maintaining a state of control throughout the product lifecycle
- Demonstrate applicability to all parts of the industry including development companies, manufacturers, equipment suppliers, contract research organizations, Contract Manufacturing Organizations (CMOs), generics, 'virtual' companies, etc.

1.1 Foundation for the Good Practice Guide

An international team from many companies has brought together their experience to provide this Guide. The ISPE Process Validation Team's goal is to facilitate the practical implementation of the lifecycle approach to PV. The Team acknowledges the foundation by *ISPE Product Quality Lifecycle Implementation® (PQLI®) Guide Series* [5] that focused on understanding manufacturing process science and controlling those processes consistent with ICH Q8(R2), Q9 and Q10 [1, 2, 6]. The ISPE PQLI® Guides are:

- *PQLI® Part 1 – Product Realization Using Quality by Design (QbD): Concepts and Principles, including Overview, Criticality, Design Space and Control Strategy* (November 2011) [7]
- *PQLI® Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example* (November 2011) [8]

- *PQLI® Part 3 – Change Management System as a Key Element of a Pharmaceutical Quality System* (June 2012) [9]
- *PQLI® Part 4 – Process Performance and Product Quality Monitoring System* (June 2013) [10]

These Guides explain the principles and provide a basis for process understanding PV Stage 1 in preparation for PV Stages 2.2, 3.1 and 3.2.

Without process understanding and linkage to impacted CQAs, process consistency and robustness cannot be achieved. Understanding the variation of inputs as described in ICH Q8(R2) [1] and the subsequent link to variation in output product CQAs are also foundational to meeting regulatory expectations.

1.2 Global Acceptance/Authorization

The FDA's 2011 Process Validation Guidance [3] is often associated with enhanced PV approaches; however, many other authorities have applicable guidance.

PV guidance approved for Europe is well established and contains similar principles on lifecycle validation. The requirements are described in three related documents:

- EU Guideline – EudraLex Volume 4, Annex 15: Qualification and Validation [11]
- EMA “Guideline on process validation for finished products – information and data to be provided in regulatory submissions” [12]
- EMA “Guideline on process validation for the manufacture of biotechnology-derived active substances and data for inclusion in the regulatory submission” [13]

The latter two documents also describe data to be provided in regulatory submissions, however, the three documents should be read together.

The EMA “Guideline on process validation for finished products” [12] contains the following statement:

“This document provides guidance on the validation of the manufacturing process, which can be considered as the second stage in the product lifecycle. The first stage (process design) is covered in the note for guidance on pharmaceutical development (ICH Q8R2/ EMEA/CVMP/315/98) and the third stage (on-going process verification) is covered under GMP (Annex 15).”

Hence, a three-stage approach is appropriate for the EU as well as the US, and when the EMA/EU PV documents are considered together [11, 12, 13] the requirements are very similar in principle to US requirements [3], with minor differences in terminology and details, such as the level of emphasis on statistical principles.

PIC/S adopted the EU GMP Annex 15 [11] (PIC/S Annex 15 [14]), and from version 12 onwards, they are identical documents; however, as PIC/S is a GMP guidance applicable to other parts of the world, it does not reference the EMA PV guidances.

The following list provides an approximate comparison of the validation requirements in different parts of the world:

FDA

- PV Guidance [3]
- Based on ICH Q8(R2), Q9, Q10 [1, 2, 6]; incorporates CQAs, CPPs, and material attributes

- Requires link between product/process development activities (PV Stage 1) and commercial scale manufacturing
- Requires verification that the process is maintained in a state of control throughout the product lifecycle – *Continued Process Verification*
- Deliberate use of statistics to characterize variability
- Applies to all drug products and APIs

EU

- Annex 15: Qualification and Validation [11]; EMA Guideline on process validation for finished products – information and data to be provided in regulatory submissions [12]; and EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in regulatory submissions [13]
- Based on ICH Q8(R2), Q9, Q10, Q11 [1, 2, 6, 15]; incorporates CQAs, CPPs, and material attributes
- Requires a link between product/process development activities (PV Stage 1) and commercial scale manufacturing
- Requires verification that the process is maintained in a state of control throughout the product lifecycle – *Ongoing Process Verification*
- Recognizes traditional – minimum of three-batch PV, with supplementation from ongoing verification and continuous verification as an alternate approach
- Allows for a traditional PV approach or continuous verification as an alternative approach for processes developed with QbD and/or utilizing PAT. Hybrid (combination) approaches are also allowed.
- Europe requires PV data in the dossier for sterile products and complex dosage forms. A PV scheme is required for all products.
- EU GMP contains other qualification/validation guidance
- Annex 15 [11] applies only to drug products, optionally to APIs; however, there is a specific EMA guidance for biotechnology-derived APIs [13]
- Contains specific PV requirements for non-standard processes (“...determined by a combination of the nature of the active substance, the nature of the finished product, the actual process itself, and the production experience of the manufacturer.” [12])

PIC/S

- Annex 15 – as adopted by many regulatory authorities in other countries [14]
- Released 30 March 2015, Operational 1 October 2015, concurrent with EU cGMP as PIC/S version 12 [16]
 - **Note:** PIC/S membership does not mean the latest version of Annex 15 must be adopted by a member authority. PIC/S only requires that GMPs are “similar” to the PIC/S guideline [14].
- Changes to PIC/S GMP guides and EU GMP guides are developed in parallel, so that the documents are essentially the same [14].

Japan

- MHLW adopted revised PIC/S Annex 15 [14] into GMPs [17].
- A number of Japanese pharmaceutical companies supplying the local market have started to introduce lifecycle validation.

China

- National Medical Products Administration (NMPA) (formerly CFDA [18]) published a draft Annex to GMP Regulation 2010 Revision on Qualification and Validation in July 2014 [19]
- Final version effective December 2015
- No official CFDA English version
- Aligned with FDA and PIC/S lifecycle PV [3, 14], includes Quality Risk Management (QRM), QbD, CQAs, CPPs
- Requires Continued Process Verification (in a protocol/report format)

India

- [Schedule M] Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products [20]
- The draft rules of Gazette Schedule M were updated on 5 October 2018 to include validation guidance equivalent to WHO-GMP requirements for lifecycle validation [21]

Asia Pacific

- ASEAN Mutual Recognition Arrangement on GMP Inspection was signed in 2009 [22]. All countries will have a PIC/S equivalent GMP [14]; however, to date only Singapore, Malaysia and Indonesia, and Thailand have obtained PIC/S membership [23]
- Various authorities use different versions of PIC/S GMP guideline [14]; therefore, the adoption of lifecycle practices is not as widespread as it may appear. Very few authorities insist on lifecycle validation; however, they will accept these practices.

South Korea

- MFDS (formerly KFDA) uses wording similar to and perhaps based on PIC/S Annex 15 [14]; however, it is from a version prior to PIC/S GMP version 12 [16] and therefore does not reference enhanced PV approaches [24]

Canada

- On 20 November 2018, Health Canada released a draft guide to validating drug dosage forms (GUI-0029) for public comment [25]
- At the time of publication of this ISPE Good Practice Guide, the final comment period had closed, but the Health Canada guide was not published
- The draft guidance included updates on the lifecycle approach to validation programs, guidance related to analytical method validation and equipment/facility qualification, and uses terminology based on ICH Q8(R2) [1], which are aligned with FDA and PIC/S lifecycle PV guidance [3, 14] with some minor differences.

WHO

- Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation WHO TRS No. 992 2015 [26]
- Intended to support the concept of PV linked to QRM and QbD principles as described by WHO and ICH [1, 2]
- Applicable to non-sterile finished pharmaceutical dosage forms, but may be applicable to APIs and sterile products

Maturity/experience with lifecycle validation in other parts of the world varies across markets. Generally, adoption of lifecycle validation is slower outside the US and Europe.

1.3 Scope

This Guide applies to:

- Active Pharmaceutical Ingredients (APIs) – large and small molecules
- Vaccines
- Combination products (drug product portion)
- Pharmaceutical drug products both sterile and non-sterile
- Veterinary drugs

While not specifically referenced, and without case study examples, the principles and approaches in this Guide generally also apply to antibody conjugates, orphan drugs, etc.

This Guide does not review the validation of packaging processes at this time. It is noted that beyond the product definition, risk level, and the technologies used, packaging validation differs little from the validation of processes used for drug manufacture. Similarly, equipment used in packaging processes may be commissioned and qualified by following the same general guidelines as those used for drug product manufacturing equipment. Further information can be found in the *ISPE Discussion Paper: Overview of Packaging Validation for Drug Products* [27].

This *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* can be applied in other cases where regulatory requirements require enhanced PV approaches.

1.4 Purpose

The intention of this Guide is to facilitate the implementation of the lifecycle approach to PV (as described, for example, by FDA's Process Validation: General Principles and Practices [3], EU PV Guidances [11, 12, 13], and GMPs published by other regulatory authorities) and concepts presented in ICH Q8(R2), Q9, Q10, Q11 [1, 2, 6, 15].

This Guide provides step by step implementation approaches to PV and leverages process understanding to promote best practices.

1.5 Benefits

It is hoped this Guide will help companies advance a science and risk-based methodology for validation processes throughout the product lifecycle to support the provision of a reliable supply of consistent quality products to patients, while meeting regulatory expectations and providing business benefits.

The methodologies in this Guide have been compiled from a wide variety of companies, many of whom have applied the concepts successfully, achieving, for example, shorter process development to commercialization lead times, earlier identification of continuous improvement opportunities, and reduced deviations.

2 Basic Terms Used in the Process Validation Lifecycle

2.1 Process Validation Lifecycle Stages

“Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product” [3], thereby also assuring reliability of supply.

Lifecycle or enhanced PV should be based on the principles described in ICH Q8(R2), Q9, Q10, and Q11 [1, 2, 6, 15], and is undertaken in three stages linking product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production.

Guidances published in the US [3] and Europe [11, 12, 13] clearly outline these three stages and approach; however, some terminology differences exist. Other international guidances use terminology based on one of these two jurisdictions.

Common industry practice is to name the stages as Stage 1, Stage 2, and Stage 3. This is the approach adopted by this Guide; recognizing that there are terminology differences between regions. A summary of the stages, their goals, and typical activities completed in each are summarized in Table 2.1 and Figure 2.1.

Table 2.1: Goals and Typical Activities of the Stages of Process Validation

Stage of Process Validation	Definition	Goals	Typical Activities
Stage 1	Process Design (FDA/WHO) [3, 26] Pharmaceutical Development (EU) [28]	Define and design process	Build knowledge and understanding generated through development and scale-up activities and establishing a strategy for process control
Stage 2	Process Qualification (FDA/WHO) [3, 26] Process Validation (EU/PIC/S) [11, 14]	Process design is evaluated to determine if the process is capable of reproducible commercial manufacturing	Design of a facility and qualification of utilities and equipment Manufacture of a number of Process Performance Qualification (PPQ) batches to confirm the process design and demonstrate that the commercial manufacturing process performs as expected in the commercial manufacturing facility Level of sampling may be higher than routine monitoring; the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches
Stage 3	Continued Process Verification (FDA/WHO) [3, 26] Ongoing Process Verification EU/PIC/S) [11, 14]	Ongoing assurance that the process remains in a state of control	Ongoing programs to collect and analyze product and process data (monitoring plans) to assure the state of control of the process and verify impact of variability Evaluating the performance of the process identifies potential issues and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control

Figure 2.1: Process Validation Comparison

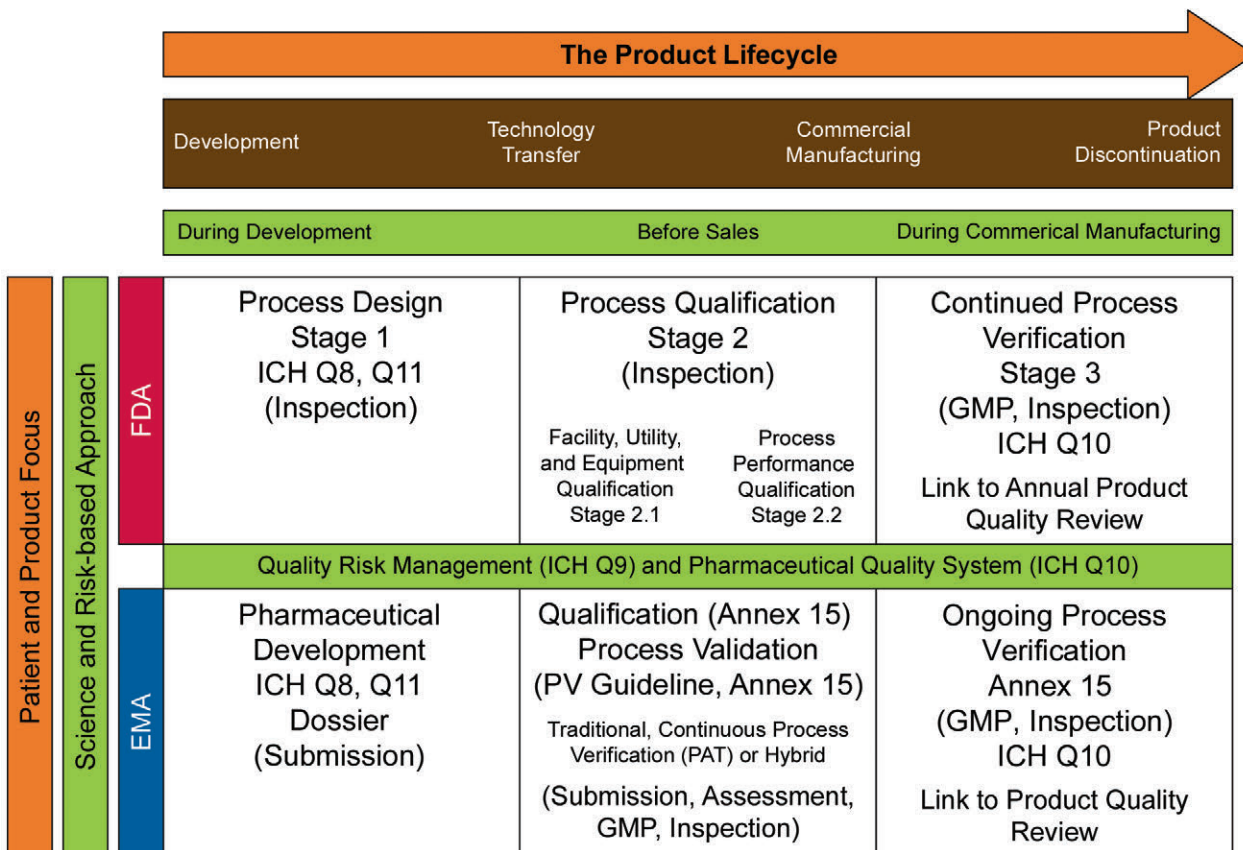


Table 2.2 (later in this chapter) summarizes the similarities/differences between the FDA PV Guidance [3], the EMA Guidelines [12, 13] and Annex 15 [11]. **Note:** the scope of the PIC/S guidance [14] only covers the manufacturing stages of the lifecycle, although a reference exists to EMA regulatory guidance [12, 13] for EU markets.

Lifecycle PV and QbD activities share many concepts and terms; however, some key terms are fundamental to PV activities and are discussed in the following sections. Comprehensive coverage of QbD terminology is contained in the *ISPE PQLI® Guide Part 1 – Concepts and Principles* [7].

2.2 Stage 1 Process Design/Pharmaceutical Development

Lifecycle PV is fundamentally concerned with the development, verification, and maintenance of the control strategy. The conclusion of process design activities provides a control strategy, which is validated in subsequent PV stages. ICH Q8(R2) [1] defines control strategy as:

“A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.”

From a validation perspective, the key focus of a control strategy is on CQAs, CPPs, and material attributes. ICH Q8(R2) [1] defines a CQA as:

“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.”

and a CPP as:

“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(R2) [1] does not use the term Critical Material Attribute (CMA); however, it is used quite frequently by industry and in this Guide. The definition for CMA for this Guide is:

A material attribute of either a raw/starting material or intermediate that has an impact to a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. Examples of CMAs are a reagent CQA, a CQA for an excipient added at a blending stage, and a packaging material CQA.

While the focus of PV is on CQAs, CPPs, and CMAs, this does not mean that non-critical quality attributes, parameters, and material attributes should be ignored in validation. These non-critical indicators remain important to other aspects of product and process understanding for business purposes.

2.3 Stage 2 Key Terms and Substages

The FDA PV Guidance [3] discusses a subdivision of Stage 2. The initial substage (referred to hereinafter as Stage 2.1) is where the fitness of facilities and equipment for intended use is assured and documented.

Following that is where the proposed commercial manufacturing process is shown to be consistent and reproducible, resulting in product meeting all required quality criteria with a high degree of assurance. Called Stage 2.2 in this Guide, it concludes with Process Performance Qualification (PPQ) runs prior to subsequent commercial distribution of the new or modified product.

The EU PV guidance [11, 12, 13] follows a similar approach and is more deliberate and detailed in its definition of the elements of Stages 2.1 and 2.2.

During Stage 2.1, EMA and PIC/S guidances (Annex 15) [11, 14] suggest completing the following qualification activities as applicable:

- User Requirements Specifications (URS)
- Design Qualification (DQ)
- Factory Acceptance Testing (FAT)/Site Acceptance Testing (SAT)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Additionally, Annex 15 [11, 14] describes specific verification/validation requirements for transportation, packaging, utilities, test methods, and cleaning.

Stage 2.2 is described as *Process Performance Qualification* in the FDA guidance [3] and identified as *Process Validation* in the EMA's Annex 15 [11]. In this ISPE Good Practice Guide, the term PPQ is used to describe activities in Stage 2.2 to avoid confusion with the use of the word *validation*, which can also apply to the overall program.

The EMA guidance [12] describes two approaches to product development:

“Traditional approach: A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.”

“Enhanced approach: A development approach where risk management and scientific knowledge is used to identify and understand the material attributes and process parameters which influence the critical quality attributes of a product.”

PPQ (FDA) [3] and Process Validation (Annex 15) [11] can be considered to be the same. In either case, and regardless of the development approach, manufacturers are required to determine an appropriate number of batches for the PPQ study.

The EMA guidances [12, 13] also describe an approach termed *Continuous Process Verification*, defining it as:

“An alternative approach to process validation in which manufacturing process performance is continuously monitored and verified.”

This term is intended to apply to the use of PAT principles and should not be confused with the FDA terminology of *Continued Process Verification* (CPV) [3].

Additionally, the EMA defines a process validation (PPQ) strategy called a *hybrid approach*, which includes a combination of traditional process validation and continuous process validation. This can apply to products that may have been initially developed under a traditional development approach [12].

2.4 Stage 3 Continued (Ongoing) Process Verification and Substages

FDA, WHO, EMA, and PIC/S guidances [3, 26, 11, 12, 13, 14] adopt ICH principles [1, 5, 6] requiring manufacturers to continue validation throughout the lifecycle of the product. Terminology differs between these documents, with FDA and WHO [3, 26] calling this phase *Continued Process Verification* (CPV), and EMA and PIC/S [11, 12, 13, 14] designating the same phase *Ongoing Process Verification* (OPV).

The term CPV is used throughout this ISPE Good Practice Guide. The objective of CPV is to provide:

“...continual assurance that the process remains in a state of control (the validated state) during commercial manufacture” [3].

CPV starts following successful completion of PPQ and is divided into two phases.

FDA PV guidance [3] requires:

“...continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates.”

After which time:

“Monitoring can then be adjusted to a statistically appropriate and representative level.”

Annex 15 [11] is less prescriptive but requires the extent and frequency of monitoring to take into account the current level of process understanding and performance. These requirements are widely understood to be the same.

This Guide defines the two stages in Sections 2.4.1 and 2.4.2.

2.4.1 Stage 3.1 – Heightened Monitoring Phase

Stage 3.1 is the phase where PPQ has been completed; however, the manufacturer maintains sampling and testing at the level of PPQ (heightened monitoring) for some or all parameters until additional confidence or process understanding is developed. The criteria for that point is defined by the manufacturer in the CPV monitoring plan.

The point at which this phase ends may be determined statistically or using other science and risk-based methods.

Following this, the validation sampling and testing can be reduced, and the validation program enters Stage 3.2 – Routine Monitoring Phase. If the process drifts to an extent that it is out of the expected trend, it is appropriate to reinstate Stage 3.1 – Heightened Monitoring Phase, for some or all parameters until the cause of the shift is understood and accounted for in the validation program.

2.4.2 Stage 3.2 – Routine Monitoring Phase

During this stage, the process is expected to be well controlled and stable; therefore, the sampling and testing strategy may be reduced, reflecting the level of process understanding and control (routine monitoring).

This stage has the following objectives:

- Ongoing process verification over the life of the product to demonstrate that the process remains in control
- Identification of trends that may be within normal process variability, but indicates a future potential to trend outside expected limits
- Continuation of understanding of the sources of process variability and their impact
- Implementation of process improvement actions to reduce such process variability if deemed necessary

Table 2.2: Summary of Terminology Used in this Guide

Stage	Terminology in this Guide	Relates to:
Stage 1	Process Design	Pharmaceutical Development (EU and PIC/S [28, 6])
Stage 2	Stage 2.1 Qualification of Utilities and Equipment	Qualification including URS, DQ, FAT, SAT, IQ, OQ, and PQ (EU [11, 12, 13])
	Stage 2.2 Process Performance Qualification (PPQ)	Process Validation (EU and PIC/S [11, 12, 13, 14])
Stage 3	Continued Process Verification (CPV)	Ongoing Process Verification (EU and PIC/S [11, 12, 13, 14])
	Stage 3.1 – Heightened Monitoring Phase Stage 3.2 – Routine Monitoring Phase	

2.5 Key Statistical Terms

Interpretation of the language of the PV guidances related to use of statistical methods requires understanding of some fundamental statistical terms. Some key terms include:

Robust Process: A process that demonstrates acceptable quality and performance while tolerating input variability.

State of Control (as defined in Annex 15 [11]): *A condition in which the set of controls consistently provides assurance of continued process performance and product quality.* **Note:** this definition differs from the definition of a Stable Process under statistical control.

Stable Process: *A process in a state of statistical control (constant mean and variance) subject only to random causes (ISO 3534-2 [29]).* **Note:** this state does not imply that the random variation is large or small, within or outside of specification; but rather the variation is predictable using statistical techniques. Also, very importantly, a process can fail to meet the definition of a Stable Process due to shifts in the mean, but still be considered in a State of Control.

Variability: A measure of the spread or dispersion of a distribution of data. Intra-batch variability reflects variability *within* a batch; Inter-batch variability reflects the variability *between* batches.

Statistical Distribution: A mathematical function that describes the probability of occurrence of possible outcomes of a population.

Confidence (Statistical): The confidence level associated with a statistical interval (such as confidence or tolerance intervals) is equal to the percentage of similarly computed intervals that contain the true parameter value or claimed population proportion. More generally speaking, statistical confidence reflects the sufficiency of data-based evidence to support a hypothesis or claim.

Capability (Statistical): A measure of the ability of a process to meet specification or acceptance criteria (often computed as a ratio of a statistical estimate for the process range compared to the specification or acceptance criteria).

3 Design Development Phase (Stage 1)

Stage 1 is the developmental phase in which a product's commercial manufacturing process is determined. In this Guide, Stage 1 is known as Process Design. See Chapter 2 for the different terminology used by regulators.

Science and risk-based development brings expectations for a more systematic, deliberate approach to product and process development with direct linkage to patient needs. This enhanced understanding of the product and process is an enabler of successful validation and subsequent commercial manufacturing. The FDA has the following statements in the 2011 PV Guidance [3]:

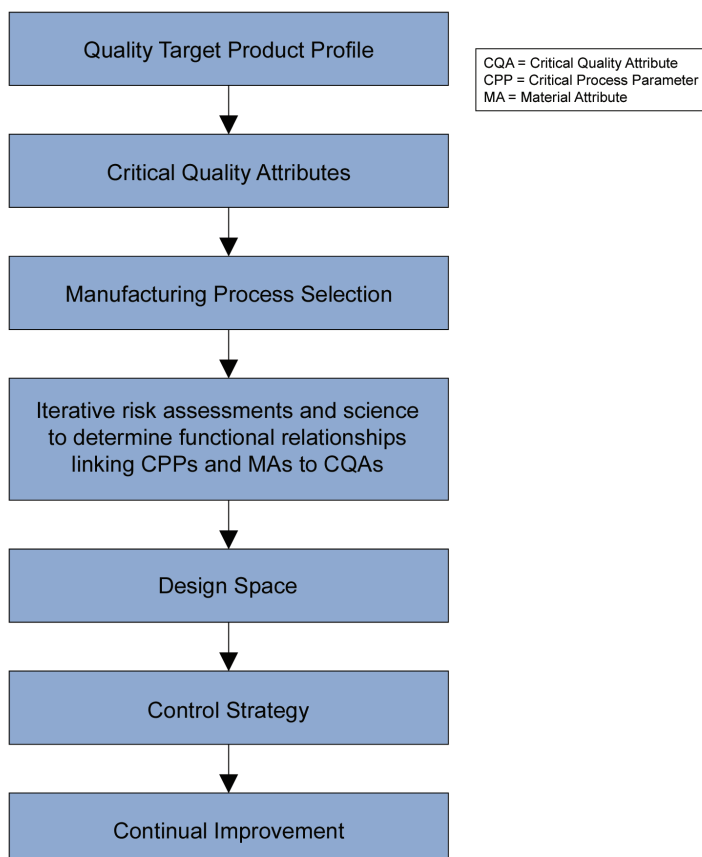
*“Each manufacturer should judge whether it has gained sufficient understanding to provide a **high degree of assurance in its manufacturing process** to justify commercial distribution of the product.”*

*“The number of samples should be adequate to provide **sufficient statistical confidence of quality** both within a batch and **between batches**.”*

In order to reach an accurate conclusion about the acceptability of the manufacturing process, input and process control variation should be included in PV Stage 1. Figure 3.1 shows key elements of Stage 1 useful for moving to Stages 2 and 3.

Process manufacturing results from PV Stage 1 should be considered together with PV Stage 2 results in making the overall conclusion about the adequacy of the manufacturing process control strategy. Prior to entering PV Stage 2, viability of the process should be assessed including evaluation of incoming and output variability. Section 3.4 and Table 3.2 provide guidance on selecting Stage 1 batches suitable for use when evaluating Stage 2.2 data.

Figure 3.1: Flow Diagram Outlining the Key Elements of Stage 1 Leading into Stage 2 and Stage 3 Activities [8]



3.1 Apply Statistics in PV Stage 1

Statistics is the science of making decisions in the face of uncertainty. Any time there is data, or more broadly information or knowledge, there is a statistical method or approach that can be employed to assess the data and determine if the desired outcome has been achieved.

Knowledge is defined as facts, information, and skills acquired through experience. As such, knowledge can be gained through the theoretical or past understanding of a process and does not need to be recreated for every product being developed, but should be created where necessary. That is, in the design process, teams leverage relevant existing data along with fundamental knowledge to make initial decisions, perform risk assessments to identify gaps, and take actions to gain more knowledge.

Statistical tools are a component of the data collection, summarization, and quantification of Stage 1 knowledge. These statistical tools fall into broad categories of data-based decision making, data collection and experimental design, simple data analysis, and complex modeling.

Some of the Stage 1 statistical methodologies are:

Visualization: The benefit of effective and simple graphical display of information cannot be overstated and the ability to take a set of data, summarize the information, and visually display this information is both an art and a science. A primary goal of data visualization is to communicate information clearly. Graphics may be used to illuminate data, and in some cases can be more revealing than conventional statistical computations and definitely increase clarity over tabular summaries.

There are many graphical tools available in good spreadsheet and statistical software programs. Some common graphical tools include:

- Data exploration: y versus x, x1 versus x2
- Data trending: y versus time, and x versus time
- Data distribution: histogram, stem and leaf plot, box plot, pareto charts

Simple Descriptive Statistics: Descriptive statistics is the discipline of quantitatively describing a set of data. This usually includes a description of the central tendency of the data (mean, geometric mean, median, or mode) and a measure of the dispersion or variability in the data (range, standard deviation, or variance).

The data summary can be displayed visually as a box plot, histogram, or individual value plot by itself or with other groups of similar data as a comparison.

Summary statistics can also be calculated for attribute data (pass/fail) or count, which may include total counts, proportions, and percentages (e.g., proportion or percent of sample with a given non-conformance).

Statistical Intervals: Statistical intervals are a useful tool for quantifying uncertainty. These intervals include:

- **Confidence:** A confidence interval reflects the sampling uncertainty regarding a population parameter, such as the mean, standard deviation, or proportion non-conforming.

For example, a 95% confidence interval on the mean implies that if repeated samples from the same population were taken and confidence intervals calculated from each sample, 95% of them will include ("cover") the true population mean. In other words, confidence can be thought of as the probability of being correct about the value of the population parameter.

- **Prediction:** A prediction interval for one or more future observations is an interval that will, with a specified degree of confidence, contain one or more randomly selected observation(s) from a population.
- **Tolerance:** A tolerance interval provides limits with confidence on a proportion of a population. More specifically, a $100 \times p\%/100 \times (1-\alpha)$ tolerance interval provides limits within which at least a certain proportion (p) of the population falls with a given level of confidence ($1-\alpha$). For example, a 95/90 tolerance interval would provide limits within which 95% of the population falls with a 90% level of confidence.
- **Bayesian Credible Interval:** A Bayesian credible interval is an interval within which a population parameter (mean, standard deviation, proportion non-conforming) lies with the stated probability (not the same as confidence – see above).
- **Bayesian Prediction Interval:** A Bayesian prediction interval is an interval within which a future individual value from the population will be, with stated probability.

Sampling Plans: In the pharmaceutical industry Chemistry, Manufacturing and Control (CMC) applications, sampling plans are used for many applications, including making batch release decisions, demonstrating homogeneity of drug substance and drug product, accepting batches of raw material, and selection of units for environmental monitoring. Sampling decisions include the sample size, sample location, and sampling method, all to test a specified hypothesis.

Monte Carlo Simulation: Simulation is most useful for studying future events that can be predicted from historical data or knowledge. The impact of considered changes can be simulated to obtain an understanding of future outcomes under various possible scenarios.

Measurement System Analysis (MSA): These analyses are referred to as Repeatability and Reproducibility (R&R) in some industries. They involve the design and analysis of experimental data to understand, quantify, and reduce the variability in the measurement system (analytical method).

Variability in the measurement system is normally reduced to categories of bias, linearity, stability, precision, accuracy, repeatability, and reproducibility. This type of data analysis is critical for the development of useful analytical methods. MSA experiments are applicable for both continuous and attribute data.

Hypothesis Testing: Hypothesis tests are statistical analyses to assess the strength of empirical evidence to reject one hypothesis (the “null hypothesis”) in favor of another (the “alternative hypothesis”).

If the data collected is sufficiently unlikely under the assumption of the null hypothesis, then it is rejected; the probability of the observed results if the null hypothesis is true is referred to as the p-value. Lower p-values lead to rejecting the null hypothesis (typically the threshold to reject null hypothesis is set to $p \leq 0.05$ but the threshold selected depends on the situation).

Notes for proper interpretation:

1. A p-value greater than the threshold alone does not necessarily mean the null hypothesis is true; it can only be claimed there is not enough evidence to reject. Further statistical assessment is required to assess the likelihood of the null hypothesis or other statements regarding the hypothesized parameter.
2. Statistical significance indicated by a p-value less than some threshold value is not the same as practical significance. Practical significance of a statistical conclusion should always be assessed using a risk-based approach incorporating patient context and possibly additional statistical analysis.

Empirical Modeling: Data-driven models are those developed through fitting models to data.

In Stage 1, there is often data related to the process or compound being developed. Sometimes, as is the case with material property data, chemical structure data, and processing data, large data sets exist and data-driven models are developed and refined to describe relationships between inputs and outputs.

In the case of a material property data base, relationships between material properties and product attributes are examined and data-driven models developed to predict product properties based on the material attributes. These data-driven models permit a decrease in experimentation, or at least provide a starting point for further experimentation. Examples of data-driven models include simple linear regression, regression trees, partial least squares regression, and support vector machine.

First-principle or Fundamental Models: First-principle, engineering, physics, or fundamental models explain or hypothesize relationships between parameters, material attributes, or manufacturing factors and product attributes. These models seek to predict product attributes directly from established laws of science.

While first-principle models are not considered statistical tools, the models may need data collection and some statistical analysis to estimate parameters in the fundamental model. Prior to running experiments, whether via One-Factor-at-a-Time Studies (OFAT) or through Design of Experiments (DoE), information based on either first principles or data-driven models can be used to help identify relationships between inputs and outputs, and to give direction for experimentation.

Design of Experiments: DoE is a highly-used tool to investigate relationships within the QbD framework of Stage 1. DoE provides a systematic approach to study prioritized factors/parameters/inputs and establish a relationship with quality or in-process attributes.

The strength of DoE is in the application of a systematic approach to data-based decision making along with the selection of a study design; the DoE approach facilitates the study of factors and interactions between factors in an efficient manner.

Due to the complexity of most processes, interactions often have an effect on quality attributes. An interaction means that the effect a process parameter has on the response may depend on the levels of another process parameter. Statistical experimental designs permit the estimation of interactions whereas changing OFAT does not.

Additionally, the statistical design approach provides a proper experimental plan that, when combined with the analysis method, maximizes the amount of information for the minimum number of runs (i.e., the knowledge development process is highly efficient).

Designing an efficient process with an effective process control strategy is dependent on the process knowledge and understanding obtained. DoE studies can help develop process knowledge by revealing relationships, including multifactor interactions, between the material or process parameters and the resulting quality attributes measured on process outputs (e.g., in-process material, intermediates, or the final product).

Efficiently determining an approximate mathematical representation of the underlying physical equation is best accomplished by DoE and an effective experimental strategy.

Greater discussion and use of these statistical tools are provided in Burdick, et al. [30].

3.2 Assess Variability in Stage 1

Assessing the input variability realized in PV Stage 1 batches or studies helps establish the process control requirements prior to proceeding to Stage 2.2. Provided sufficient understanding is established ahead of Stage 2.2, then the process is more an exercise of verifying manufacturing consistency and reliability. The level of understanding of variability for each input can be categorized as either low or medium risk. High risk items need to be mitigated prior to initiating Stage 2.2. Low risk items are verified at the time of Stage 2.2 execution. Medium risk items may lead to continued assessment during Stage 2.2 and possibly more testing and/or monitoring in Stage 3.

Stage 1 process development consists of laboratory-scale, pilot-scale, or large-scale studies and/or batches that help confirm the designed process as a robust manufacturing process within which the impact of design space parameter ranges on product quality attributes is understood.

During process development, sources of variability should be identified and, where possible, variability should be induced in order to characterize and understand its impact on product quality attributes. These sources of input variability may include:

- Batch size
- Manufacturing site
- Manufacturing date (e.g., time of year)
- Drug substance batches (e.g., consider batches at ends of control ranges such as full range of particle size or impurity levels)
- Excipient batches (e.g., consider batches at ends of control ranges)
- Storage conditions for raw materials
- Shipping conditions of raw materials (e.g., capsule shells shipped overseas)
- Multiple raw material batches per drug product batch
- Container/closure component batches
- Consumable material batches or types (e.g., disposable filter sets, sampling materials)
- Manufacturing equipment sets (e.g., use of multiple sets or different makes/models)
- Manufacturing suites or processing lines
- Manufacturing shifts or operators
- Manufacturing environment (e.g., temperature or light control)
- Manufacturing process conditions (e.g., Batch at target conditions? Batch with challenged ranges? Commercial manufacturing control strategy in place?)
- Varied hold times or processing times
- Process interruptions
- Batch reprocessing/recovery
- Sampling methods/equipment
- Analytical testing laboratories' methods qualification state (development mode, validate, etc.) and/or personnel

Practical tools can be used to summarize the input variability planned or experienced. Table 3.1 provides a simple table used to capture relevant variables across Stage 1 batches. Such a table may also be a version-controlled "living tool" that can be carried through Stages 2 and 3 batches to continue to assess the extent that process knowledge has been gained from input variability.

Alternatively, a color-schemed matrix could help visualize how variability has been incorporated across Stage 1, as provided in an example in Figure 3.2.

Table 3.1: Solid Dosage Form Stage 1 Variability Summary Tool

Process Development Variability Summary Tool					
Batch Number	A000001	A000002	A000003	A000004	A000005
Manufacture					
Manufacturing Site					
Purpose of Batch					
Target Batch Size (kg)					
Date of Manufacture					
Equipment (Examples Shown)					
Wet Granulator Make/Model					
Roller Compactor Make/Model					
I-bar Blender Make/Model					
Encapsulator Make/Model					
Compression Machine Make/Model					
Coating Pan Make/Model					
People (Examples Shown)					
Roller Compaction Operator					
Blender Operator					
Compression Operator					
Coating Pan Operator					
Process Hold Times and Interruptions (Examples Shown)					
Final Blend Hold Time (Days)					
Compression Interruption (Hours)					
Core Tablet Hold Time (Days)					
Coating Suspension Hold Time Before Spraying (Hours)					
Analytical					
Laboratory Site/Location					
Analytical Equipment					
Analyst					
Method Version					
Materials					
Drug Substance Batch Number					
Raw Material 1 Batch Number					
Raw Material 2 Batch Number					
Raw Material 3 Batch Number					
Raw Material 4 Batch Number					
Critical Material Attribute #1					
Critical Material Attribute #2					

Figure 3.2: Parenteral Product Input Variability Color Map (colors represent discrete results for clarity)

Variable	Batch								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
	Engineering Batch	Primary Stability Batch	Primary Stability Batch	Primary Stability Batch	Development Batch	Development Batch	Process Validation Batch	Process Validation Batch	Process Validation Batch
Batch Size (units)	20,696	20,543	21,658	20,693	14,864	20,903	20,620	14,222	21,415
Processing Condition	Target	Target	Target	Target	Challenge (high end parameter ranges + time limits)	Challenge (low end mixing)	Target	Target	Target
Month of Year Manufactured	July	August	August	August	February	April	May	June	June
Compounding Starting Shift	Night Shift	Night Shift	Night Shift	Night Shift	Day Shift	Night Shift	Night Shift	Night Shift	Day Shift
Vial Filling Starting Shift	Day Shift	Day Shift	Day Shift	Day Shift	Day Shift	Day Shift	Day Shift	Day Shift	Night Shift
Drug Substance Batch	A	B	C	D	E	F, G	H	I	J
Excipient #1									
Excipient #2									
Excipient #3									
Excipient #4 (critical)	1	2	3	4	5	6	7	8	9
Excipient #5	Aa	Bb	Cc	Bb	Bb	Dd, Ee, Ff	Gg	Gg	Gg
Vial									
Stopper									
Seal									

These tool examples are qualitative ways to capture the process inputs that have been varied. This information contributes to understanding the process and control strategy and allows decisions to be made in terms of residual risk prior to PPQ and/or the need for continued input variability assessment in the later PV stages. For example, a parameter that is particularly critical or more directly impacts a critical drug product attribute may require continued induced input variability in order to gain needed experience and confidence.

Alternatively, an input or parameter may not have been varied in Stage 1, creating a knowledge gap; therefore, the extended control strategy can outline where continued monitoring and/or testing in later stages might be required if induced variability cannot occur. Some inputs are not easily varied (e.g., a critical specification for an excipient) without some intervention. Continued monitoring of such an instance in Stage 3 may allow an opportunity to experience additional input variability not previously seen.

The tools described in Section 3.2 help assess the robustness of the process to study input variability without necessarily requiring quantitative algorithms; however, consideration could be given to assess the risk associated with input variables and the possibility of yet unforeseen variability.

It may be helpful to establish a mechanism to qualitatively or quantitatively score the associated risk. A risk assessment prior to Stage 1 experience, which would leverage prior experience with similar formulations or processes, published literature, or first principles knowledge, may provide an initial baseline against which to compare a post-Stage 1 or later assessment. These risk assessments can vary in their level of complexity and quantitation, such as a formal risk assessment tool, or simply documenting the risk rationale and need for additional evaluation within the protocol of Stage 2 or 3 batches.

Whether the evaluation of input variability in Stage 1 is via simple qualitative tables or a highly-automated IT solution, the assessment is valuable in establishing the process and control strategy boundaries of knowledge. The understanding gained from Stage 1 is the basis for defining what further input variability evaluation should occur in Stages 2 and 3.

3.3 Leverage Stage 1 Data

When determining and justifying the number of Stage 2.2 batches needed to provide sufficient batch and data information to be collected as part of the testing program, it is appropriate to use current product and process knowledge gained from Stage 1 data, or data from similar products and similar manufacturing process steps (e.g., same composition but used for another filling volume).

The intent of leveraging Stage 1 batches is to support the existing body of knowledge and demonstrate the control strategy in order to potentially justify the number of Stage 2.2 (PV batches) to be manufactured to establish the validated state of the process.

For a new product, Stage 1 data typically includes development, clinical trial, technology transfer, engineering batches, and primary stability batches. Whereas for an existing commercial product, Stage 1 data is typically represented by the commercial batches manufactured (prior knowledge batches) at the site and/or technology transfer batches manufactured at a receiving site, as long as the process design has not been significantly changed.

Stage 1 data is leveraged in designing Stage 2.2 in many ways. Specifically, with respect to determining and justifying the number of Stage 2.2 batches needed, Stage 1 data provides information on process capability and reproducibility, feeding into the residual risk assessment regarding how much additional confidence is needed.

Representative Stage 1 batches can be appropriately incorporated into Stage 2.2 data analysis using a number of statistical approaches. These approaches may range from visual and summary statistics comparisons between Stage 1 and Stage 2.2 batches, to statistical intervals combining Stage 1 and Stage 2.2 batches (with proper accounting for within and between campaign variability), or even Bayesian methodology using Stage 1 data to generate prior distributions for parameters.

No matter how it is done, combining Stage 1 and Stage 2.2 batches should be based on a scientific assessment of how representative the Stage 1 batches are using proper statistical methodology to assess data differences and account for campaign effects.

Following a risk-based assessment to determine the number of batches to be manufactured under Stage 2.2, the number of Stage 1 batches that could be included can be calculated.

In situations where multiple strengths of a drug product are manufactured using a similar process and will be validated collectively or separately, consideration should be given to whether grouping Stage 1 batch data is most appropriate. Factors should include:

- Similarities in drug load and formulation
- Process parameter Proven Acceptable Ranges (PAR)
- Control strategy aspects
- Historical comparative performance with respect to CQAs, etc.

Stage 1 batches should be considered based upon manufacturing date chronology, with the most recently manufactured batches studied first. No batches should be excluded simply based upon their performance results if that batch was manufactured in a manner representative of the intended commercial process.

Each Stage 1 batch should be individually evaluated to determine its suitability for use in the justification of the number of Stage 2.2 batches. Evaluation of the batches should be based on the representativeness or relatedness of the Stage 1 batches to the process under validation and not on the outcome of the process performance and testing results.

How relevant Stage 1 batches are can be determined by assessing:

- Executed process
- Process execution conditions (CPP setpoints, ranges)
- Related control strategy
- Level of automation
- Analytical testing program including enhanced sampling
- Operators
- Raw material lots
- Hold times
- Storage conditions

The selected batches should contribute to and support the overall process understanding.

Table 3.2 contains an example risk assessment tool developed for solid oral dosage forms that provides a means to assess whether a given Stage 1 batch adequately represents the intended commercial process to be validated. In the risk assessment, 10 risk criteria are considered, each with three risk levels (low, medium, and high) and corresponding risk points (1, 3, and 5). Table 3.2 may be modified as applicable to the process/product being evaluated.

Table 3.2: Stage 1 Batch Selection Risk Assessment Tool (e.g., for human solid dosage form)

	Criteria	Risk Level	Risk Points	A000001		A000002		A000003	
1	Was batch manufactured at intended launch facility under GMP controls? • Case 1 = Manufactured at intended launch facility under GMP controls • Case 2 = Manufactured at another facility under GMP controls • Case 3 = Manufactured without GMP controls	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Medium	3	Medium	3
2	What scale was used to manufacture the Stage 1 batch? • Case 1 = $\geq$ Commercial scale • Case 2 = $\geq$ 10% Commercial scale • Case 3 = < 10% Commercial scale	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Medium	3
3	Is the equipment of the same SUPAC operating principle? • Case 1 = Same operating principle/subclass • Case 2 = Same operating principle/different subclass • Case 3 = Different operating principle	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Low	1
4	Is process control strategy similar to the commercial control strategy? • Case 1 = Same control strategy • Case 2 = Minor differences that do not significantly impact CQAs • Case 3 = Significant differences in control strategy	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Medium	3	Medium	3

Table 3.2: Stage 1 Batch Selection Risk Assessment Tool (e.g., for human solid dosage form) (continued)

	Criteria	Risk Level	Risk Points	A000001		A000002		A000003	
5	Are the process parameters within the established commercial NORs? - Case 1 = Batch run at nominal process conditions - Case 2 = Batch was run away from target but within established NOR - Case 3 = Batch or portion was run outside the established NOR	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Medium	3	Medium	3	Medium	3
6	Have raw material suppliers changed since the batch was manufactured? - Case 1 = No changes to raw material suppliers - Case 2 = No changes in supplier for key raw materials - Case 3 = Changes to key raw material supplier	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Medium	3
7	Was the API representative of the commercial API process? - Case 1 = API from validated process - Case 2 = API representative of validated process - Case 3 = API not representative of validated process	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Medium	3	Medium	3	Medium	3
8	Was the formulation (unit formula) the same as intended commercial? - Case 1 = Formulation was the same - Case 2 = Formulation difference was minor for the purpose of simulating material CQA differences or to improve processability - Case 3 = Formulation was significantly different	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Low	1
9	Was the analytical method used representative of the validated method? - Case 1 = Validated - Case 2 = Qualified and/or representative - Case 3 = Development and/or not representative	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Low	1
10	Was the batch reprocessed or recovered? - Case 1 = Batch was not reprocessed or recovered - Case 2 = Some reprocessing/recovery steps occurred - Case 3 = Batch was reprocessed or recovered	Case 1 = L Case 2 = M Case 3 = H	L = 1 M = 3 H = 5	Low	1	Low	1	Low	1
Total				Score	14	Score	18	Score	22
Risk Level				Low		Medium		High	

Note that the high-risk rank for several risk criteria is highlighted in bold red, which denotes that a Stage 1 batch meeting these criteria would automatically be excluded from consideration when determining the number of batches or assessing inter-batch variability, regardless of the results of the remainder of the risk assessment for that batch.

The cumulative risk points for a batch are compared to the criteria in Table 3.3 to determine the suitability of the Stage 1 batch for inclusion in the combined Stage 1 and Stage 2.2 batches. The Overall Risk Scores presented in Table 3.3 were constructed such that when 4 or more of the 10 criteria are determined to be medium risk, the overall risk is medium. Likewise, when there are 5 or more medium risks, or 2 or more high risks, the overall risk is high.

These criteria are sufficiently conservative to ensure that variability associated with the product and process are included in the data set while ensuring the batches selected do not represent unrealistic variability, which would result in artificially wide tolerance intervals when evaluating between batch variability.

Table 3.3: Stage 1 Batch Representation Score Interpretation

Overall Risk Scores	Stage 1 Batch Risk Level	Risk Level Description
< 16	Low	Batch included in combined Stage 1 and Stage 2.2 batches
16 – 20	Medium	Batch requires justification before inclusion in combined Stage 1 and Stage 2.2 batches
> 20	High	Batch is not suitable for inclusion in combined Stage 1 and Stage 2.2 batches

3.4 Determine Design Space and Control Strategy

3.4.1 Determination of the Design Space

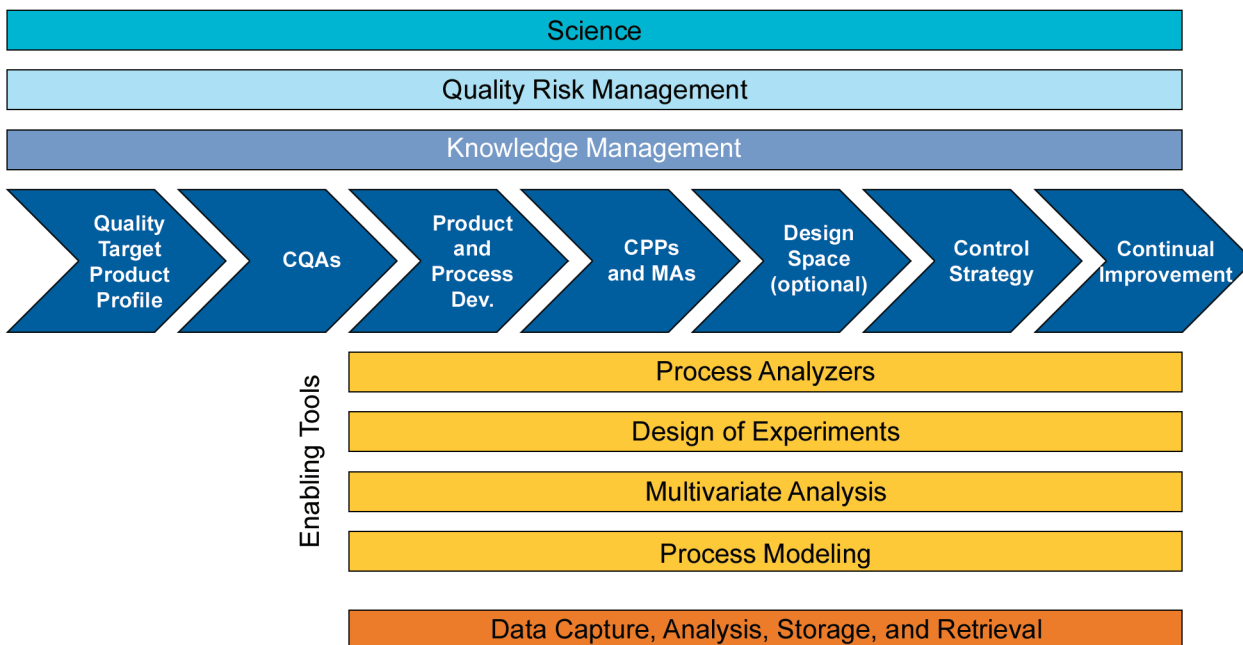
The design space is one of the QbD elements. Table 3.4 lists the terms described in ICH Q8(R2) [1] and outlined in the QbD roadmap, Figure 3.3. More information about QbD, how to identify CQAs, CPPs etc., can be found in the *ISPE PQLI® Guides* [7, 8].

The design space is optional to establish and submit to health authorities; however, the underlying methodology is very useful for generating process understanding, identifying CPPs, detecting interactions between parameters and/or attributes, and establishing ranges for CPPs.

Table 3.4: Quality by Design Terminology Also Used for Process Validation

QbD Element	Acronym	Definition
Quality Target Product Profile	QTPP	<i>A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8(R2) [1])</i>
Critical Quality Attribute	CQA	<i>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. (ICH Q8(R2) [1])</i>
Critical Process Parameter	CPP	<i>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(R2) [1])</i>
Critical Material Attribute	Material CQA or CMA	<i>A critical quality attribute of a material (raw, feed, solvent, in-process, intermediate, excipient, drug substance, packaging, etc.) whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality.</i>
Design Space		<i>The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8(R2) [1])</i>
Control Strategy		<i>A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10) (ICH Q8(R2) [1])</i>

Figure 3.3: QbD Approach Showing Overarching Principles and Some Enabling Tools [7]



ICH Q8(R2) [1] defines design space as (cf. Table 3.4):

“The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.”

In other words, it is the multivariate combination of CMAs and CPPs that assures one or more CQA requirements are met. It is a process window, that when the process is operated in this specific space, the CQAs are met and the QTPP assured.

The understanding of the CQAs and the multivariate aspect are the main difference from the conventional method of establishing ranges for process parameters, PAR and Normal Operating Range (NOR), which does not reflect interactions and nonlinear effects quite common in complex biological, chemical, and physical systems.

ICH Q8(R2) defines PAR as [1]:

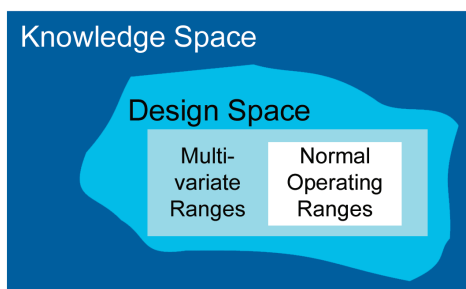
“A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.”

EMA defines NOR as a [31]:

“...Region around the target operating conditions that contains common operational variability (variability that can’t always be controlled).”

That is, NOR is a subset of PAR or of ranges derived from a multivariate design space. See Figure 3.4.

Figure 3.4: Relationship between Knowledge Space, Design Space, and Derived Normal Operational Ranges



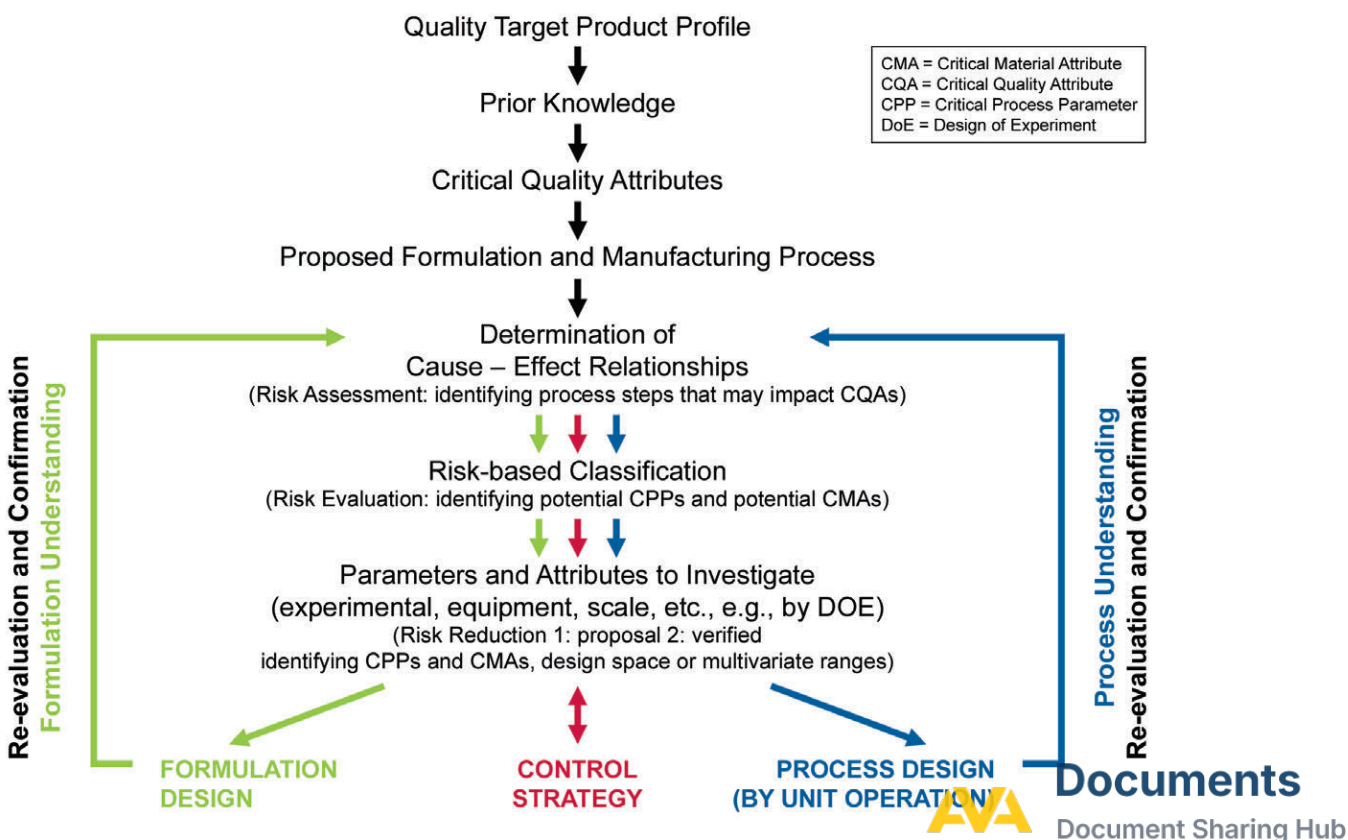
The complexity and robustness of the design space depends on the level of process understanding, the process complexity, the CPPs, CMAs, the number of unit operations covered, and the level of experimental work conducted to establish the design space.

Design space is established using an iterative science and risk-based approach linking the CQAs to the CPPs and CMAs (from raw material and other materials to be added to the process) and intermediate CQAs (e.g., blend uniformity or an intermediate impurity). It may include information regarding site, equipment, and scale of manufacture, depending on the level of process knowledge and the sensitivity of process performance on those aspects. See Figure 3.5.

Statistical considerations in design space development are not discussed here but can be found in articles such as "Statistical Considerations in Design Space Development," *Pharmaceutical Technology* [32].

The process flow for design space determination as a QbD element of the product and process development process is discussed in detail in *ISPE PQLI® Guide Part 1 – Concepts and Principles* [7].

Figure 3.5: Iterative QbD Approach including QRM Steps [7]



Establishing Design Space

The generation of design space begins with the QTPP and the related CQAs that it represents. The question is how the process and the materials for use affect these CQAs (factors).

Starting with a risk assessment identifying potential CPPs and potential CMAs results in identification of areas where there is a confirmed risk and a need to mitigate or control, or where additional work is needed for further understanding if risk is present.

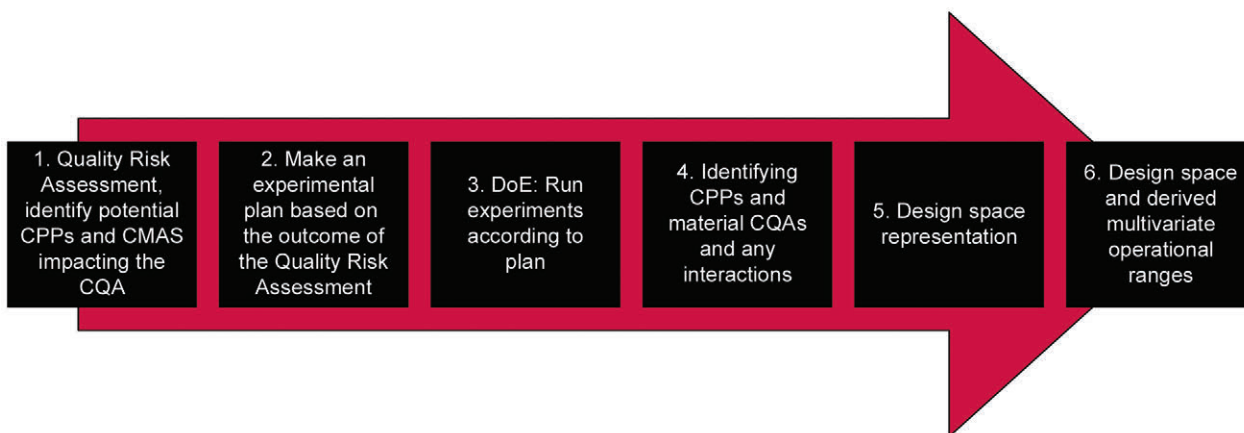
Typically, for the additional work required, a DoE is used. The output from the experimental data is an identification of CPPs and CMAs or intermediate CQAs from the potential critical factors, and any interactions between these and the space where the process can be operated to meet the CQA expectations. See Figure 3.6.

The DoE also identifies the non-CPPs and material attributes with no impact on the CQAs that can be disregarded in the design space.

DoE as a multifactor tool is based on prior knowledge and requires a risk assessment focusing on material and process impact on the CQAs. The experiment design is established in such a manner that as few experiments as possible should be performed to get enough information to understand the impact on the CQAs. The risk assessment should be updated after the experiments and analysis to reflect the outcome from the DoE.

Examples of how to determine the design space can be found in detail in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

Figure 3.6: Typical Work Flow for Establishing a Design Space



The following are examples of output from the different steps:

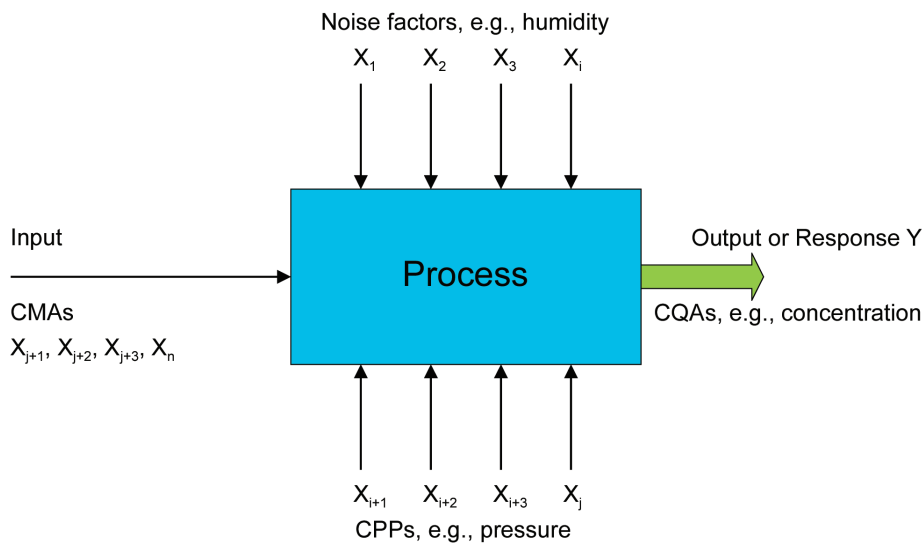
Step 1: Quality Risk Assessment identifying potential CMAs and CPPs (see Figure 3.7)

Figure 3.7: Quality Risk Assessment Example

Product CQAs	Process Steps						Process Parameters					Formulation Variables		
	Pre- roller Blending	Roller Compaction	Milling	Final Blending and Lubrication	Compression	Coating	Inlet Temp	Atomizer Pressure	Compression Force	Number of Mixing Revolutions	Tabletting Speed	Lactose MCC Ratio	Magnesium Stearate Amount	Input Material att.
Identity	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Appearance	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	High	Low	Low	Low
Assay	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Impurity	Low	Medium	Low	Low	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low
CU	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Medium	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low
Disintegration Time	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Hardness	Low	Low	Low	Low	High	Low	Low	Low	High	High	Low	Low	Medium	Low
Content Uniformity	High	High	Medium	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Weight	Low	Low	Low	Low	High	High	Low	Low	Medium	Low	Low	Low	Low	Low
Friability	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low
Thickness	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Step 2: The DoE concept, investigating impact of potential CMAs and CPPs on CQAs in a systematic experimental setup (see Figure 3.8)

Figure 3.8: Design of Experiment Concept



Step 3: Experimental DoE plan and execution (see Figure 3.9)

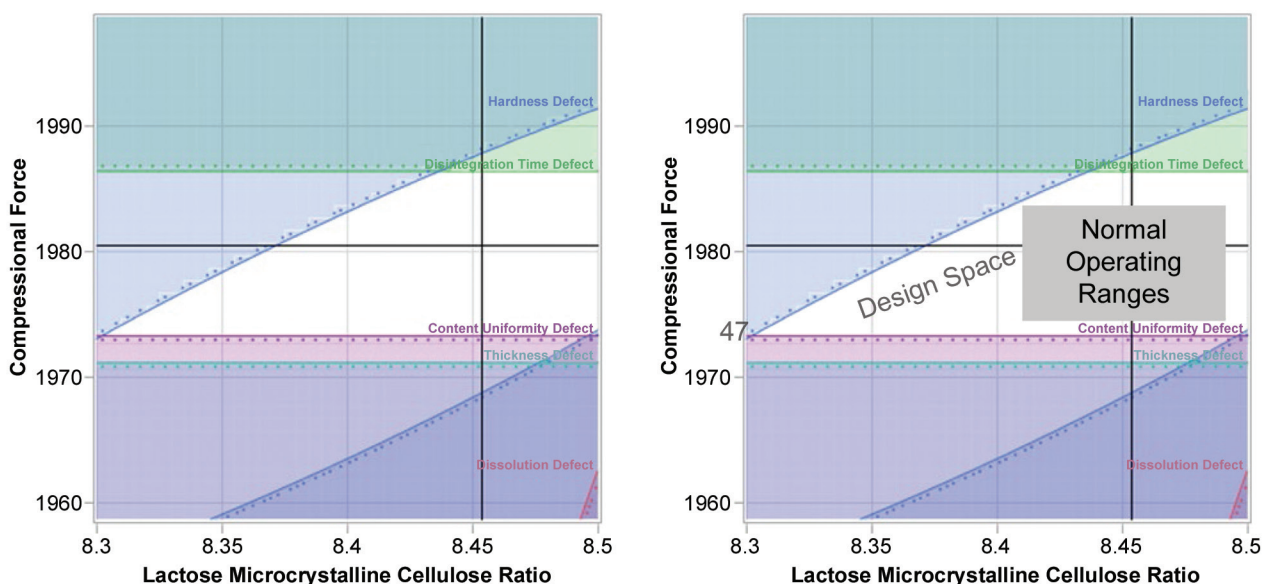
Figure 3.9 Example Design of Experiment Data

	API Particle Size	Mill Time	Screen Time	Blend Time	Blend Speed	Compressor	Force	Coating Viscosity	Inlet Temp	Exhaust Temp	Spray Rate	Atomizer Pressure	Dissolution
1	Small	30	3	11	59.5	Compress2	25	86	108	72	418	57	64.6
2	Medium	17.5	4	17	62	Compress2	25	110	108	72	418	62	73.6
3	Medium	30	4	11	57	Compress2	24	110	104	69.5	418	57	67.8
4	Medium	30	4	11	57	Compress1	25	86	106	72	388	62	66.1
5	Small	5	3	17	62	Compress1	25	86	108	69.5	388	62	75.7
6	Medium	30	3	17	57	Compress2	25	110	108	67	388	57	79.2
7	Medium	30	3	17	62	Compress2	24	86	104	72	388	59.5	83.4
8	Small	30	4	14	62	Compress1	24	110	108	72	388	57	72.5
9	Medium	5	4	11	62	Compress2	24.5	86	108	67	388	57	64.4
10	Small	30	4	17	57	Compress2	24	86	108	67	403	62	68.4
11	Medium	5	4	17	59.5	Compress1	24	110	104	67	388	62	70.9
12	Small	30	4	11	62	Compress2	25	110	104	67	388	62	66.7
13	Medium	5	3	17	57	Compress1	24	86	108	72	418	57	61.1
14	Medium	5	3	14	57	Compress2	25	86	104	67	418	62	64.8
15	Medium	30	4	17	62	Compress1	25	86	104	67	418	57	57.2
16	Small	5	4	11	62	Compress1	24	86	104	72	418	62	55.9
17	Small	5	3	17	62	Compress2	24	110	106	67	418	57	70.6
18	Medium	30	3	11	62	Compress1	24	98	108	67	418	62	70.4
19	Small	5	4	11	57	Compress1	25	110	108	67	418	59.5	69.9
20	Medium	17.5	4	14	59.5	Compress2	24.5	98	106	69.5	403	59.5	68.7
21	Small	5	4	17	57	Compress2	25	98	104	72	388	57	69.9
22	Small	30	3	17	57	Compress1	24.5	110	104	72	418	62	76.5
23	Small	17.5	3	11	57	Compress1	24	86	104	67	388	57	77.3
24	Small	5	3	11	57	Compress2	24	110	108	72	388	62	71.5
25	Medium	5	3	11	62	Compress1	25	110	104	72	403	57	75.9
26	Small	17.5	3	14	59.5	Compress1	24.5	98	106	69.5	403	59.5	74.8

Step 4: Identification of CPPs and material CQAs and any interactions

Steps 5 and 6: Representation of the design space. The identification of CMAs and CPPs as well as the applicable design space where operation within will meet the CQA acceptance criteria, is an outcome of the DoE. The design space can be represented, for example, by a mathematical expression or as shown here, graphically (Figure 3.10). The right-hand picture shows an example of normal operational (operating) ranges.

Figure 3.10: Representation of the Design Space



The design space is a direct outcome of the DoE studies. The identified CMAs and CPPs can thus be selected for inclusion in the final design space. Independent design spaces can be presented for one or more unit operations, or there may be a single design space that covers multiple operations in the manufacturing process.

Multivariate Ranges – Used for Process Performance Qualification/Process Validation

The operating ranges for the CPPs can be the entire design space expressed as a set of dependent equations or a range; however, from a practical perspective, they are often extracted from the design space in a linear combination, shown in Figure 3.10 as the solid box, and each CPP range becomes a simple linear range from a minimal to a maximum value.

As these ranges are multivariate derived, the conventional definition of PAR cannot be applied. These DoE-derived multivariate-derived ranges of the CPPs are based on understanding the process and the potential interactions parameters and/or materials might have on the finished product quality.

When designing experiments to determine the multivariate ranges or PARs of CPPs, both measurement uncertainty and common cause variability of the commercial manufacturing equipment should be considered. Every measurement has uncertainty, and estimates based on samples should include sampling variability. Similarly, the common cause variability in regard to the ability to control a parameter should be taken into account.

To design processes that can be routinely managed within limits in the commercial manufacturing facility, develop experimental ranges wide enough to allow compensation for measurement uncertainty and common cause variability when the process is run in commercial manufacturing.

Measurement uncertainty is commonly managed by reducing the PAR or multivariate limits (as applicable) to a value inside the limit determined during development. These tighter limits can be included in the batch records as alert limits or decision limits. Typically, these new limits are determined based on a selected level of statistical assurance that the actual value is within the PAR or multivariate range for interacting parameters.

The likelihood of not meeting the CQA acceptance criteria when operating within these ranges is extremely low, assuming model uncertainty and response variability have been accounted for in estimating the design space. This is not the case when PARs have been established using the conventional OFAT approach.

The design space is likely established at the laboratory scale unless the laboratory and commercial scale are the same, as in the case of many continuous manufacturing operations. QRM and scale-up models/algorithms are used to scale the design space to pilot and/or commercial scale.

It is important that scalability of the design space and/or the multivariate ranges be addressed during process design to avoid having to redo the development work at commercial scale. The commercial proposed ranges are evaluated and tested after technology transfer, and set points and ranges defined for the PPQ.

3.4.2 Determination of the Control Strategy

The control strategy is:

“A planned set of controls derived from current product and process understanding that assures process performance and product quality.” [6]

It is product centric and incorporates all those controls that should be implemented to ensure product safety, efficacy, and quality. It can be established using QbD principles or a traditional approach.

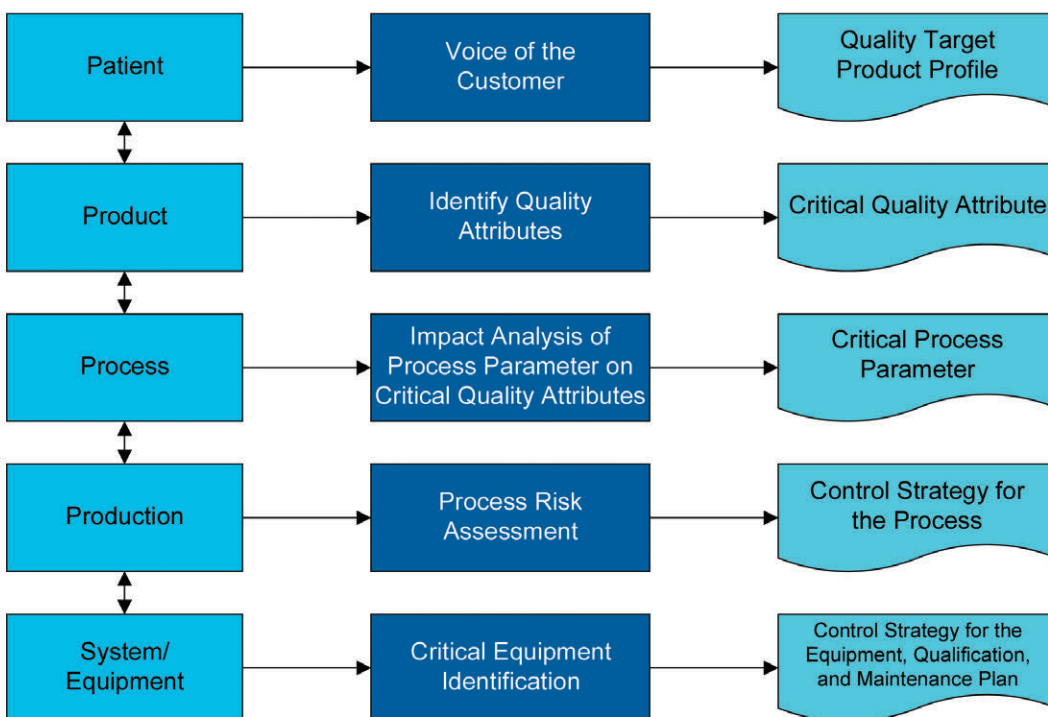
The control strategy aims at ensuring a product with the right CQAs and consistency is being manufactured and therefore in alignment with the expectations as expressed by the QTPP (patient focus). This focus should be applied throughout the product lifecycle from product and process design through to final product, including API and finished product manufacture, packaging, and distribution.

The control strategy is vital to producing products and drives the strategy for how processes should be validated or verified during the PPQ stage (Stage 2.2). In short, the control strategy is verified at this stage.

Development of a control strategy requires a structured process involving a multi-disciplinary team of Subject Matter Experts (SMEs) linking pharmaceutical development to the manufacturing process and engineering controls of process equipment. This team may include representatives from formulation development, drug substance development, process development, analytical development, Quality Control (QC), Quality Assurance (QA), Regulatory Affairs, Manufacturing, Engineering, Validation, and PAT. See Figure 3.11.

To ensure that a product with the right CQAs is manufactured, CPPs, CMAs, and intermediate CQAs should be identified and controlled as elements of the control strategy. Ideally the process should be designed to accommodate variability during processing to ensure that the final product CQAs are consistent within and between batches. QbD principles and PAT tools are enablers in this case.

Figure 3.11: A Simple Illustration of the Different Activities from Development to Designed Facility, Input, Interactions, and Output



Patient → Product

The patient requirements or expectations in terms of clinical performance, drug delivery method etc., are input on how the product ideally should be designed. The patient's needs are expressed by the Voice of the Customer and outlined in the QTPP, where the high-level quality characteristics are described, including administration form, dosage, purity, container closure system, etc.

Product → Process

From the defined QTPP, the CQAs are identified and rated according to criticalities such as patient safety, product release kinetics, product interaction with primary packaging materials, etc. The process steps are evaluated for their impact on the CQAs, and thus the critical process steps are identified. Further discussion on this criticality assessment is found in the *ISPE PQLI® Guide Part 1 – Concepts and Principles* [7].

For legacy products this might be an opportunity for improvement, as typically neither the QTPP nor the CQAs are defined. It is useful to define CQAs for a legacy product as it puts the validation into perspective (validation efforts commensurate with the level of risk to the patient and therefore risk from changes to the CQAs). Several discussion papers on how to define CQAs for legacy products have been published by ISPE [33, 34, 35].

For the critical process steps, the CPPs are identified as those process parameters having a direct impact on a CQA. In a similar way, CMAs are identified. These need to be monitored and/or controlled.

Process → Production

For each identified critical process step, the risk is determined according to the severity rating of the CQA, the facility-dependent evaluation of occurrence for the failure in question, and the probability of detecting the failure if it happens.

The outcome of the process risk assessment (e.g., a process FMECA or FMEA) provides input to the control strategy, including the identified risk control measures, and/or monitoring setup.

Production → Equipment/System

The aspects of manufacturing systems and equipment that can impact CQA, for example a CPP and its control systems or the design of a piece of equipment, should be identified during the process risk assessment, and if relevant, included in the equipment qualification plan (Stage 2.2).

Critical Aspects

The identified part of the equipment or manufacturing systems that are aspects as discussed above are often referred to as Critical Aspects (CAs). These are further discussed in Section 4.1 and in ASTM E2500 [36], which provides this definition:

“Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding.”

The CAs can also be derived from the control strategy as discussed later in this chapter.

Intermediate Critical Quality Attributes

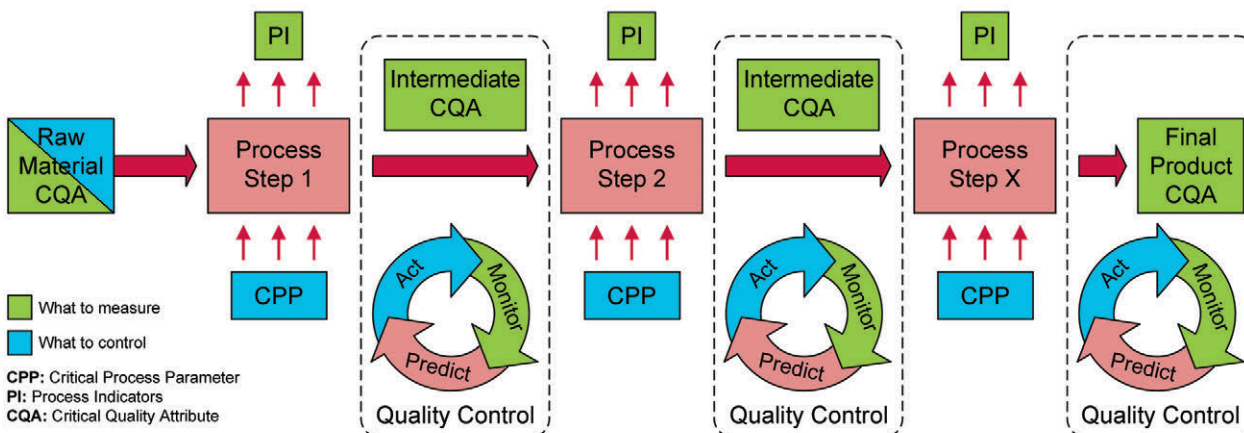
In Figure 3.12, a manufacturing process is illustrated with a set of process steps. During Stage 1, CPPs for each step were identified, showing how the different process steps can be characterized in terms of intermediate CQAs – a quality attribute of an intermediate stage that has a direct impact on a final product CQA. In the case of an oral solid dosage product, blend uniformity is normally an intermediate CQA as it has a direct impact on the CQA Content Uniformity of the final product.

The intermediate CQA might be measured directly by a process analyzer (e.g., NIR for blend uniformity) or measured indirectly by a process indicator (e.g., power consumption) during processing.

An example of how the control strategy controls CQAs and CPPs during processing is shown in Figure 3.12. The measured output of each step is preferable as an intermediate CQA or a final product CQA; however, if these cannot be measured directly, other measurements might be possible that indicate the performance and quality of the process. These are referred to as process indicators.

The outcome of the measurement of the intermediate CQAs or process indicators is used to adjust the process in real time to minimize variability during processing. There might be cases where a decision has been made to test the product CQAs at the end of processing rather than measuring and controlling intermediate CQAs or process indicators during processing. This decision should be made keeping the patient risk in mind.

Figure 3.12: Robust and Effective Control Strategy Example



The control strategy evolves throughout the product lifecycle. During development, the focus is on “how to establish the product and process” and “what to control and how” to ensure the CQAs and meet the expectations of the QTPP.

Later, after scale-up and technology transfer, the control strategy should be updated and verified to reflect any changes in parameter ranges or set points due to changes in scale and equipment type/brand.

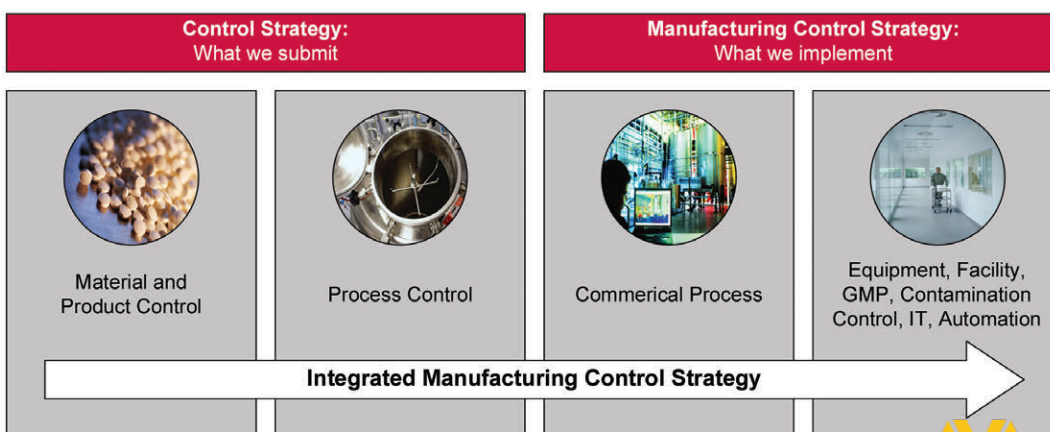
The control strategy should also be expanded to include controls related to the process equipment, utilities, facility, the process control system, cleaning aspects, and supporting quality controls to ensure product quality.

3.4.2.1 Manufacturing Control Strategy

The expanded overarching control strategy used during commercial manufacturing is often considered as the ‘Manufacturing Control Strategy’. It helps ensure patient safety and product quality during manufacturing by establishing a robust process operated within suitable equipment ranges that are controlled by the manufacturing control strategy. This strategy connects all of the controls from CQAs, CMAs, CPPs, equipment, facility, and other GMP controls.

Figure 3.13 illustrates the regulatory relationship between the control strategy and the manufacturing control strategy. The control strategy established during development linking CQAs, CPPs, CMAs and intermediate CQAs needs regulatory approval, whereas the overall manufacturing control strategy is subject to health authority inspection as it includes GMP controls not normally submitted within the dossier.

Figure 3.13: The Manufacturing Control Strategy: The Expansion of the Control Strategy to Include Equipment, Facility, GMP, and Process Performance Controls



The manufacturing control strategy may include, but is not limited to:

- Controls related to the fundamental control strategy
 - Control of CMAs: CMAs such as drug substance, excipients, primary packaging materials and their sampling plans, analytical methods, and acceptance criteria
 - Control of CQAs: Intermediate and product CQAs, specifications, sampling plans, analytical methods, acceptance criteria, procedural controls
 - Controls of CPPs and other process parameters, operating ranges, set points, process control systems
 - Predictive models (if submitted)
 - A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models
- Controls added to the manufacturing control strategy:
 - Facility controls, utilities, cleaning, environmental systems monitoring, process control systems, operating conditions
 - Controls for unit operations that have no impact on product quality but are important for operating a robust and consistent process

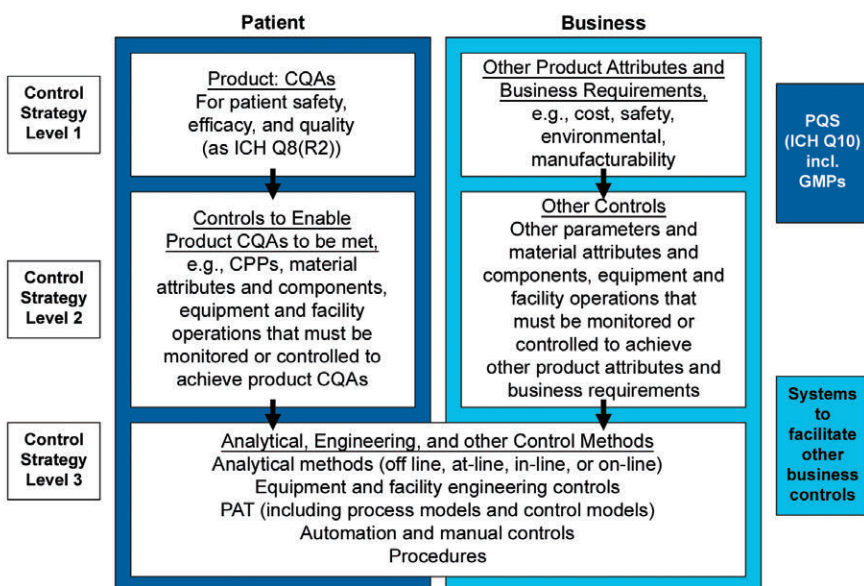
3.4.2.2 Production Control Strategy

Controls related to business performance might also be included in the manufacturing control strategy as it embraces all controls relevant from a patient protection and business point of view.

These “business controls” might not be subject to health authority inspections as they are not covered by GMP, but to limit some complexity, firms may manage them in the same way as GMP controls. This is a decision that has to be made at the site.

A model using PQLI® [8] as an example (see Figure 3.14) is helpful when defining the production control strategy.

Figure 3.14: The PQLI® Control Strategy Model Applied to Identify the Production Control Strategy



The PQLI® Control Strategy Model in Figure 3.14 illustrates how patient and business requirements can be considered in parallel. The process can be described as follows:

1. CQAs and other requirements are identified.
2. CPPs, CMAs, intermediate CQAs, and CAs on equipment identified.
3. The analytical, engineering, automation, PAT, and other controls required for the identified parameters and attributes are defined. Typical controls could include:
 - Off-line testing of an attribute of a starting material, component, or in-process material
 - Monitoring and feedback control of a material attribute during processing (manual or automated)
 - Monitoring and feedback control of an equipment parameter during processing (manual or automated)
 - Monitoring and feed forward control of a material attribute or process parameter (manual or automated)
 - Procedural control of an operation
 - Equipment and facility design
 - Process design, for example the addition of specific operations during drug substance manufacture to reduce the level of impurities
 - Procedures to be followed in the event of a malfunction

Using this approach for establishing the control strategy results in clear links between CQAs, process steps, CMAs, CPPs, and actual controls. An example for an oral solid dosage product can be found in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

An example of a control strategy table is shown in Table 3.5. Not only does such a control table provide a clear overview of the submitted control strategy but it can also be used to plan for process qualification activities. The table can be expanded with more specific columns to include activities to be performed during PV Stages 2.1, 2.2, and 3. Examples of activities for Stages 2.1 and 2.2 are shown in Tables 3.6 and 3.7, respectively.

Table 3.5: Example of a Control Strategy

CQA	Unit Operation	CPP or Material CQA	Controls
Dissolution	Dispensing	API PSD	• Laser diffraction measurement
		MgSte level	• CoA
	Roller Compaction	In-process material CQA: ribbon density CPP: roll pressure CPP: roll gap	• In-line NIR – feedback control of roller pressure. Ribbon density to comply with specified range. • Equipment control
	Milling	In-process material CQA: granule PSD CPP: mill screen size	• Laser diffraction • Mill screen size to be within the PAR
	Lubrication	CPP: Time	• Time control
	Compression	In-process material CQA: hardness CPP: compression force	• Hardness tester • Maintain hardness • Compression force based on ribbon density • Controlling compression force, pressure control device

In the planning for Stage 2.1, the control strategy can be used to identify CAs and high-level qualification activities. The full qualification program will be equipment specific and therefore more detailed. A high-level example for the roller compaction step is shown in Table 3.6.

Table 3.6: Example Control Strategy Used for Planning Equipment Qualification Activities

Process Parameter	Assignment	Critical Aspect	Control Strategy	Stage 2.1	Good Engineering Practice
Roll Pressure	CPP	Yes	20 – 65 bar (to achieve a ribbon density 1.0 – 1.2 g/cc – needed for proper dissolution)	Verify roll pressure and control system	Motor speed, pressure system, motor rating, wiring, maintenance access
Roll Gap	CPP	Yes	PAR: 1.2 – 2.4 mm	Verify roll gap and control system	
Roll Speed	Criticality undermined	Yes	Setting fixed based on previous experience: 8 rpm	Verify roll speed	
Feed Rate	Non-CPP	Maybe	Dependent on roller parameters		Feed rate, FAT and/or SAT
		Material of rollers		Material of rollers, vendor certificate	
		Material of feed system		Material of feed system, vendor certificate	

Often process equipment are qualified using a generic approach not related to a specific product. In such cases, a gap analysis should be conducted to ensure the qualification performed is in line with the product-specific control strategy; that is, the design of the equipment reflects the design proposed during Stage 1 and the equipment has been qualified over the range of the specified CPPs. If gaps are identified, the remaining qualification activities should be performed.

After successful equipment qualification (Stage 2.1), Stage 2.2 or the PPQ can be planned as a verification of the control strategy. The example in Table 3.7 shows how dissolution is impacted during the roller compaction step and how the PPQ plan is derived from the control strategy overview established during Stage 1 including scale-up and technology transfer.

Table 3.7: Example Control Strategy Used for Planning Process Performance Qualification Activities

CPP/CQA	Operational Range/Method	Control Method	Specification Comments	Stage 2.2 PPQ Activities
Roll Compactor	Alexanderwerk WP200 (roll diameter 200 mm, roll width 75 mm)			Run X PPQ batches according to an execution plan
Roll Pressure	31 – 102 bar	Automated control		Monitor parameter
Roll Gap	2.0 – 4.0 mm	Mechanical control		Monitor parameter
Roll Speed	8 rpm	Fixed	Setting fixed based on previous experience	Monitor parameter
Mill Speed	60 rpm	Fixed	Setting fixed based on previous experience	Monitor parameter
Mill Screen Size	0.6 – 1.4 mm	Mechanical control		Monitor parameter
Ribbon Density	Envelope density analyzer	In-process control (at-line)	Relative ribbon density 0.68 – 0.81	- Sample plan - Monitor ribbon density throughout the batch according to sample plan
	Settings relevant to the NIR model	NIR in-line	1.0 – 1.2 g/cc	- Verify NIR method and compare to ribbon density test - Sample frequency - Monitor ribbon density, roller compaction parameters, intermediate CQAs
Granule Size Distribution (D50)	Sieving method	In-process control	250 – 500 mm	
Dissolution	Dissolution method pH 1.2; 2% SLS, 75 rpm	End product dissolution method as per release specification	NLT 80% @ 30 mins	- Sample plan - Monitor dissolution, correlate to ribbon density

3.5 Validation Master Plan

A Validation Master Plan (VMP) formally communicates steps to be taken and the deliverables required for PV. EU Annex 15 Clauses 1.4 and 1.5 [11] provide clear direction on VMPs. It is expected that the key elements of the site qualification and validation program be clearly defined and documented in a VMP or equivalent document.

Additionally, the VMP should define the qualification/validation system necessary to execute the validation effort.

A structure for the VMP includes scope, references, responsibilities, risk management, and methodology. In cases where the system is not overly complex, a VMP can be combined with the validation protocol.

Why write a separate plan?

- It provides the strategy and rationale for design.
- It gives alignment with partners (e.g., stability, engineering, cleaning).
- Stability protocols can be written from information in the plan, which may be ready long before the protocol.
- It can be used to approve bracketing.
- It stipulates the justification for manufacturing at risk requirements.

While a plan often accelerates preparation on the front end of the project, the report needs to be cross checked against two documents (plan and protocol) to assure all requirements have been met.

3.6 Readiness for Stage 2 (Process Performance Qualification)

PV Stage 1 Checklist

Prior to PV Stage 2.2 (the process validation exercise), it is recommended that firms perform a risk assessment using knowledge from Stage 1. Table 3.8 is an example of a high-level checklist that can be utilized to help assure PV prerequisite data has been obtained from Development.

Table 3.8: Example Process Validation Stage 1 Checklist

Prerequisite	Status
CQAs and limits determined	
CPP ranges appropriately stressed to reflect operational capability at intended commercial site	
Map of CQAs impacted by each unit operation, and associated CPPs impacting those CQAs in each unit operation (where applicable) completed	
Identification of critical raw materials and understanding of variability with respect to product quality achieved	
Design space/multivariate interactions identified	
Design space models fully verified or validated	
Meaning of identified PAR understood by Manufacturing and documented. <i>This is important as although the ICH Q8(R2) definition of PAR is univariate [1], PAR is utilized by some firms to represent a multivariate limit.</i>	
Validation of scale-down models considered if applicable	
Effects of scale fully explored or not. <i>Manufacturing Clinical Trial and/or development batches at full scale during PV Stage 1 can greatly improve knowledge of viability of the commercial manufacturing process.</i>	
Available information about impact of extended control strategy (such as hold time limits between various unit operations) reviewed	
Control strategy risk assessment finalized	
Understanding of impact of variation on product and process quality attained. <i>PV will proceed more smoothly with more accurate results when a concerted effort to introduce variability and study impact has occurred during Stage 1.</i>	
Knowledge management plan prepared. <i>This plan should explain the transfer of information to Manufacturing and how process knowledge documentation will be updated as learning occurs during commercial manufacturing.</i>	
VMP in place	

Assessing the probability of failing specifications and/or PPQ criteria to determine if advancing to Stage 2 is appropriate and recommended. One approach is to use heatmaps/contour plots of development data (or historical data for in-line products) to assess this risk. Vukovinsky et al. [37] and Burdick et al. (see Chapters 3 and 9) [30] provide examples of how this can be done.

Validation Readiness

The decision to commence Stage 2.2 PPQ should be taken when Stage 2.1 qualification activities have been approved and readiness has been demonstrated, that is, the risk of not being able to manufacture a consistent product meeting its CQA acceptance criteria (specification) is low.

Validation exercises are time consuming and costly, and failing validation due to equipment issues, lack of training, missing analytical or cleaning validation studies or other issues is avoidable when proper care and attention are exhibited via a readiness checklist or project management.

The purpose of the validation readiness assessment is to ensure a successful validation by identifying issues before the validation process begins. A systematic approach is recommended to assess and learn from previous experiences (collect and analyze data); to identify recurring issues; and to develop a mitigation plan that resolves issues before PPQ execution.

Written and approved prior to the execution of PV, the readiness assessment is often a compilation of assessments written by various manufacturing and quality system owners covering principal activities prior to PV. An overall summary written by technical experts is included.

Sites perform formal (documented) assessments of supporting equipment (including evaluation of validated equipment ranges as compared with the operational ranges of the intended process), utility, system, method validation, and training to ensure supporting processes/systems/procedures/training are in place for validation.

This more detailed readiness checklist (Table 3.9) can be used as a project management tool to plan for PPQ and to evaluate the risk of moving forward to PPQ.

Table 3.9: Readiness for Stage 2.2 Checklist Example

Readiness Prerequisites	Status
Process design is assessed and found to be acceptable. Process is characterized adequately and well understood.	
Control Strategy including automation, process control, In-Process Controls (IPCs), sample plans, PAT-based controls including back-up systems, and approved, implemented, verified, and updated Risk Assessment are complete	
Starting materials (including classification of raw materials, intermediates, etc.) and packaging materials are approved for use in manufacturing	
Verification of IT system used for data entry, calculations, and reporting (if applicable) completed	
Aspects of operator shifts, breaks, logistics reviewed	
Determination of whether or not to conduct supplier and CMO audits prior to initiation of PPQ completed	
Product Assessment Review conducted: - Review of deviations, trends, adverse events, and complaints - Open recommendations from Annual Product Review (APR) - Quarterly (or more frequent) product and process assessment - Change requests including equipment, facility, and/or product, countermeasures - Previous validation recommendations	

Table 3.9: Readiness for Stage 2.2 Checklist Example (continued)

Readiness Prerequisites	Status
Assessment of potential deviations during PPQ and an executed plan to minimize this risk completed. For example: - Where do deviations and non-conformities typically occur - Operating conditions, sampling, acceptance criteria, operator error - Equipment maintenance, calibration, available spare parts, and back-up systems - Statistical analysis of data from similar processes (control chart to identify normal behavior)	
Gemba walk through the production procedures performed [38]	
Process Flow Document and Master Production Record approved prior to protocol approval	
Master Production Record, Process Flow Document, Standard Operating Procedures (SOP) and Process Automation Controls are aligned and reflect appropriate regulatory commitments	
Batch records approved reflecting the process to be validated. - CPPs and corresponding acceptance limits (clearly visible to the operator) - Forward processing requirements/in-process specifications - Processing instructions - Sequences to be followed - Time limits for completion (individual processing steps and the total process). <i>These are reflective of process understanding gained from Stage 1 or technical assessments of similar products/platforms and defined in batch records, SOPs, and applicable validation protocols.</i> - IPCs and corresponding acceptance criteria - Storage requirements - Specific instructions (<i>Do not use “approximately” or “mix to form vortex,” which may lead to unintended interpretation.</i>) - End points should be quantitative and defined for repeatability (end of compression/end of fill through qualified level sensors, etc.) - Batch record ranges should be reasonable (not 5° to 150°C) and operators should be provided with a target within a range - Record actual values obtained (not Yes/No the range was met)	
Preparation and storage of process solutions (e.g., buffers) determined	
Hold times and critical processing times during PV identified	
Validated analytical methods and approved specifications (for commercial) product implemented	
Chromatography resin and ultrafiltration membrane re-use evaluated	
Training conducted and documented prior to the start of validation. Operations is a critical part of PV and thus operators participating in PV should be trained and/or qualified on equipment operation, process and process control, batch production record, parts of validation they will execute according to the protocol (e.g., sampling), and related GMPs and procedures.	
Interactions with product contact materials (e.g., extractables and leachables) assessed	
Packaging validation for drug product should be considered. - Equipment used for packaging should undergo an appropriate level of qualification - The packaging process may be validated prior to PV or carried out concurrently with the PV - Also consider packaging equipment cleaning PV if applicable	
Equipment and Utilities Qualification – ensure equipment used in manufacturing operations is qualified or re-qualify as necessary. - Assure/verify process ranges are covered - Verify calibration status of all equipment, across ranges required by the process being validated - Equipment qualification should include a traceability matrix showing how all of the user requirements have been met	

Table 3.9: Readiness for Stage 2.2 Checklist Example (continued)

Readiness Prerequisites	Status
Computer system validation completed. <i>Computer system validation has unique qualification elements such as disaster recovery, security, data storage, data transmission, monitoring, decision and control capabilities, and source code verification. Include an evaluation of data integrity expectations</i> (see ISPE GAMP® publications [39]).	
Critical Operating Data /Measurement Uncertainty – common cause variability of controlling each parameter impacting a CQA understood and accommodated. <i>Typically, allowable operating range limits are reduced to achieve a high degree of certainty that the actual parameter value (not just the measured value) is within the allowable range and thus does not have a detrimental impact on a CQA.</i>	
Cleaning Validation – cleaning processes and procedures defined and appropriate validation planned or completed. Analytical methods and recovery methods validated.	
Prior to PV, address parenteral drug product validation special requirements such as sterility assurance testing, including media fills and container closure integrity evaluations.	
For aseptic processes, sterilizing activities including filter sterilization validated	
Critical/key process indicators to be monitored during and/or post validation defined or referenced in the validation protocol	
Transportation of drug substance and drug product (where applicable) determined	