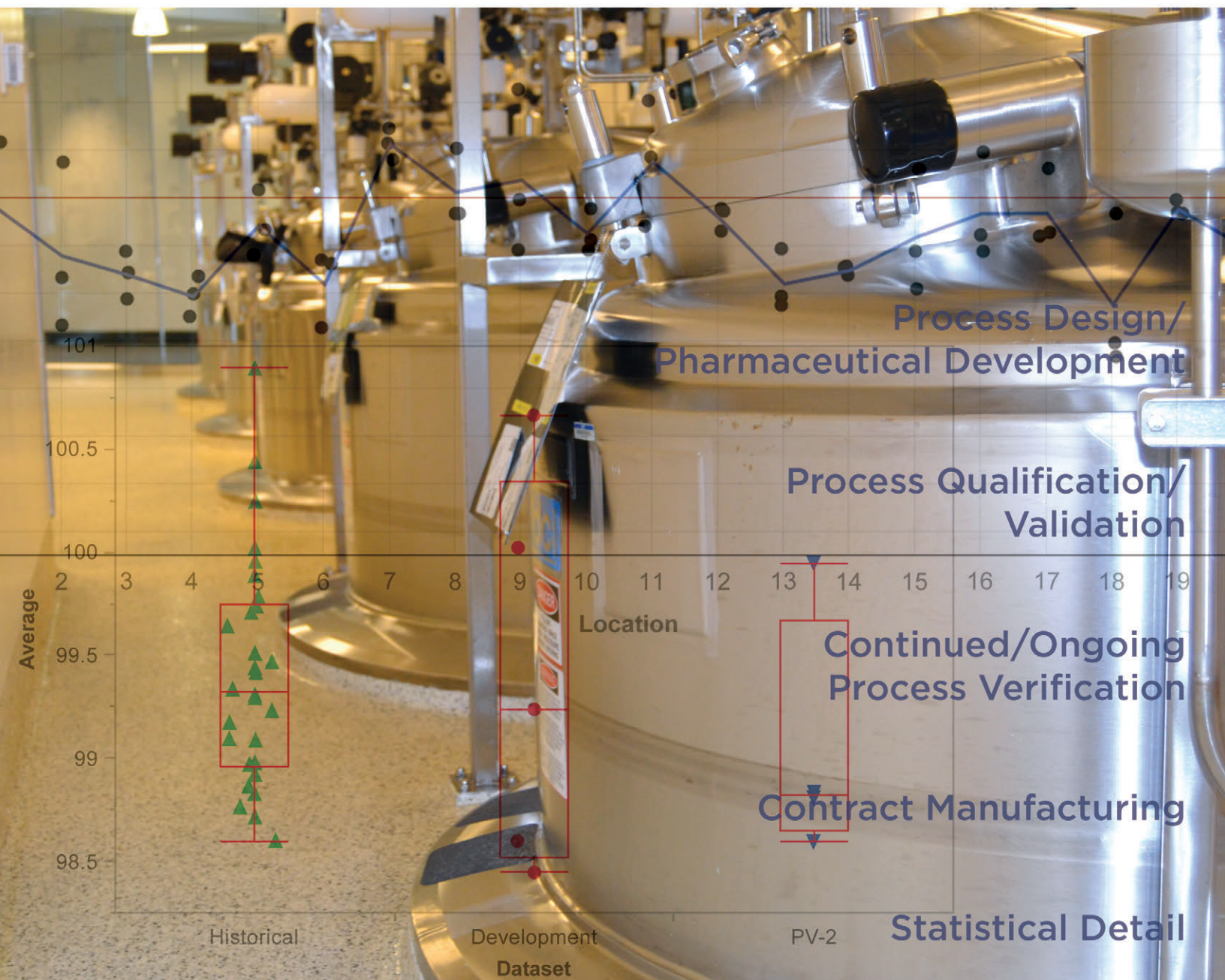


GOOD PRACTICE GUIDE:

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.

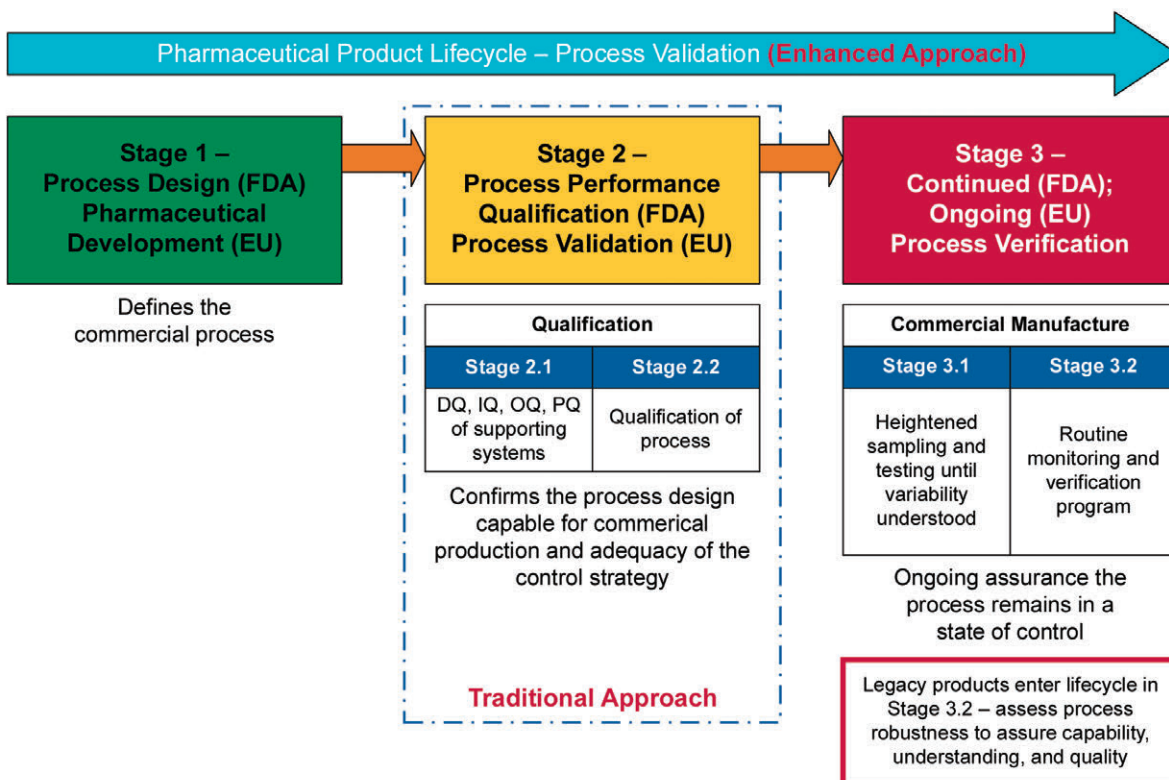
PV demonstrates manufacturing control strategy adequacy and robustness and provides ongoing assurance that the process remains in control. It is defined in the 2011 FDA PV Guidance as [3]:

“...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 in terminology

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

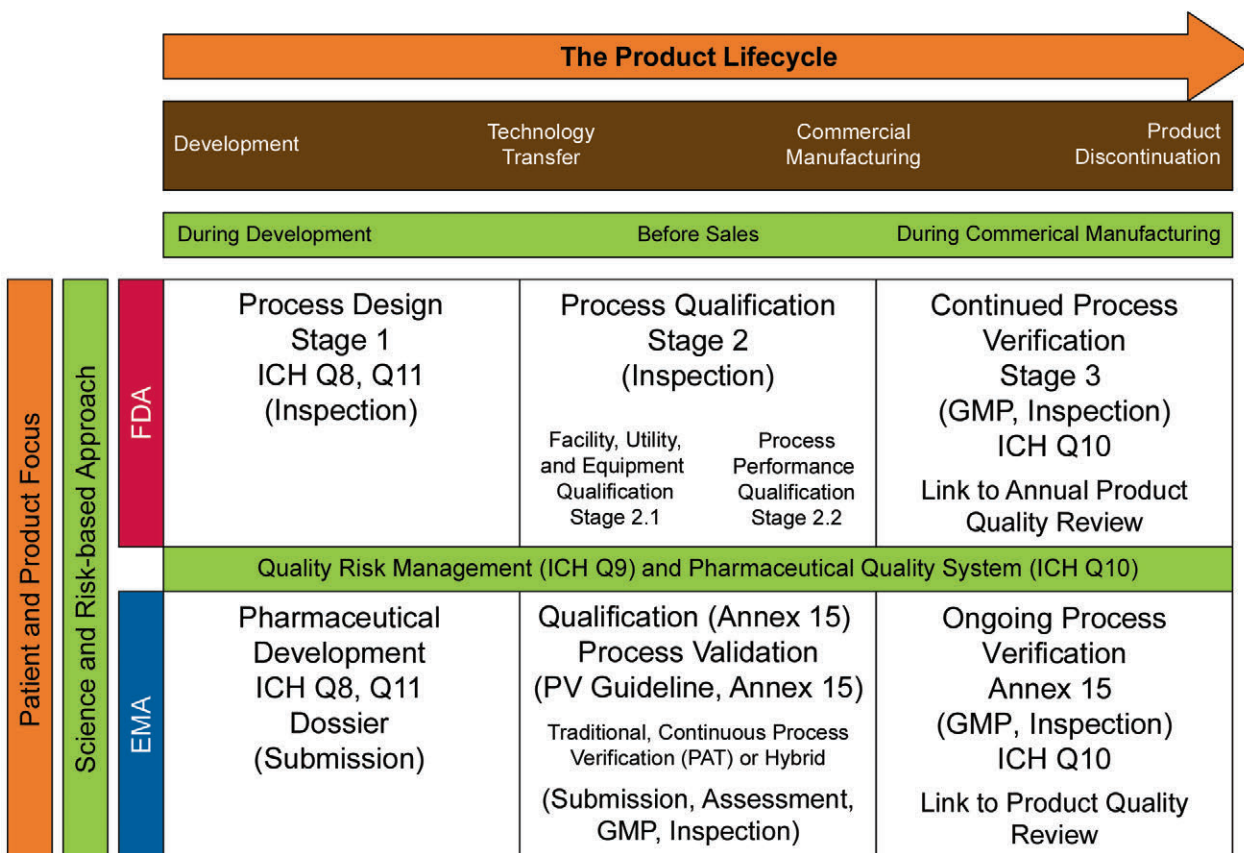


Table 2.2 (later in this chapter) summarizes the similarities/differences between the FDA PV Guidance [3], the EMA Guidelines [12, 13] and Annex 15 [11]. **Note:** the scope of the PIC/S guidance [14] only covers the manufacturing stages of the lifecycle, although a reference exists to EMA regulatory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

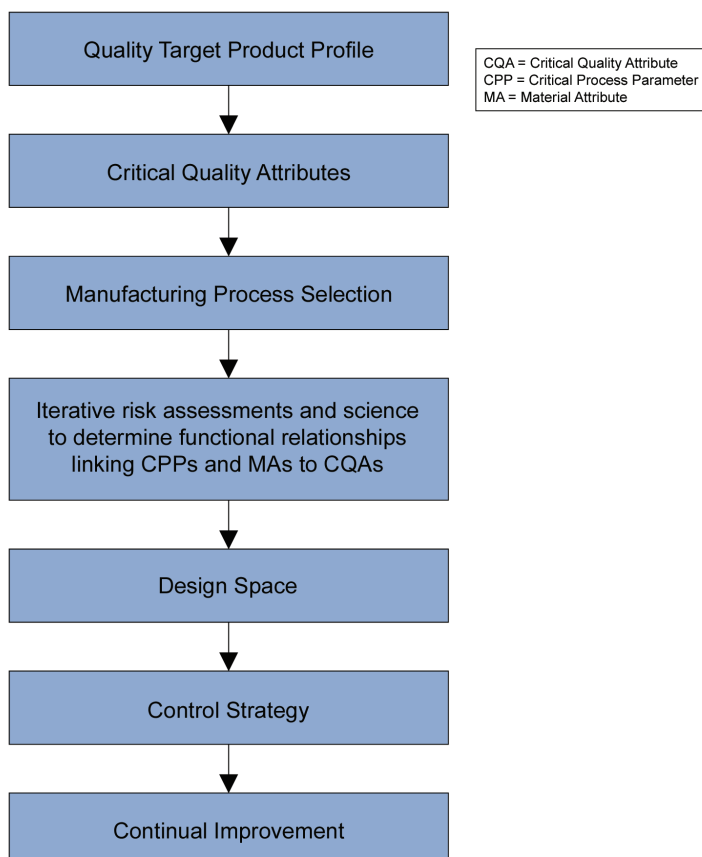
*"Each manufacturer should judge whether it has gained sufficient understanding to provide a **high degree of assurance in its manufacturing process** to justify commercial distribution of the product."*

*"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 or 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

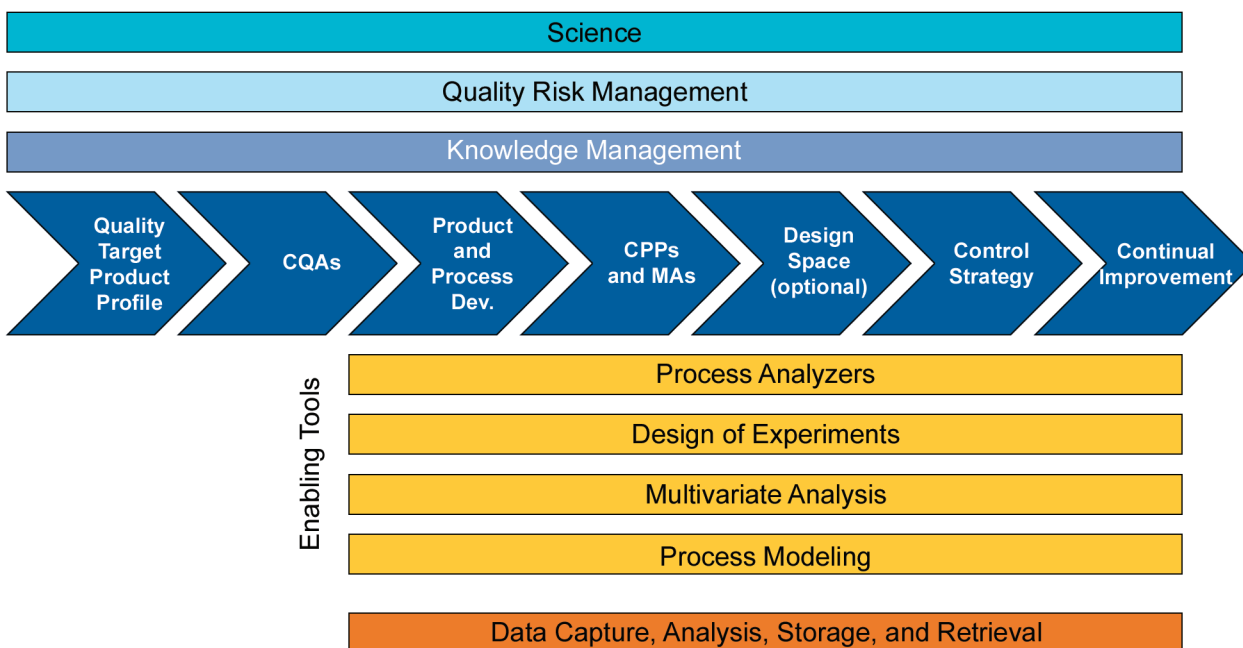
The design space is one of the QbD elements. Table 3.4 lists the terms described in ICH Q8(R2) [1] and outlined in the QbD roadmap, Figure 3.3. More information about QbD, how to identify CQAs, CPPs etc., can be found in the *ISPE PQLI® Guides* [7, 8].

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]:

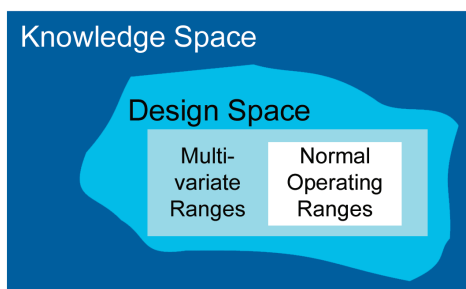
“A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.”

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



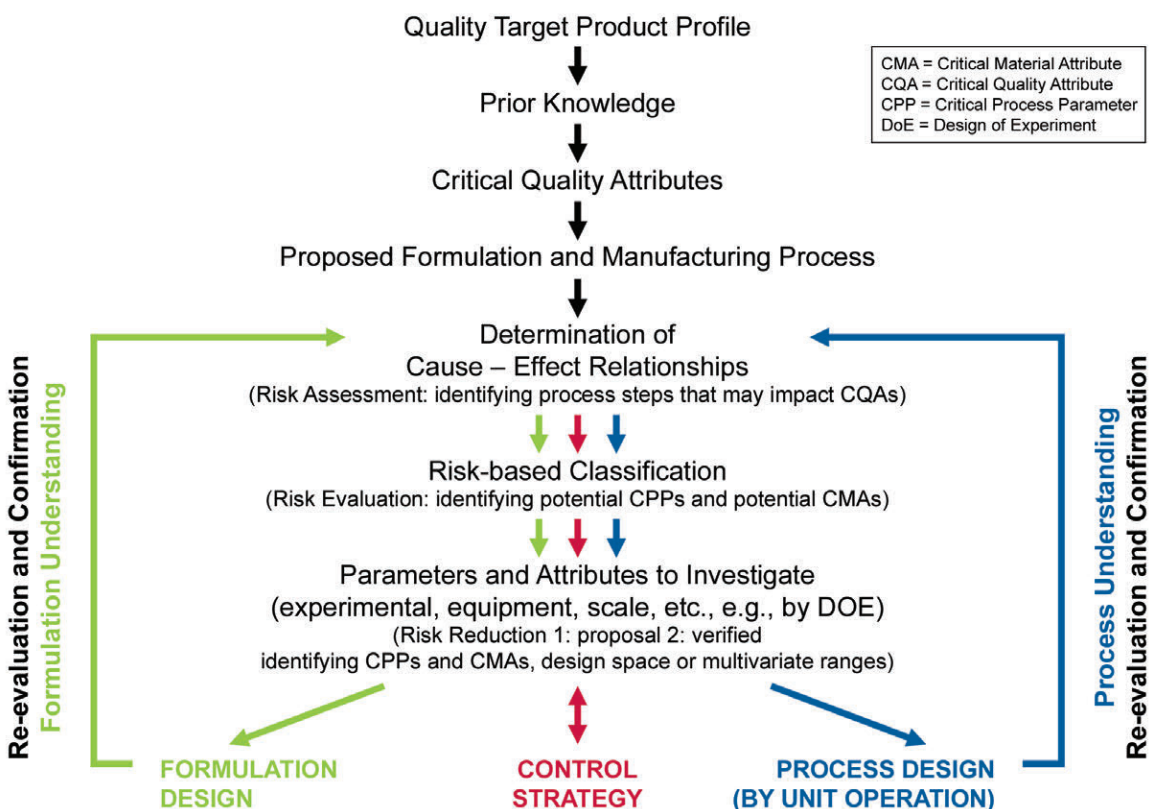
The complexity and robustness of the design space depends on the level of process understanding, the process complexity, the CPPs, CMAs, the number of unit operations covered, and the level of experimental work conducted to establish the design space.

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.

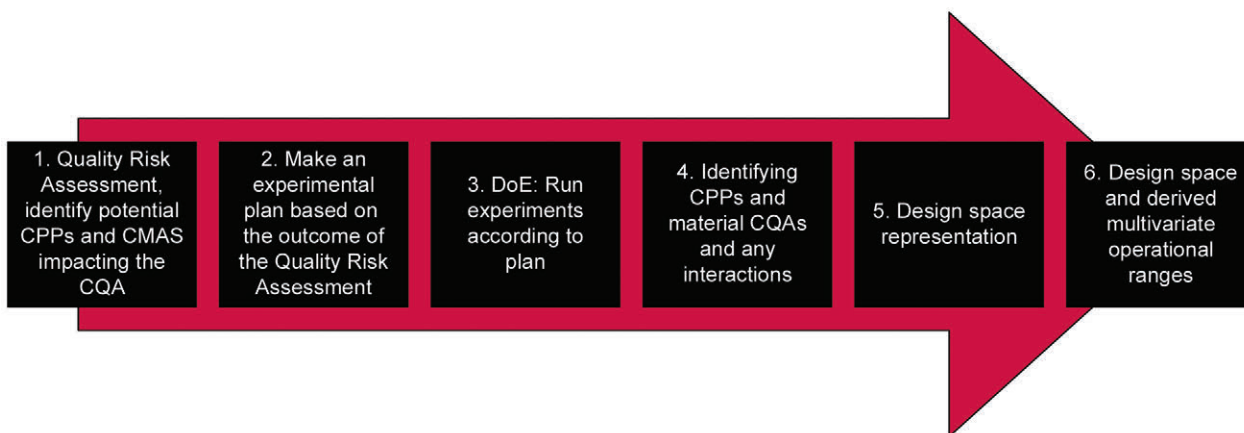
Typically, for the additional work required, a DoE is used. The output from the experimental data is an identification of CPPs and CMAs or intermediate CQAs from the potential critical factors, and any interactions between these and the space where the process can be operated to meet the CQA expectations.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

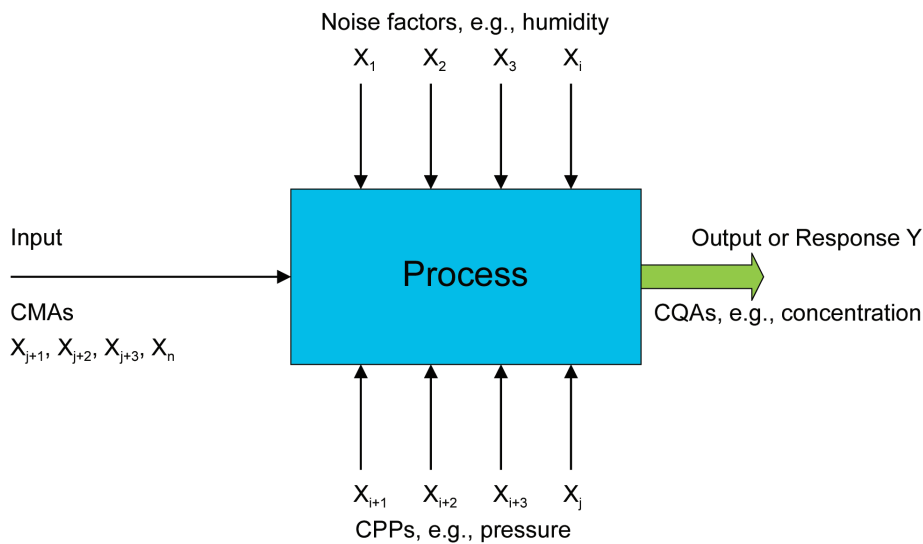
Step 1: Quality Risk Assessment identifying potential CMAs and CPPs (see Figure 3.7)

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)

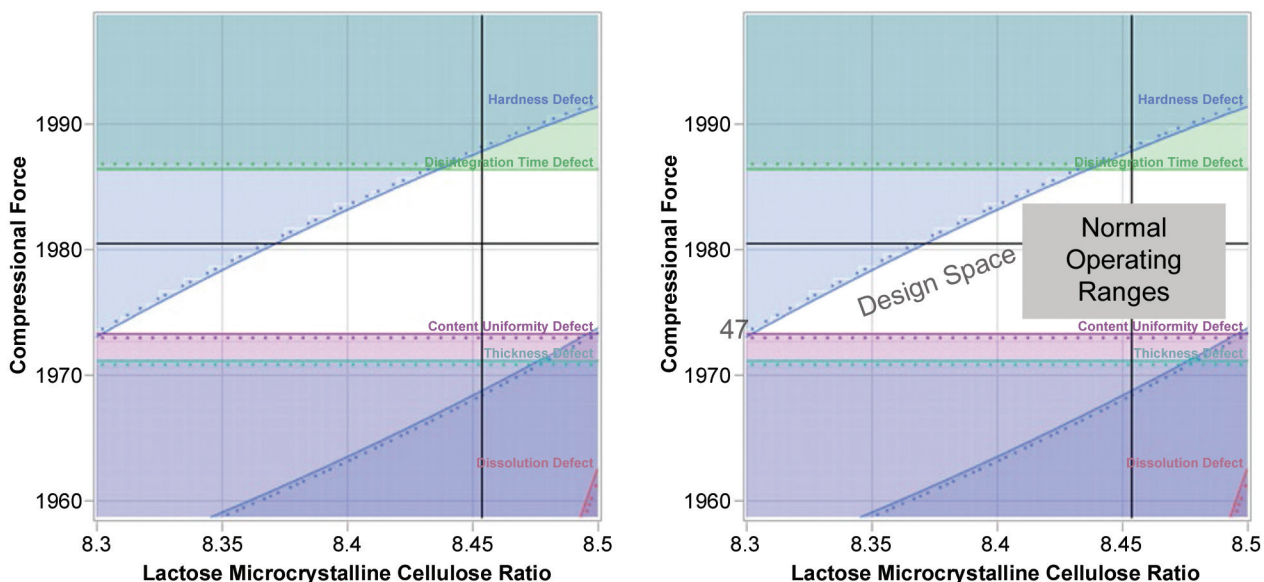
Figure 3.9 Example Design of Experiment Data

	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.

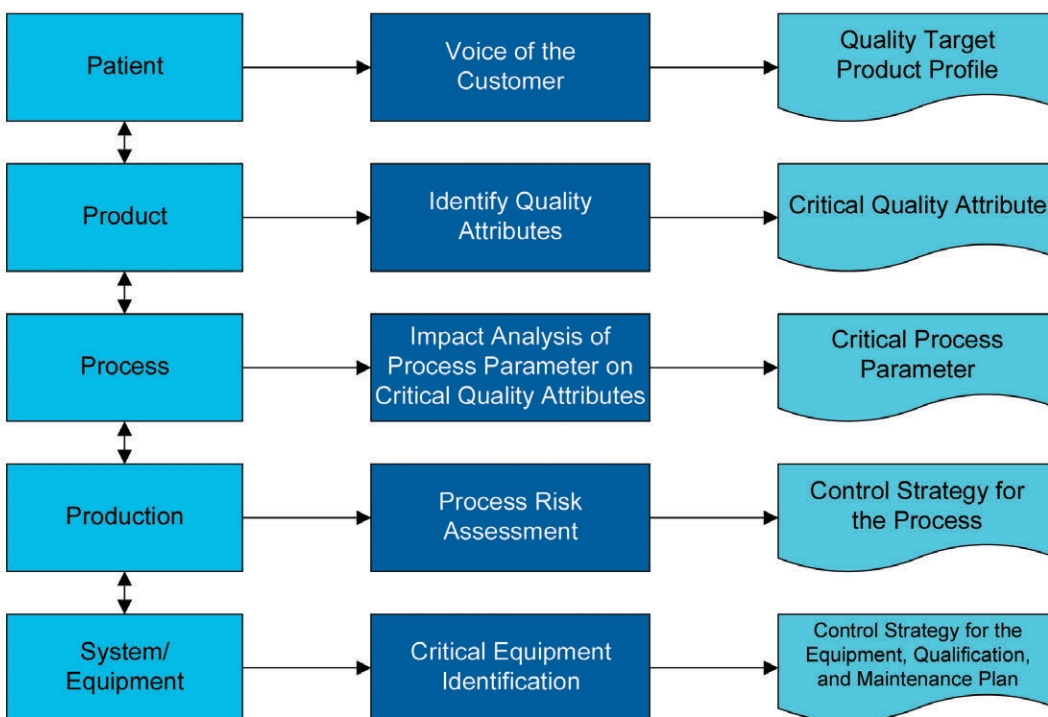
The control strategy aims at ensuring a product with the right CQAs and consistency is being manufactured and therefore in alignment with the expectations as expressed by the QTPP (patient focus). This focus should be applied throughout the product lifecycle from product and process design through to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

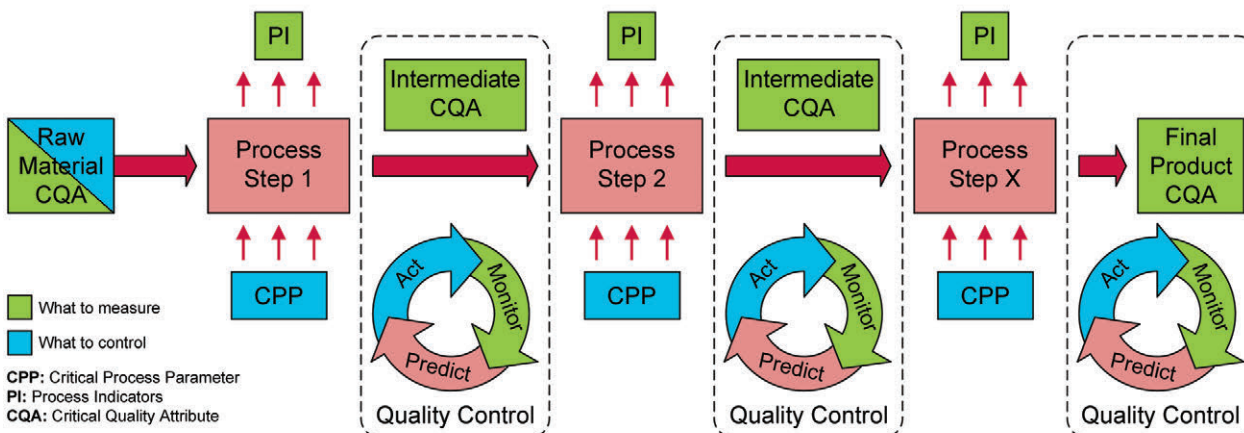
In Figure 3.12, a manufacturing process is illustrated with a set of process steps. During Stage 1, CPPs for each step were identified, showing how the different process steps can be characterized in terms of intermediate CQAs – a quality attribute of an intermediate stage that has a direct impact on 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.

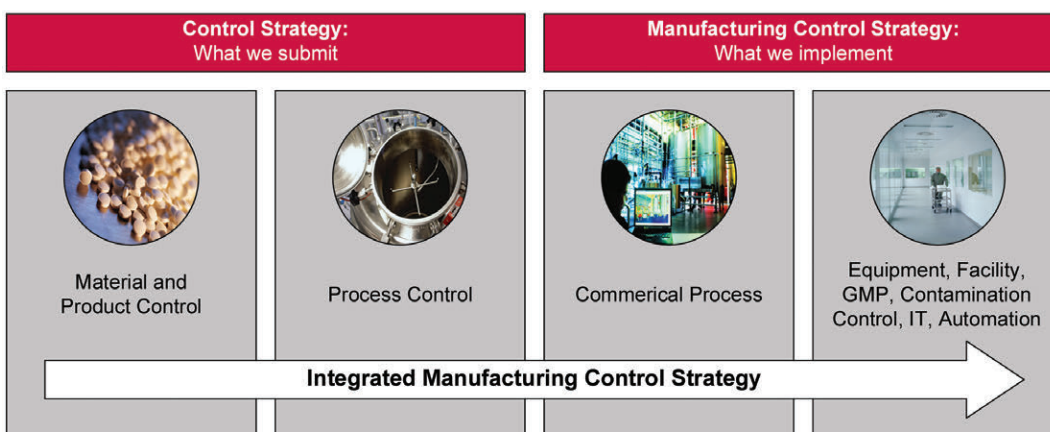
The control strategy should also be expanded to include controls related to the process equipment, utilities, facility, the process control system, cleaning aspects, and supporting quality controls to ensure product quality.

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

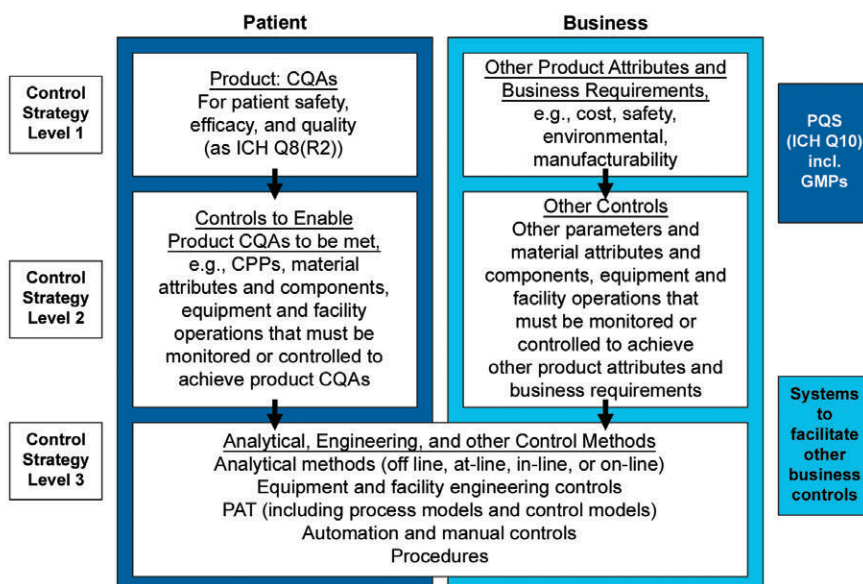
3.4.2.2 Production Control Strategy

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	

4 Design and Qualification of Facility, Utilities, and Equipment (Stage 2.1)

4.1 Overview and Background

Part of the objective of PV is to ensure the fitness of facilities and equipment for intended use, commonly known as Stage 2.1 [3]. (**Note:** see Chapter 2 for a discussion on the different terminology used in PV.) Since extensive guides to the design and qualification of facilities, utilities, and equipment are available from various sources such as ISPE [40] and ASTM E2500 [36], this chapter provides only an overview of these activities.

Manufacturers need to control the CAs of their operations through qualification and validation over the lifecycle of the product and process. CAs, which are identified in the design space (see Figure 3.6), include equipment used in the manufacturing and analysis of the product.

Equipment and systems should be well designed and capable of consistently manufacturing quality products [3, 11]. The approach to the design and qualification of facilities, utilities, and equipment is based on sound science and the manufacturer's overall level of product and process understanding to demonstrate control in achieving a consistent and robust product.

Cumulative data from all relevant studies and assessments are used to establish the manufacturing conditions. *ISPE Baseline® Guide: Commissioning and Qualification* [40] defines approaches for facilities, utilities, and equipment commissioning as well as qualification processes. It is highly recommended to comprehensively understand and apply the approaches outlined in the baseline guide as each project is different. The Baseline® Guide promotes Good Engineering Practices (GEP), commissioning, and qualification practices for related engineering systems [40].

This chapter incorporates science and risk-based quality system approaches and reviews the impact products and processes have on Stage 2.1 activities prior to the initiation of Stage 2.2 PPQ.

The ASTM E2500 *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* [36] includes a new approach to enable more flexibility at this stage. This ASTM guide describes a systematic, efficient, and effective way of ensuring that manufacturing systems and equipment are fit for intended use, and that risks to product quality, and consequently to patient safety, are effectively managed to the extent that the risks are affected by such systems and equipment, including the following key concepts:

- Risk-based approach
- Science-based approach
- CAs of manufacturing systems
- QbD
- GEP
- Subject matter expert
- Use of vendor documentation
- Continuous process improvement

Verification is a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assure systems are fit for use, such as qualification, commissioning and qualification, verification, system validation, or other [36]. The level of effort, formality, and documentation of the QRM process should be commensurate with the level of risk.

4.2 Review of Establishing Equipment Qualification Ranges

This section reviews the elements required for establishing equipment ranges to be qualified. DoE studies conducted at Stage 1 establish the design space for the product, wherein operating parameters are defined as part of the initial control strategy to ensure the desired QTPP is met. The control strategy is verified in Stage 2.2 and continually improved in Stage 3.

Equipment to be used in the manufacturing process needs to be qualified. Qualification should demonstrate that the equipment is designed appropriately, built to suit user and process requirements, and fit for its intended use. *ISPE Baseline® Guide: Commissioning and Qualification* [40] provides advice and guidance relevant for qualification of equipment that is generally accepted industry wide.

Section 3.4 of this PV Guide describes how to define CPPs related to CQAs. Typically, this is done by identifying the range in which equipment and facilities need to be qualified to ensure they are capable of consistently producing specified product or results. See the example in Table 4.1.

Table 4.1: Example of Related Critical Quality Attributes, Critical Process Parameters, Equipment, and Qualification Ranges

Critical Quality Attributes	Critical Process Parameters	Equipment	Qualification Range
Content Uniformity (CU)	Blend uniformity Unit dose	Blender Tablet press HPLC – testing	Agitator speed ± 3 rpm Weight ± 5 mg Injection precision $< 2\%$
Viscosity	Rate of addition	Dosing pump	5 L/min $\pm 3\%$
Purity	Cleanliness of product contact equipment	Washer	Residual cleaning agent < 20 ppm/L

4.3 Impact of Product and Process on Facilities, Utilities, and Systems

The introduction of a new product and/or process has an impact on existing or newly commissioned facilities, utilities, and systems. Multiple factors should be considered for a new product launch or site transfers to a new or existing facility. This section describes industry best practices and factors to consider when introducing a new product, process, or both that impact facilities, utilities, and other systems.

The direct impact system is designed and commissioned in line with GEPs as well as qualification practices. In relation to facilities, utilities, and equipment, the following factors should be considered:

- GMP design and installation with operational, maintenance, statutory, and regulatory requirements, as well as other elements such as health, safety, and environmental conditions
- Documentation of design, drawings, tests, manuals, inspections, and certifications
- Construction management, standard procurement practices, installation, and commissioning

It is good practice to include a design verification document covering all of the facilities, equipment, and utilities to verify that each of the relevant systems has been reviewed to demonstrate their capability to meet the process requirements outlined during the design phase.

Technology Transfer Considerations

Process design stages and a technical transfer project should consider the risks associated with the transfer of product/process from Research and Development to commercial manufacturing, or in the transfer of product/process between sites.

The *ISPE Good Practice Guide: Technology Transfer* [41] provides a standardized process and recommends a minimum base of documentation in support of transfers. A gap analysis comparing the product control strategy and technical risk assessment with the facility, utility, system, and equipment should be performed to identify the requirements associated with adapting existing equipment or the need for acquiring new equipment. Assessment considerations are summarized in Table 4.2.

Table 4.2: Considerations for a Gap Assessment When Performing a Technology Transfer Using Existing Equipment

Task	Components
Process Transfer: Manufacturing and Packaging	• Development history and report • Process description • Process flow chart • Rationale for specifications • Change control assessment • Critical process parameters • Master batch manufacturing and packaging record
Facility Assessment	• Plans and layouts of facility • Building (construction, finish) • Qualification status (DQ, IQ, OQ)
Equipment/Utilities Selection and Transfer	• List of all equipment and associated utilities, systems • Make and model • Qualification status (DQ, IQ, OQ, PQ) • Drawings and manuals • SOPs (setup, operation, cleaning, maintenance, calibration, storage)
Key: DQ = Design Qualification OQ = Operational Qualification IQ = Installation Qualification PQ = Process Qualification	

The building facility and location of all equipment should be considered when the process maps/process flow charts are developed, as well as the flow of personnel and material. The impact of manufacturing the new products on the same equipment as existing products should be determined.

5 Initial Process Qualification Activities (Stage 2.2)

The goal of PPQ is to demonstrate that the activities in Stage 1 have yielded a process/product design and control strategy that will deliver a commercial manufacturing process that will consistently perform as expected. (**Note:** this Guide uses Stage 2.2 and PPQ for this verification portion of PV. See Chapter 2 for a discussion on the different terminology used in PV.)

For a successful PPQ, good planning is key and essential for activities such as:

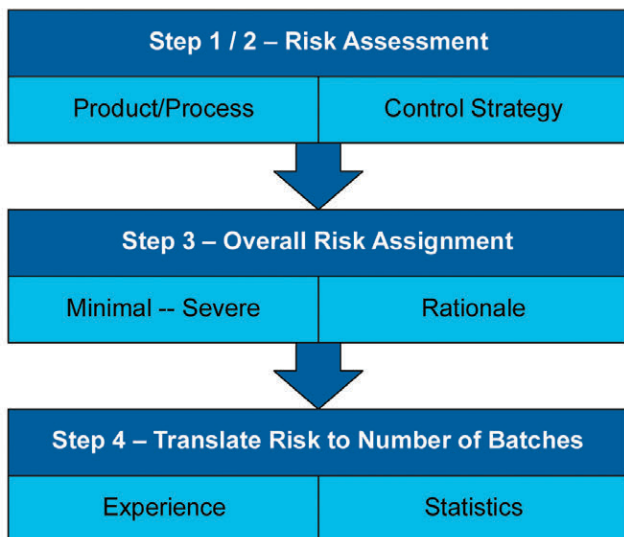
- Determining the number of PPQ batches
- Producing a well written protocol providing instructions for execution
- Establishing the representative number of samples to assess process performance and to determine variability
- Developing clear specification of acceptance criteria and expectations for successful PV
- Evaluating data and test results obtained from PPQ
- Generating a concise summary of test results, observations from PPQ batches, and a closure statement concluding acceptance of the validation activity

This chapter provides guidance for PPQ planning, discussing strategies for determining the number of PPQ batches, developing the sampling plan and acceptance criteria (with some examples), and evaluating and interpreting the data generated from PPQ batches.

5.1 Determine an Appropriate Number of Initial Process Validation Batches and Inter-Batch Variability Assessment

Traditionally, PV acceptance criteria were based on the number of batches produced during validation. Under a science and risk-based paradigm, the focus also includes determining the degree of control exhibited over the process (inter-batch variability).

Determining the number of batches necessary to demonstrate that acceptable control over the process has been achieved begins with assessing residual risk based on product knowledge, process understanding, and control strategy effectiveness (see Figure 5.1). Turning this risk knowledge into the justification for the number of validation batches to manufacture can be based on experience, statistics, or a combination of both.

Figure 5.1: Process Risk Assessment Translating into the Number of Batches

The number of PPQ batches depends on the residual risk remaining following Stage 1 and the expected inter-batch variability, with an understanding of the sources that influence product quality. Manufacturers should justify the number of validation batches and the design of the PPQ study based on this product knowledge and process understanding (see Table 5.1).

Table 5.1: Example Elements of Process Risk Assessment, Prior to Process Validation Stage 2.2

Category	Elements
Product Knowledge	CQA variation on patient
	Product characterization
Process Understanding	Degree of understanding including interactions
	Predictability and modeling
	Variability understanding
	Effects of scale
Control Strategy Effectiveness	Raw material impact
	Equipment capability versus process requirements
	Process performance to date
	Monitoring/detectability
	Level of uncertainty

Risk Assessment Following Stage 1

The risk assessment should consider the knowledge gained through Stage 1 activities and the similarity of the Stage 1 manufacturing process to the process undergoing PPQ.

For example, when process knowledge is high – including an understanding of process robustness to the input variability from raw materials, excipients, and drug substance – then the residual risk is low and a minimally-sized PPQ could be appropriate, for example, three batches.

When the risk assessment identifies some potential knowledge gaps (e.g., only one excipient batch was used in Stage 1), then there is a higher residual risk and it is appropriate to include a larger number of PPQ batches to address that gap. For example, when multiple excipient batches are included in the PPQ, more PPQ batches may be needed.

The risk assessment following Stage 1 should be a structured evaluation of the knowledge and evidence that the manufacturing process is capable and robust, and that the control strategy ensures acceptable product variability.

An example, based on the inter-related considerations of product knowledge, process understanding, and process control strategy, comes from ASTM E2475 [42] and is detailed in Sections 5.1.1 – 5.1.3.

Manufacturers may choose other factors to include in their risk assessment, place maximum emphasis on the control strategy, or both.

The assessment should:

- Consider all product CQAs, either in combination or individually. If considered individually, the assessment should include the CQAs with the highest associated residual risk and highest associated severity levels. The number of PPQ batches should be commensurate with the highest residual risk.
- Be performed by a cross-functional team with representation from manufacturing, technical services, process development, quality assurance, statistics, and PV.
- Be aligned with QRM principles and provide justification for the evaluation and ranking of each factor.

5.1.1 Assess Product Knowledge [42]

Identified product quality requirements as outlined in ICH Q8(R2) [1] are referred to as the QTPP, which can be further related to the CQAs of the drug product or drug substance.

At a minimum, the severity and probability of variation that might impact product safety or efficacy should be documented in the risk assessment. The confidence in CQA acceptance ranges depends on the strength of experimental data (laboratory, clinical, non-clinical), predictions/information from proven models, and other sources of knowledge.

Even in circumstances where the drug's mechanism of action is not well understood, efforts made to understand CQAs may help to mitigate the risk to safety or efficacy.

5.1.2 Assess Process Understanding [42]

Understanding the relationships between material attributes, process parameters, and CQAs is the fundamental tenet of assurance of product quality. The design and effectiveness of the control strategy depends on the correctness of these relationships.

Process understanding can be established from several sources, including:

- *Development phase* – an understanding of variability from development and product characterization, primarily from Stage 1 of the product lifecycle, including impact of material CQA variability and input and parameter interaction. This depends on sufficient analytical capability to evaluate the consequences of variability.

Process understanding from the development phase may be lacking for legacy products or for generic manufacturers, thus requiring process understanding from other sources. However, in the case of legacy products, production data can be evaluated in place of Stage 1 data.

- *Prior knowledge* – understanding from prior experience with similar processes or platform technology. For a mature product, APRs, product quality reviews, deviation investigations, complaint investigations, and change control information may be used as sources of process understanding.
- *Degree of process understanding/unit operation* – the extent of knowledge gained/explored during the development of each unit operation, including the potential impact from personnel, selection and performance of equipment, and other factors such as environmental considerations.
- *Process predictability and modeling* – understanding the effect of scale on performance, and the usefulness of a laboratory or small-scale model to predict the effects of variation at commercial scale.

5.1.3 Assess Control Strategy Risk [42]

The process control strategy evolves through the development of process and product knowledge in Stage 1. It is designed to control input variability from materials, environment, and operational practice so that the desired product quality and performance is maintained or improved.

Factors that could be considered in the risk assessment of the control strategy include:

- **Raw material variability:** The potential impact and management of variability of CMAs and interaction with other input or control variables
- **Equipment capability versus process requirements:** Manufacturing facilities and process equipment are qualified for the commercial process. These activities may include batches produced at full scale, or at a scale that is considered representative of full scale. Equipment capability derived from these qualifications can be compared with process requirements as one contributor to risk determinations.
- **Experiences with process performance:** Successful performance of development or historical batches resulting from adequate management of process variability and control for scale effects (as applicable) provides evidence of process reproducibility.

5.1.4 Determine Residual Risk Level

Following the risk assessment of the factors of product, process, and control strategy understanding, a residual risk level should be determined. This residual risk level reflects the confidence in performance of the commercial process and can be used as an input to the decision for determining the appropriate number of PPQ batches.

When high residual risk is not minimized or mitigated, it is reasonable to expect that more batches will be required to confirm that the process is capable of reproducible commercial manufacture; however, increasing the number of PPQ batches is not a substitute for insufficient process development or understanding. Reasonable efforts should be made to identify and mitigate higher risks before attempting process qualification.

Application of a QbD approach to development of the process, product, and control strategy should result in lower residual risk by improving process understanding, and therefore minimize the number of required PPQ batches.

Identification of a severe or high residual risk indicates there are significant gaps in process knowledge, control strategy, or both. Additional effort should be invested in improving process knowledge and the control strategy before preparing PPQ batches.

Further explanation of the ASTM E2475-based risk assessment and scoring system [42] is located in Appendix 5 (Section 13.1), along with an example application to the *ISPE PQL[®] Guide Series Part 2 – Illustrative Example, Product and Process* [8] (Appendix 5 (Section 13.2)).

5.1.5 Determine the Minimum Number of Batches (N)

It is recognized that a complete assessment of inter-batch variability and process robustness cannot be known until Stage 3 of the PV lifecycle due to limited exposure to inter-batch sources of variability, small numbers of Stage 1 and PPQ batches, and other factors. However, some remaining uncertainty regarding process variation after Stage 2 does not prevent progression to commercial manufacture (Stage 3), assuming there is evidence that this variation does not pose patient risk. (See Table 5.1: Example Elements of Process Risk Assessment, Prior to Process Validation Stage 2.2.)

The number of PPQ batches¹ (M) may be different from the number of batches (N, $N \geq M$) used in the PPQ report to evaluate inter-batch variability.²

The minimum number of batches (N) should be aligned with the residual risk (discussed earlier in this section) remaining from Stage 1. A process that has higher residual risk should require more batches to provide enough assurance that the inter-batch variability is adequately controlled before progression to routine commercial manufacture. On the other hand, a process that has low residual risk should require fewer batches.

Batches manufactured in Stage 1 can count toward the minimum number of batches (N) required to determine inter-batch variability. Use of Stage 1 batch data in the PPQ report is discussed in Section 3.3. Per FDA PV Guidance of 2011 [3], it is an expectation that Stage 1 data be considered together with PPQ data in making a validation conclusion.

The justification for the minimum number of batches (N) should be documented and approved prior to execution of the PPQ protocol. These justifications fall into two general categories: experience based and statistically based. A combination of the two approaches is also possible.

Many different approaches have been proposed in the literature, including two ISPE discussion papers published in 2012 (updated in 2014) [34] and 2016 [43]. Although no approach is currently considered best practice across the industry, a number of manufacturers apply a risk-based approach that relies on scientific rationales and experience to determine the number of batches.

In all cases, PPQ performance should be evaluated, along with relevant Stage 1 results, for sufficient evidence of acceptable inter-batch and intra-batch variability, along with any potential impact to quality. This evaluation continues in Stage 3.

Assurance of robustness to expected sources of variability such as raw material, equipment train, operator, and environmental conditions can influence the number of PPQ batches. Bracketing, matrixing, or a product family approach can be applied to specific situations such as multiple dosage strengths, package sizes, batch sizes, or division of drug substance batches into multiple drug product batches.

No matter the approach, the objective of PPQ is to establish scientific evidence that the process is reproducible and will consistently deliver quality products. The observed inter and intra-batch variation should be as expected based on prior performance and scientific rationale. These claims should include all relevant evidence of process understanding, control, and performance from both Stage 1 and PPQ.

¹ This is the number of batches manufactured as part of the PPQ protocol (M).

² These are the combined Stage 1 and Stage 2.2 batches as discussed in Section 3.4 (N).

5.2 Determine Science and Statistically-Based Process Validation Acceptance Criteria and Sampling Plans

The development of suitable sampling plans and associated acceptance criteria are essential to achieving the objectives of Stage 2.2. These activities are best addressed by incorporating the scientific knowledge of the product and process with statistical sampling methodology. It is important that science and statistics are leveraged so that the plans are rigorous and practical.

5.2.1 Sampling

“There is a wide body of literature on sampling. Sampling plans are used to generate the required samples that will be tested to support release of manufactured batches, PV, or for process understanding.”

“A sampling plan describes where (locations) and how the samples are taken from the batch, and the number of samples taken from each location. The sampling plan should ensure that the data collected is representative of the parameter to be measured and that the sample size is sufficient to support the conclusions needed for process qualification.” [44]

The choice of acceptance criteria is part of generating a sampling plan. The sampling plan should be justified; Operating Characteristic (OC) curves are useful for this purpose. There are three common sampling strategies:

1. Simple Random Sampling

“Simple random sampling gives each possible unit an equal probability of being chosen to be tested. A true random sample from a batch could theoretically be obtained by identifying each unit in the batch and then by a completely random process, pick ‘n’ units. To obtain a true simple random sample is nearly impossible or impractical for sampling a batch of units.” [44]

An example that is generally considered a simple random sample is taking a sample from a coating pan, since the tablets have been continuously mixed up during the coating process. A sample of units, for example 30 tablets, from the coating pan is considered a random sample.

2. Stratified Random Sampling

It is possible with simple random sampling that, just by chance, the samples may not contain units from segments of the batch that are of interest. *“For example, in process validation, the beginning and end of the batch may be of interest. So, although a simple random sample is statistically valid, one may not be satisfied with a sampling plan that does not include samples taken from the beginning or end of the batch.” [44]*

A stratified sampling strategy partitions the batch into “strata,” or groups, where differences may exist between the strata. The combination of all strata must cover the entire batch. Then random sampling is performed within each stratum.

For example, the lot may consist of 500,000 dosage units during a batch process. The strata could be defined as 20 sets of 25,000 dosage units where strata 1 is the first 25,000 dosage units in the run, strata 2 is the second 25,000 dosage units, etc. In this case, each stratum represents a part of the batch (a drum in tablet production; a tray/tub in vial/syringe fill-finish process) producing 25,000 dosage units. Then a random sample from each part of the batch, such as 2, would be taken to obtain a total of 50 dosage units for testing.

3. Systematic Sampling

“A systematic sampling strategy is performed by taking a sample(s) at equal intervals throughout the batch, typically based on the total number of units or manufacturing time. The first sample location is determined at random and then the remaining samples are taken at equal intervals.” [44]

For example, using manufacturing time, assume the manufacturing run takes 15 hours and the desired sample size is 30 dosage units. The time can be divided into 30 half-hour intervals. A time is selected in the first interval at random – 10 minutes; then samples would be taken at 10 minutes, 40 minutes, 1 hour 10 minutes, etc.

In practice, the first and last samples may be taken from the beginning and end of the batch. Then the remaining 18 samples could be done using a random time in the second interval. This is typically acceptable as long as the starting point and subsequent sampling points do not fix the samples in such a way as to potentially miss important elements of the process.

The difference between stratified and systematic sampling strategies is that stratified samples are taken at random within each stratum whereas systematic samples are taken at specified equal intervals usually based on time or total number of units in the batch.

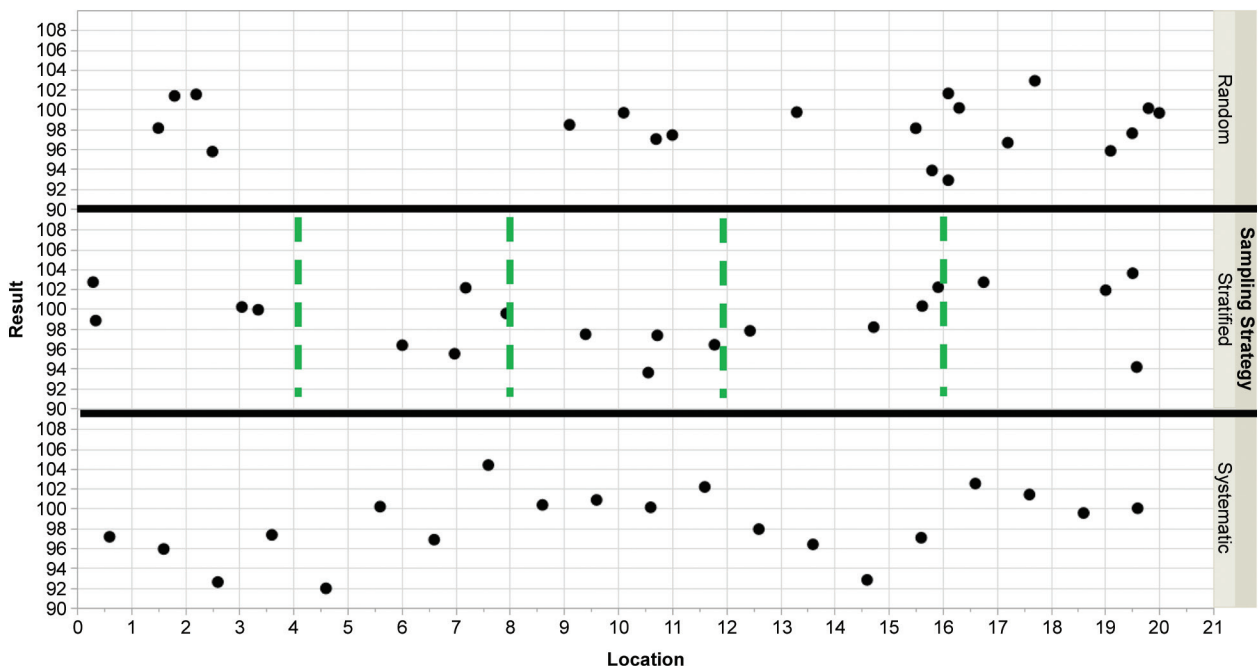
In practice, the systematic samples may not be taken exactly at the specified points but effort is taken to be as close to these points as possible, which is generally acceptable.

It also may be desirable to include the beginning and end of the batch as sampling time points. In this case, for example, if a total of 20 sampling points were desired throughout the batch, the beginning and end could be included, and then the other 18 samples could be taken using a stratified or systematic sampling plan.

The three sampling strategies described above provide ways to select locations for sampling. Typically for simple random samples, only one unit is tested from each location. For stratified or systematic sampling plans, one unit (or blend sample) or multiple units could be tested from each location.

In this document, if only one unit is tested from each location then the sampling plan is called Sampling Plan 1. Figure 5.2 plots 20 results for each sampling strategy using Sampling Plan 1. Notice that the random sampling plan produced a long gap in the batch.

Figure 5.2: Comparison of Sampling Strategies



Combinations of different strategies could be used if justified.

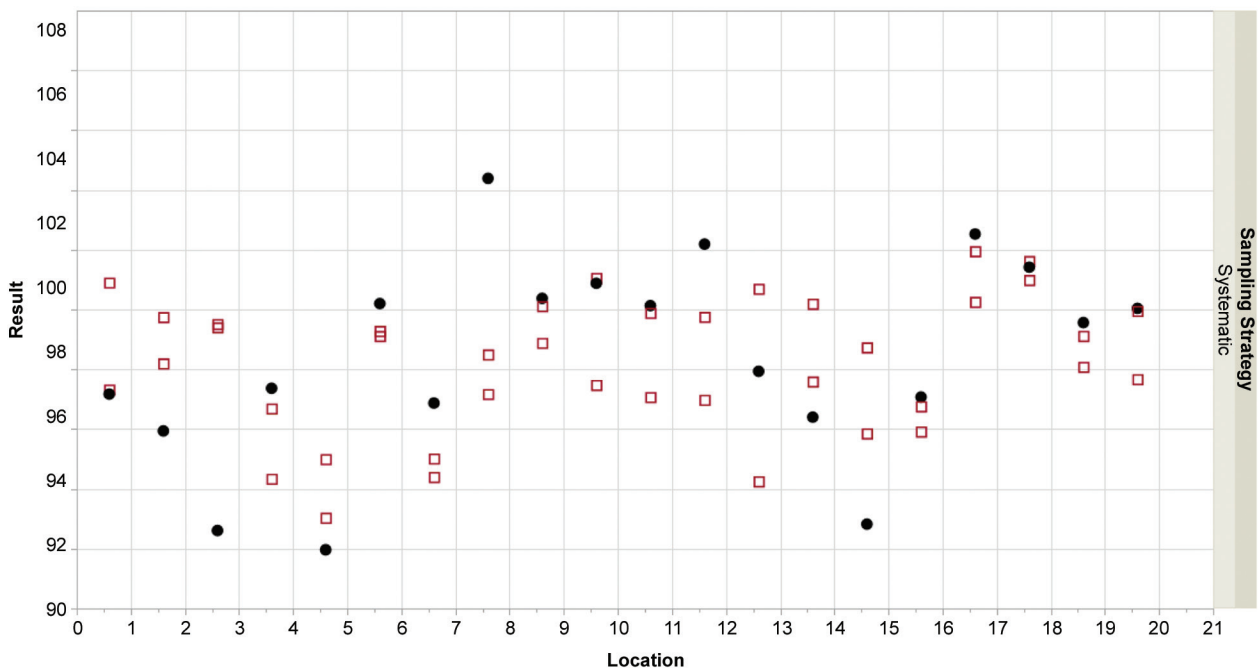
Sampling may be performed following specific events (e.g., breakdown, machine alterations) where standard adjustments were applied to ensure the process remains centered. These additional sampling locations should be evaluated during development or prior to validation, since the acceptance criteria assume that locations in the batch are not purposely selected. A company could perform additional sampling at selected locations to provide supplementary information for inclusion in the validation document; but this data may require different acceptance criteria than those that have been developed for the three sampling plans described above due to non-random sampling.

In process development and during PPQ, it is often of interest to understand the sources of variability in a process. In particular, it is of value to understand the size and relative comparisons of the within location and between location variability.

Using Sampling Plan 1, one cannot determine whether the variation among units is caused more by differences between locations in the batch or by variation within a location. However, by testing more than one unit from each location, called Sampling Plan 2, the variation between locations can be separated from the variation within location using a statistical procedure called Variance Components Analysis (VCA).

Figure 5.3 is a plot of the same systematic plan data as in Figure 5.2, but with two additional samples taken from each location. There appears to be a lot of variation within locations.

Figure 5.3: Systematic Sampling Strategy with Three Results per Location



An example of using a VCA for a sampling plan with 20 locations with 3 results per location is given for CU in Section 5.3.

5.2.2 Goal for Process Performance Qualification Sampling Plans

In order to design appropriate sample plans and criteria, it is essential first to determine how to define successful PPQ performance for each parameter. A parameter could be continuous or discrete data. The key is to develop a plan that provides confidence that the manufacturing process will consistently produce product that meets all specifications.

Criticality and risk should also be considered when developing sampling plans and criteria. It is reasonable to have greater scrutiny on parameters that have the greatest risk in terms of consistently meeting quality requirements.

It is also of significant importance to consider the risk to the patient. Drug products with greater severity, potential for harm, or both when exhibiting too much variability or being off target may require a higher level of sampling and/or more stringent criteria.

One possible goal for a PPQ sampling plan is to provide confidence that the parameter of interest will have a high probability of passing the release requirements during ongoing supply. Each manufacturer will need to define and justify the level of confidence needed in the probability of passing the release requirements. These levels may vary based on the risk associated with the attribute.

When using statistical approaches for defining sampling plans and criteria, OC curves for the proposed PPQ plan and the release test can be used to assess a PPQ plan's performance and its performance relative to the release test.

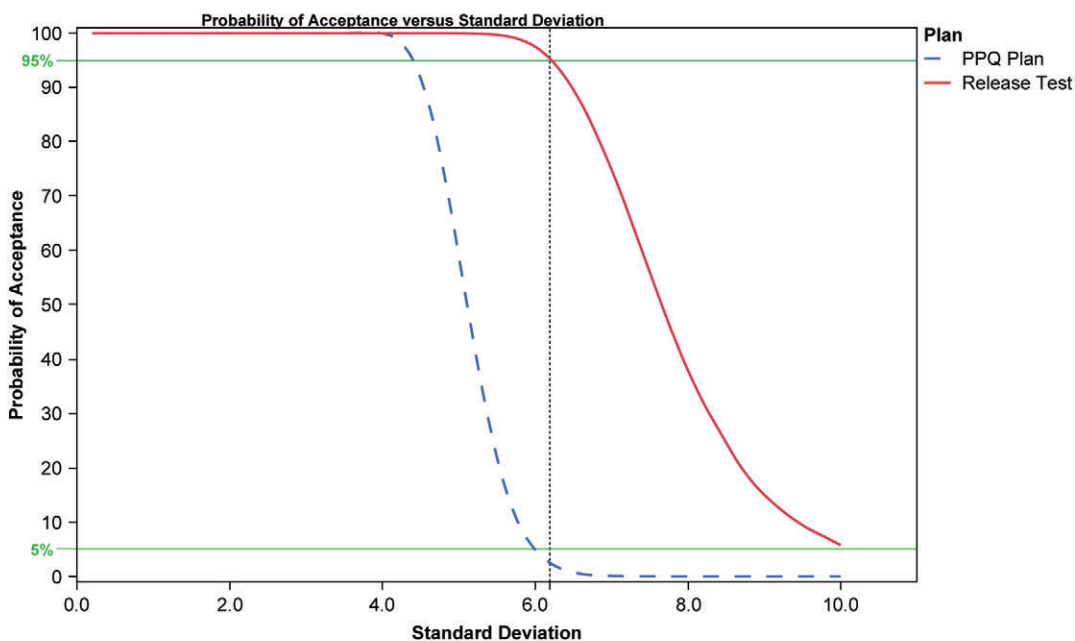
Figure 5.4 is an example of a PPQ and release test OC curve comparison. In this example, the probability of passing the release test is shown as a function of the variation in the sample.

As the data has more variation within the batch (i.e., larger within batch standard deviations), the release test is less likely to be passed. This is why the standard deviation of the data is placed on the x-axis. The y-axis is the probability to pass the sampling plan.

In this example, the relationship between the PPQ test and the release test OC curves have been set such that when the release test has a 95% chance of passing, the PPQ test has less than a 5% chance of passing. The PPQ test has been made stricter (harder to pass) than the release test to provide assurance that the PPQ study will not be successful when the process produces product that would have less than a 95% chance of passing its expected quality requirements.

Sampling plans and acceptance criteria are typically made stricter by increasing the sample size and/or adjusting the acceptance criteria. Examples provided in Section 5.3 illustrate this concept.

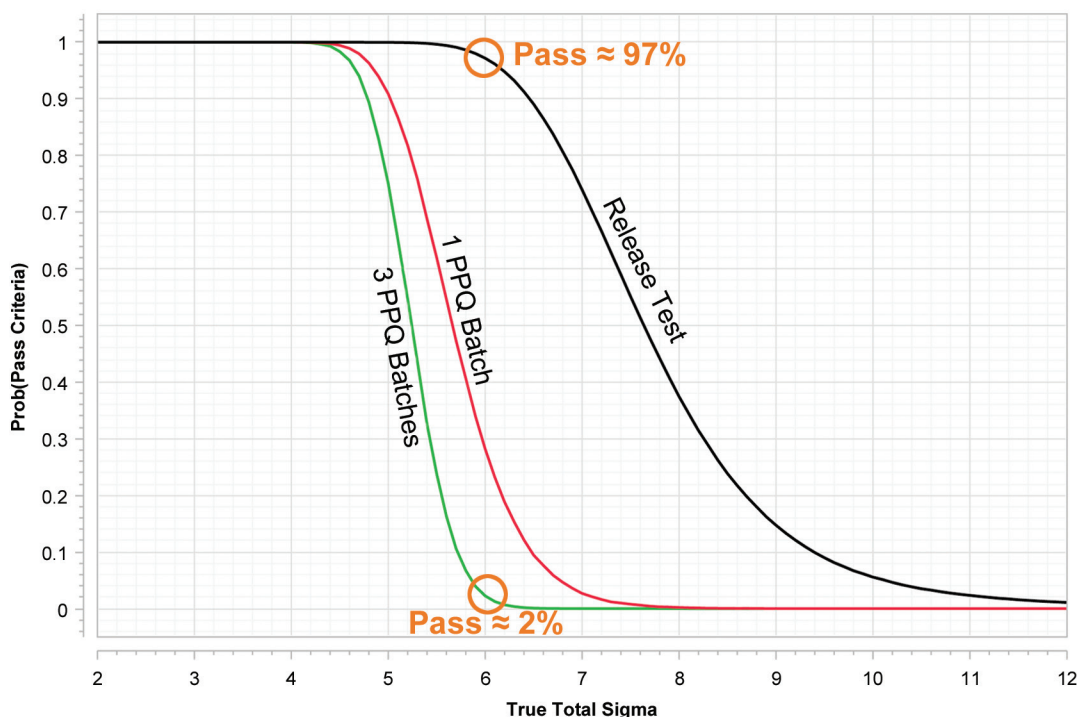
Figure 5.4: Process Performance Qualification and Release Test Operating Characteristic Curve Comparison



The PPQ OC curve shown in Figure 5.4 is for a single batch. In addition to demonstrating appropriate levels of confidence/conservativeness on a batch basis, a manufacturer may leverage the information across the batches used in the PPQ for a target overall level of conservativeness demonstrated by the PPQ exercise.

Figure 5.5 demonstrates this by showing a specified level of assurance for individual batches compared to the release test OC curve. Additionally, it shows, in the case of a three-batch PPQ, the OC curve for all three PPQ batches combined, that is, the OC curve shows the probability that all three batches pass the PPQ acceptance criteria (assuming the three batches are independent).

Figure 5.5: Operating Characteristic Curve of the Probability of Passing a Three-Batch Process Performance Qualification Compared to Operating Characteristic Curves for Passing Individual Process Performance Qualification Batches and the Release Test



In Figure 5.5, the OC curve for a single PPQ batch is significantly more conservative than for the release test (though not as conservative as in Figure 5.4). Additionally, when the three-batch PPQ is considered jointly as an overall criterion where each batch must independently pass the one-batch PPQ criteria, the OC curve for the overall three-batch PPQ is much more conservative.

In this case, when there is a true within batch variability of 6% of Label Claim (LC), the probability of passing the three-batch PPQ is about 2%, whereas the probability of a batch passing the release test with 6% variability is approximately 97%.

5.2.3 Sampling Plans/Statistically-Based Criteria for Critical Quality Attributes

Statistical techniques that have been either suggested in the literature or used in practice when conducting validation studies include computer generated acceptance tables, simulations used to estimate the probability of passing complex multiple-stage tests such as CU and dissolution, tolerance intervals, and variable acceptance sampling. These techniques are discussed below or in Section 6.3.

The example provided in Figure 5.4 focuses on intra-batch (or within batch) criteria. The acceptance criteria apply to a given PPQ batch and indicate whether that batch has met the PPQ acceptance criteria.

An acceptance criterion needs to be met for each batch in the PPQ study for a successful PPQ outcome. One advantage of these criteria is that a failure to meet the acceptance criteria clearly defines the batch or batches that are causing the PPQ failure. This can help direct the focus of a subsequent investigation. While it is still possible that the root cause of the failure applies to all batches in the study even if some batches pass the intra-batch criteria, the failure of particular batches to meet batch-specific acceptance criteria helps focus the investigation on the most likely root causes.

Intra-batch plans can be used on many different parameters where intra-batch variation is important to assess. Blend/content uniformity and protein concentration are discussed in the remainder of this section.

Blend Uniformity and Content Uniformity

Intra-batch variability is typically assessed during PPQ at blending for powders, and after sieving and transfer to a bin(s) for suspension-coated pellets as well as at forming tablets and filling of capsules. Blend uniformity with respect to a target drug load, mg active/g product and dosage units (% LC), is a common attribute for the assessment.

Intra-batch variability is typically assessed during PPQ at forming or filling for tablets and capsules, respectively. The quality attribute that is used for the assessment is the drug CU throughout the batch in terms of percent of LC on a unit dose basis.

This is typically the most extensive within batch evaluation during PPQ and provides the most insight into potential changes or trends during the manufacture of the batch because of the sample ordering.

Additionally, because of the extensive sampling and evaluation of CU, further within batch assessment of other analytical properties such as individual impurities and total impurities is not required or may be limited, for example, to performing beginning, middle, and end of batch sampling and testing.

In August 2013, the FDA withdrew its draft Guidance for Industry: Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment [45]. In the reasons for making this withdrawal, the FDA stated that acceptance criteria based on USP <905> [46] do not have sufficient statistical assurance or confidence that batches of drug products have met appropriate specifications and statistical quality control. Further, the FDA and USP have stated that the USP <905> test is not a release test but rather a surveillance test [47, 48].

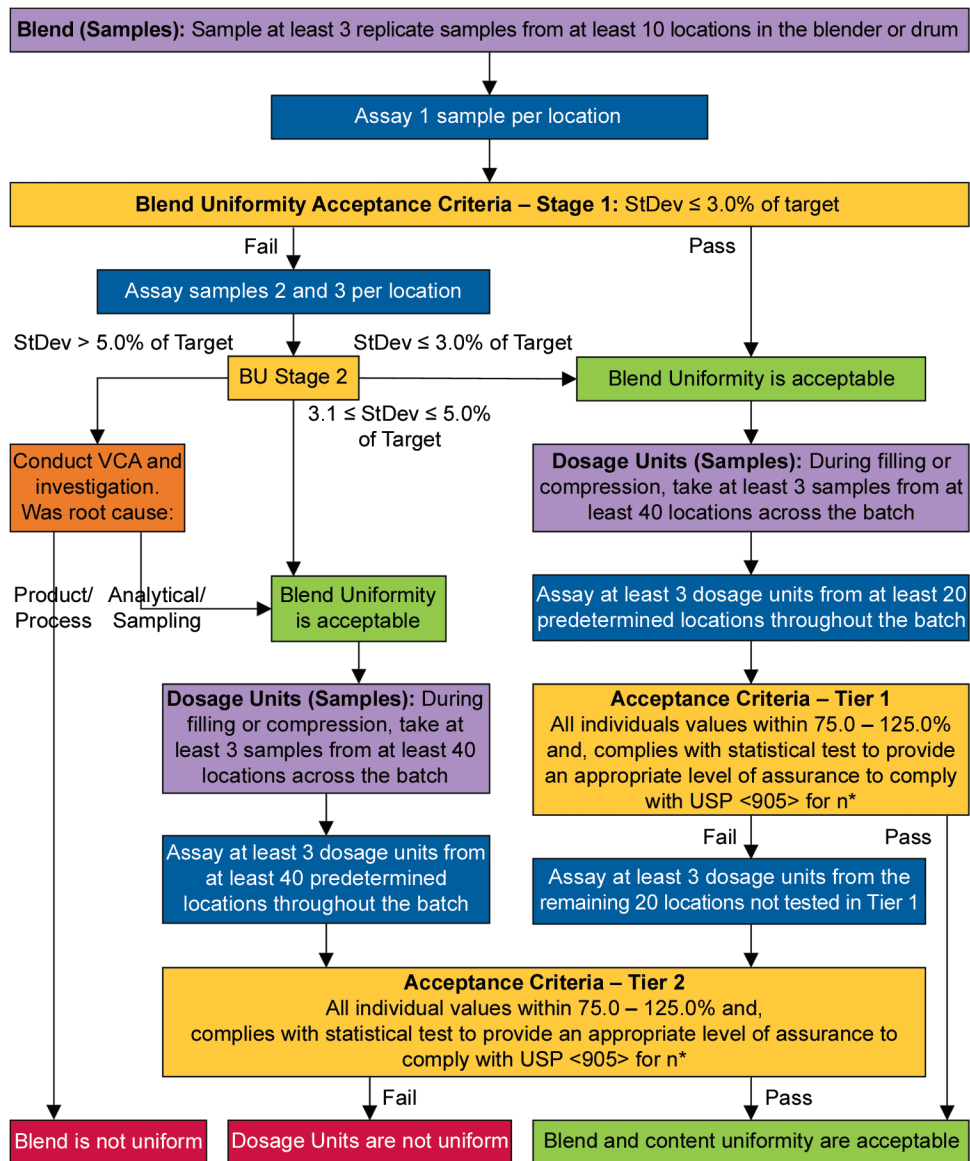
The USP Uniformity of Dosage Units (UDU) <905> test is described in Table 5.2 (assumes symmetric potency limits about 100% LC). The test consists of two stages with criteria within each stage. If Stage 1 criteria are not met based on 10 dosage units, 20 additional dosage units are tested and compared to the Stage 2 criteria. There is an “indifference” zone, meaning that if $\bar{X}$ falls between 98.5 and 101.5% LC, then the first term in the acceptance value is 0 since $M = \bar{X}$ [46].

Table 5.2: USP Uniformity of Dosage Units Test [46]

<i>All measurements of dosage units and criteria values are in percentage label claim (% LC). At each stage calculate the sample average $\bar{X}$ and the sample standard deviation s.</i>		
Stage	Number Tested	Pass stage when the criteria for the Acceptance Value (AV) is met:
S_1	10	$AV = M - \bar{X} + 2.4s \leq 15.0$, where M is defined below.
S_2	20	i) $AV = M - \bar{X} + 2.0s \leq 15.0$ using all 30 results ($S_1 + S_2$) ii) No dosage unit is outside the maximum allowed range of $0.75 \cdot M$ to $1.25 \cdot M$.
<i>M is defined as follows:</i> <i>If T is less than or equal to 101.5% LC, and</i> (i) <i>If $\bar{X}$ is less than 98.5% LC, then $M = 98.5\% \text{ LC}$.</i> (ii) <i>If $\bar{X}$ is between 98.5 and 101.5% LC, then $M = \bar{X}$.</i> (iii) <i>If $\bar{X}$ is greater than 101.5% LC, then $M = 101.5\% \text{ LC}$.</i> <i>If T is greater than 101.5% LC, and</i> (i) <i>If $\bar{X}$ is less than 98.5% LC, then $M = 98.5\% \text{ LC}$.</i> (ii) <i>If $\bar{X}$ is between 98.5% and T, then $M = \bar{X}$.</i> (iii) <i>If $\bar{X}$ is greater than T, then $M = T$.</i> <i>T is the Target content per dosage unit at the time of manufacture, expressed as percentage label claim. Unless otherwise specified in the individual monograph, T is 100.0% LC.</i>		

An ISPE-sponsored Blend Uniformity and Content Uniformity Technical Team was formed to provide recommendations to companies on the assessment of blend and content uniformity [49]. Figure 5.6 is a flow chart that shows the Technical Team's recommendations for assessment of blend and content uniformity for process design and qualification batches [50].

Figure 5.6: Process Flow Diagram for Assessment of Blend and Content Uniformity for Process Design and Process Qualification Batches [50]



*n is the total number of assay results.

The flow chart does not provide or recommend specific statistical methods for CU other than that the method should provide assurance of compliance to USP <905> [46].

The ISPE Blend Uniformity and Content Uniformity Technical Team flow chart provides a framework for performing the CU assessment [50]. Key aspects of the framework are:

- A moderately large number of locations should be sampled in a systematic/stratified approach across the batch (e.g., 40 locations with 3 samples per location, 40 × 3).
- Two tiers of evaluation: specifically, from across the batch test half of the locations and dosage units (e.g., 20 × 3) against pre-selected criteria. If the criteria are met, the batch passes; if not, test the remaining dosage units (that is, the remaining 20 × 3) and compare against the acceptance criteria (using all dosage unit data, e.g., 40 × 3). This is a two-tiered approach.

The fixed choice for the number of locations and therefore total samples may not be appropriate for all processes. For example, very short runs cannot be reasonably sampled in this manner. A company may need to link, with justification, the number of locations and total sample size to process risks and duration of the filling run. For blend uniformity or CU, a company could decide to test all samples in the same run instead of using a two-tiered approach to gain a better understanding of the variation.

The pre-selected criteria should provide a heightened level of assurance that the batch will meet the regulatory requirements (USP <905> [46], Ph. Eur. 2.9.40 [51], JP 6.02 [52]) for any additional samples obtained from the batch and tested against those requirements. The level of assurance/conservativeness that the sampling plan/test provides needs to be justified by the supplier.

Protein Concentration

Protein concentration is a key CQA for a biologic that measures the quantity of protein in the product. Regulatory authorities typically expect a specification of $\pm 10\%$ of the target concentration.

One possible intra-batch PPQ sampling plan for protein concentration is to use a prediction interval for a single new protein concentration value as a preliminary acceptance criterion where several samples are taken either randomly or systematically as the lot is produced. A prediction interval is an estimated range in which a future observation will fall with a specified probability. The evidence of capability sought for PPQ for this example is for the prediction interval to be within or equal to the specification for protein concentration. Caution: the cause of any statistical interval extending beyond specification may be statistical in nature, such as inadequate sample size, an outlier, etc. Thus, this situation should not necessarily trigger PPQ failure, as the process may in fact be quite capable. Instead of a strict failure criterion, the PPQ protocol should allow a risk-based assessment of results for intervals beyond specification to determine the path forward, with guidance from a process subject matter expert and a statistician when possible.

To develop a plan using a prediction interval, two elements must be decided:

1. Number of values used to calculate the interval
2. Confidence level for the interval

The equation for a $(1-\alpha)\%$ prediction interval is the following:

$$\bar{X} \pm (t_{1-\alpha/2, n-1}) \times (s) \times (\sqrt{1+1/n})$$

Where:

$\bar{X}$ = sample mean

n = sample size per batch

$t_{1-\alpha/2, n-1}$ = two-sided Student t value with $100 \times (1-\alpha)\%$ confidence and $n-1$ degrees of freedom

s = sample standard deviation

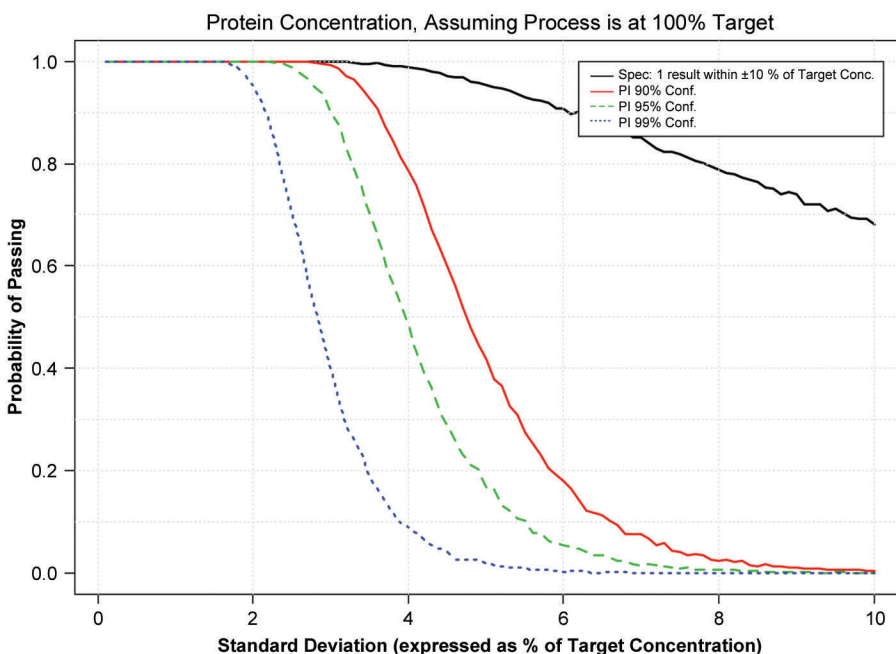
The confidence level and the sample size may be selected by evaluating a range of confidence levels and sample sizes to achieve a goal as described in Section 5.2. Assuming that this evaluation indicates that a 90% prediction interval with $n = 10$ protein concentration values for the PPQ batch is sufficient, the interval becomes:

$$\bar{X} \pm (1.833) \times (s) \times (\sqrt{1 + 1/10}) = \bar{X} \pm (1.923) \times (s)$$

Figure 5.7 shows the OC curve for this plan in comparison to the release test of a single protein concentration result within or equal to the specification ($\pm 10\%$ of the target concentration) when the process mean is at the target concentration. Also shown in Figure 5.7 are the OC curves for a 95% and 99% prediction interval. The protein concentration data is expressed as a percent of the target concentration for the graph.

When the 90% prediction interval is within or equal to the specification range, it is possible to state with at least a 90% confidence level that a future result will be within the specification. The OC curve comparison between the release test and the PPQ test (as described in this section) can also be used to describe the assurance the PPQ plan provides.

Figure 5.7: Operating Characteristic Curves for Release and Prediction Interval Process Performance Qualification Plans for Protein Concentration



Composite Assay

Composite assay is a measurement of the amount of drug substance in a product batch expressed as a percent of LC (% LC). The analytical method usually has a sample preparation that involves compositing units (typically in the range of 5 – 20 units) prior to measurement. Regulatory expectations for the specification typically are 90.0 – 110.0% LC or 95.0 – 105.0% LC.

One possible sampling plan is to use the prediction interval approach provided in the protein concentration example. When the specification is 90.0 – 110.0% LC, the OC curves are the same as shown in Figure 5.7.

5.3 Process Validation (Process Performance Qualification) Acceptance Criteria

Acceptance criteria are developed to provide statistical approaches to sample and to evaluate dosage forms sampled during manufacture of a batch that would ensure, with high confidence, that the batch would pass the USP UDU <905> [46] and possibly USP Dissolution <711> tests [53].

All of the statistical methods in this section and Section 6.3 require the user to choose a confidence level and a probability of passing the USP test. Based on the sampling plan, confidence level, and probability of passing the USP test, an acceptance limit table is generated.

If the acceptance limit, based on the sample results, is met, then the conclusion is that with the desired confidence, the probability of passing the USP test is at least the desired probability. For example, if the confidence level is 90% and the probability of passing the test is 95% and the sample passes the acceptance criteria, then with 90% confidence, there is at least a 95% probability of passing the USP test.

Recall from the sampling discussion (Section 5.2.1) that Sampling Plan 1 tests one unit from each sampling location in the batch. Sampling Plan 2 tests more than one unit from each sampling location. Sampling Plan 2 is the plan shown in the Figure 5.6 flow chart during filling or compression whereas Sampling Plan 1 is generally used for routine release. Sampling Plan 2 allows estimation of both between and within location variability and their relative contribution to the total variability.

There are three statistical methods:

- ASTM E2709/E2810 method proposed by the ISPE Blend Uniformity and Content Uniformity Technical Team [44]
- Tolerance Intervals
- An “Exact” test based on variable sampling (or its acceptance polygon approximation) described in Section 6.3 for routine release

The ASTM E2709/E2810 [44] and tolerance interval methods have been developed for PPQ when using Sampling Plan 2 and are compared in this section.

The “Exact” test may also be developed for PPQ. In situations during PPQ where the units cannot be kept in chronological order, Sampling Plan 1 may be appropriate. An example is when the active ingredient is contained in the coating. In this case, the dosage units are continually mixed so that the sampling strategy would be a simple random sample with one dosage unit per location.

Acceptance limits using Sampling Plan 2 require more calculations since there is a between and within location variance component. The acceptance limit table used for Sampling Plan 1 only requires the user to compute the sample mean and standard deviation whereas Sampling Plan 2 requires a computation of the standard deviation of the location means, the within location standard deviation, and the overall sample mean.

For ASTM E2709/E2810 [44], the pictorial (Figure 6.5) in Section 6.3 also applies when using Sampling Plan 2. The only difference is that the standard deviation and the upper limit on the standard deviation (ULS) are computed differently due to the two variance components (i.e., between and within location).

The ISPE website [49] contains useful information for ASTM E2709/E2810 that includes:

- Blend Uniformity and Content Uniformity Group flow charts for PPQ and routine release
- Common acceptance tables for Sampling Plans 1 and 2
- Excel spreadsheets that perform all the computations for the Sampling Plan 2 that tests 3 dosage units at each of 20 or 40 locations
- Validated SAS program that constructs acceptance limit tables for CU and dissolution for Sampling Plans 1 and 2 (supporting validation documentation included)

The Two-Sided Tolerance Interval approach is based on the coverage discussed in Section 6.3, which states if 99.34% of CU results fall between 83.5% and 116.5% LC, then there is a 95% probability of passing the USP UDU test [46]. The Two-Sided Tolerance Interval for two variance components has been published [54]. The formula for calculating the tolerance interval endpoints is given in Appendix 6 Section 14.10. As with Sampling Plan 1 in Section 6.3, if the endpoints of the tolerance interval are contained within 83.5% to 116.5% LC, then there is at least a 95% probability that future samples from the batch will pass the USP UDU test [46].

The Two-Sided Tolerance Interval method can be compared to ASTM E2709/E2810 [44] using OC curves. Figures 5.8 and 5.9 show the probability of passing each method when the lot mean is 100% and 96% LC for Sampling Plan 2 with three test results from each of 20 (20×3) or 40 (40×3) locations

The probability of passing ASTM E2709/E2810 [44] or the Two-Sided Tolerance Interval method depends on how much of the proportion of the total variation is due to location to location variability.

If there were no location variation, then the probability of passing would be similar to Sampling Plan 1 with 60 (20×3) or 120 (40×3) locations, but if almost all of the total variability is due to location, then the probability of passing would be closer to Sampling Plan 1 with 20 or 40 locations.

OC curves are shown for the situations where 0%, 50%, and 90% of the total variation is due to location variability. As can be seen from the plots (Figures 5.8 and 5.9), the ASTM E2709/E2810-based method [56] has a higher probability of passing compared to the Two-Sided Tolerance Interval method when the lot mean is 100% LC. When the lot mean is 96% LC, ASTM2709/E2810 has a higher probability of passing up to a total standard deviation of about 3 – 4%, but the Two-Sided Tolerance Interval is higher for total standard deviations greater than 3 – 4%.

Figure 5.8: Operating Characteristic Curve Comparison of ASTM E2709/E2810 [44] to Two-Sided Tolerance Interval (Lot Mean = 100% Label Claim)

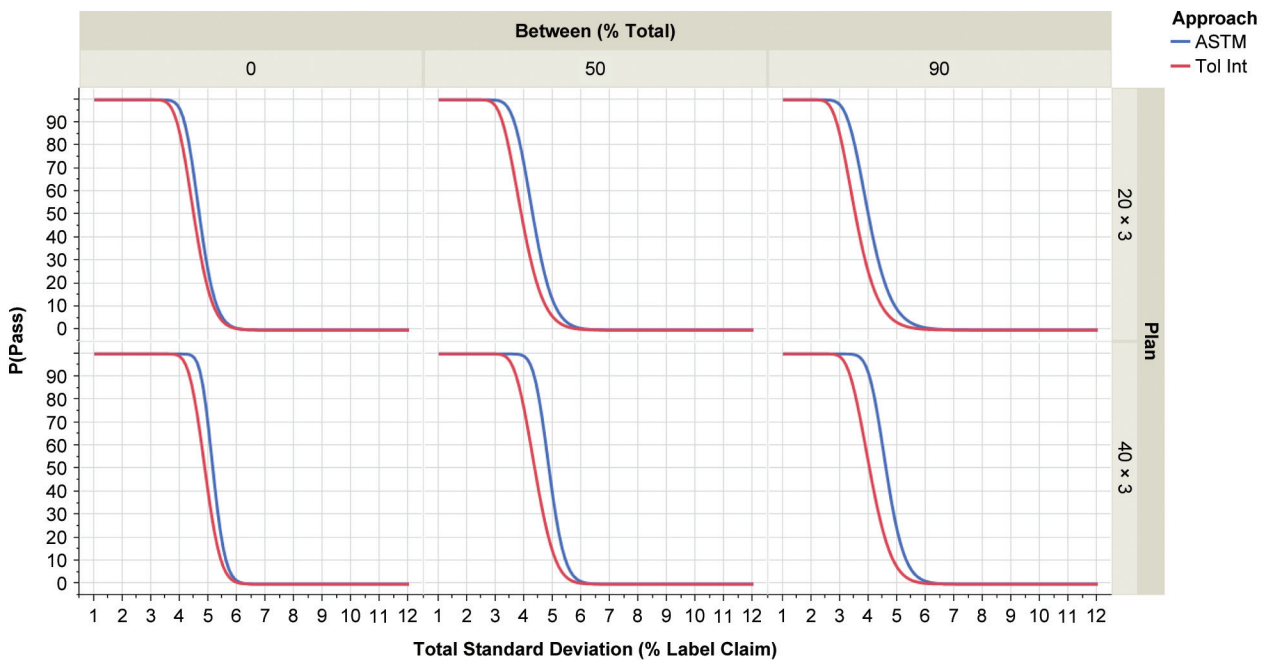
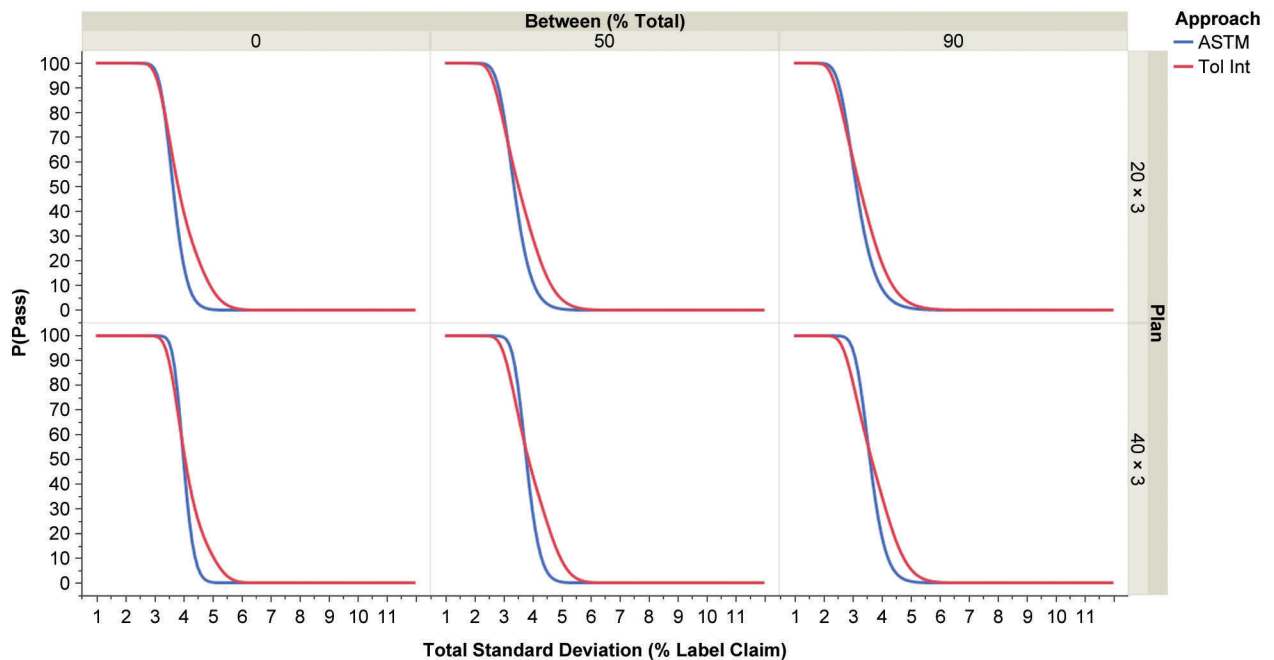


Figure 5.9: Operating Characteristic Curve Comparison of ASTM E2709/E2810 [44] to Two-Sided Tolerance Interval (Lot Mean = 96% Label Claim)**Example [44]**

Following the ISPE Blend Uniformity and Content Uniformity Technical Team's recommendation [50], a lot is sampled at 40 locations evenly spaced throughout and the blend was shown to be uniform. Then 3 dosage units from 20 of the 40 locations (perhaps at locations 1, 3, 5...17, 20, 22, 24...40) are tested. The CU data is as shown in Table 5.3 (for simplicity, the locations have just been listed as 1 through 20).

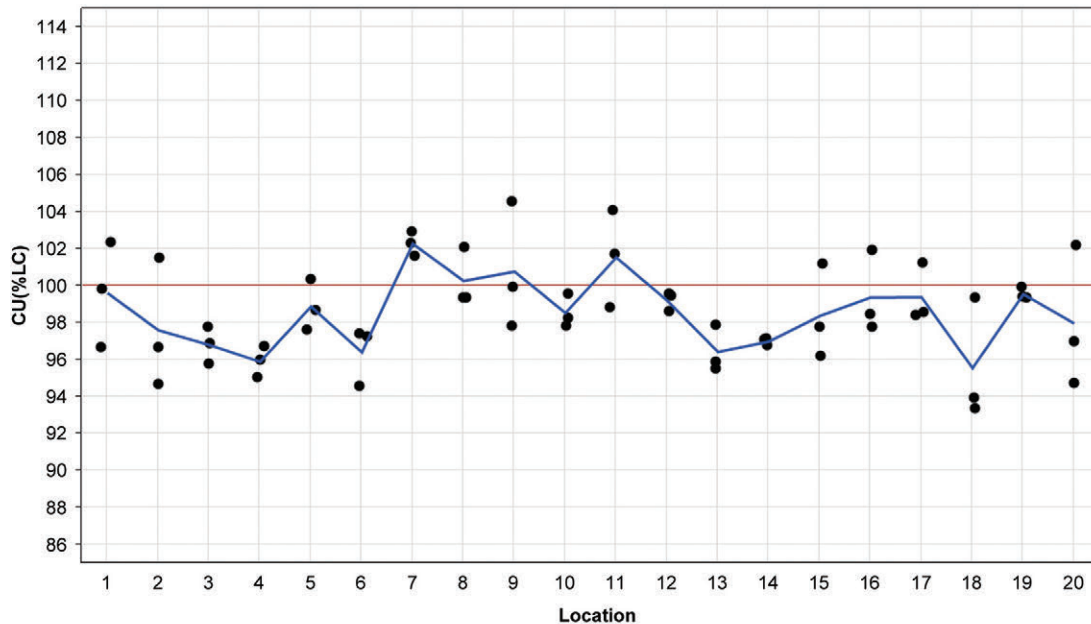
Table 5.3: Raw Data Display

Location	Dosage Unit		
	1	2	3
1	102.37	96.68	99.86
2	96.67	101.51	94.68
3	96.90	97.77	95.79
4	95.03	96.71	95.99
5	100.36	97.62	98.71
6	97.29	97.41	94.58
7	102.30	101.65	102.95
8	99.37	99.38	102.12
9	104.59	99.95	97.85
10	99.56	97.83	98.27

Location	Dosage Unit		
	1	2	3
11	104.11	98.86	101.71
12	99.46	99.57	98.63
13	95.90	97.89	95.54
14	97.13	96.78	97.11
15	101.19	96.21	97.77
16	97.77	98.47	101.93
17	101.25	98.55	98.40
18	93.97	93.36	99.37
19	99.40	99.37	99.93
20	97.00	94.76	102.20

Figure 5.10 is a plot of the data that can be useful to look for trends or unusual patterns. Plotting the data is highly recommended.

Figure 5.10: Data Display Content Uniformity versus Location



A VCA should be used as part of the data review. Variance components split the overall variability into between and within location components. The VCA is useful to determine the relative magnitudes of within and between location variability.

In the example, the variance components are given in Table 5.4.

Table 5.4: Variance Components

Component	Variance Component	% of Total	Plot %	Standard Deviation
Between Locations	2.003	30.6		1.415
Within Locations	4.535	69.4		2.130
Total	6.538	100.0		2.557

The analysis shows that the total standard deviation for all results is 2.557, with 30.6% of the total variation due to between locations, which is statistically significant (p-value = 0.012 for null hypothesis that the variance for between locations is equal to zero).

The variance component analysis is useful to determine whether or not the location to location (between location) variability is significant, both statistically and practically, as well as how much of the total variation is due to location to location variability. A company would have to decide if a total standard deviation of 2.557% with about 30% of the variation due to locations is worth the resources to investigate the between location variability.

Note that the within location standard deviation is 2.13%, so reducing or eliminating the location to location variability may only result in reducing the total standard deviation from 2.557% to about 2.13%.

It is also important to note that the tests and acceptance criteria proposed assume that all dosage units in a given batch have an equal probability of reaching a given consumer. One way to look at this is that all dosage units are blended together such that any location differences are minimized prior to final packaging.

There are two approaches to analyzing the data: using the ASTM E2709/E2810 method [44] or using a Two-Sided Tolerance Interval.

1. ASTM E2709/E2810 [44]

The statistics required to use the ASTM E2709/E2810 acceptance limit table for Sampling Plan 2 are:

- Overall mean
- Within location standard deviation (i.e., the square root of the average of the 20 location variances, which is the same as the within location standard deviation from the variance component analysis)
- Standard deviation of the 20 location means (**Note:** this is not the square root of the between location variance component)

Table 5.5 shows the overall mean, the within location standard deviation (SE), and the between location standard deviation.

Table 5.5: Example – Sampling Plan 2

Descriptive Statistics (% Label Claim)	
Overall Mean	98.59
SE (Within Location Standard Deviation)	2.13
Standard Deviation of Location Means	1.87

Table 5.6 is a subset of the entire acceptance table for Sampling Plan 2 that contains limits for the overall mean. Acceptance criteria tables have been posted for the ASTM E2709/E2810 approach including the complete 20 × 3 table [55].

The first column is the within location standard deviation (SE) and the first row is the standard deviation of the location means. To use the acceptance limit table, the SE and Standard Deviation of Location Means are rounded up to the nearest tenth from 2.13 to 2.2 and 1.87 to 1.9, respectively to be conservative. The limits on the overall mean are 92.8 to 107.2% LC.

Since the overall mean is 98.59% LC, the sample passes the limits; therefore, with 90% confidence, there is at least a 95% chance that samples from the batch will pass the USP UDU test [46].

Table 5.6: 90%Conf/95%Prob(Pass USP) for ASTM E2709/E2810 Approach [55]

	Standard Deviation of Location Means		
	1.8	1.9	2.0
SE	LL UL	LL UL	LL UL
2.1	92.3 107.7	92.6 107.4	93.0 107.0
2.2	92.5 107.5	92.8 107.2	93.1 106.9
2.3	92.6 107.4	92.9 107.1	93.2 106.8

2. Two-Sided Tolerance Interval

Table 5.7 is the acceptance limit table for the overall mean based on the Two-Sided Tolerance Interval approach.

Table 5.7: 90%Conf/95%Prob(Pass USP) for the Two-Sided Tolerance Interval Approach

	Standard Deviation of Location Means		
	1.8	1.9	2.0
SE	LL UL	LL UL	LL UL
2.1	91.8 108.2	92.1 107.9	92.5 107.5
2.2	92.0 108.0	92.3 107.7	92.6 107.4
2.3	92.1 107.9	92.4 107.6	92.7 107.3

Using the Two-Sided Tolerance Interval approach, the limits for the mean are 92.3 – 107.7, which are slightly wider than the ASTM E2709/E2810 limits but still provide 90% confidence that there is at least a 95% probability of passing the USP UDU test [46].

5.4 Stage 2.2 Process Review

5.4.1 Graphical Tools

After Stage 2 PPQ execution is complete, graphical tools such as run charts, individual value plots, and (in some cases) box plots can be used to confirm that the process performance is similar to that expected based on Stage 1 data. As the number of PPQ batches will typically be small, a visual assessment is usually the most appropriate way to assess inter-batch variability in Stage 2.

In the case of an in-line product, historical data can also be used. Figure 5.11 shows a control chart for the average of the UDU data with the historical, Stage 1, and Stage 2 data combined. In this case, the historical data is used to set the control limits, and the Stage 1 and Stage 2 results fall within the control limits, demonstrating consistent performance after the process change (scale change, etc.).

Figure 5.12 shows side-by-side boxplots of the UDU averages. Here it is clear that the data from all three sets (historical, Development/Stage 1, and PPQ/Stage 2.2) overlap.

Figure 5.11: Control Chart of Average Uniformity of Dosage Units Results: Historical (▲), Stage 1 (●) and Stage 2 (▼)

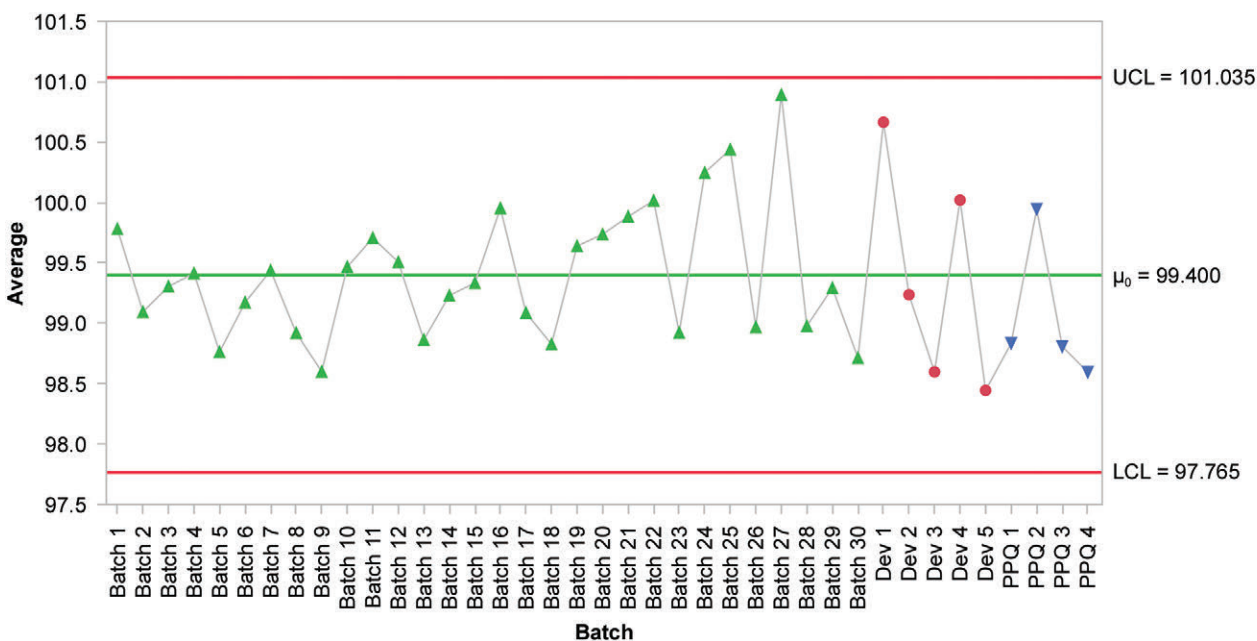
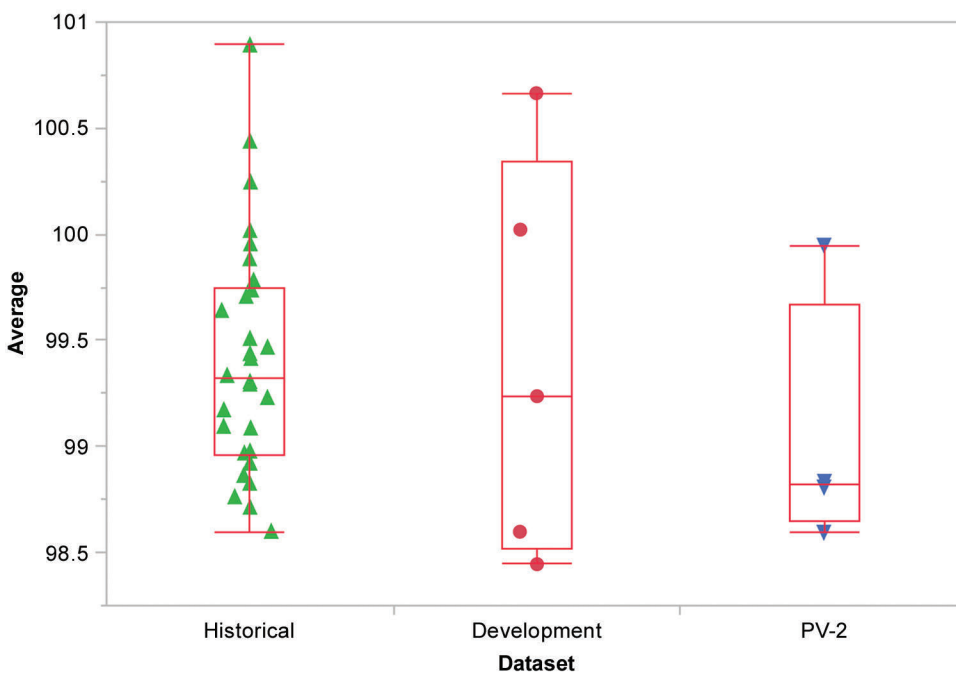


Figure 5.12: Side-by-Side Boxplots of Average Uniformity of Dosage Units Results



5.4.2 Validation Prior to Submission Approval

In cases where validation data must be submitted with the registration application, it is possible that approved specifications will be more restrictive than the requested limits. It is also possible that the granted expiration dating may be shorter than requested. In these cases, it is important to revisit validation results prior to releasing product.

When specifications are tightened, results need to be compared to the new limits, reduced for analytical variation and degradation on stability. **Note:** when the approved specifications are tighter than those in the Marketing Authorization Application, impact on CPP and PAR/NOR also need to be assessed.

Note: be careful about the relaxing of release limits. Expiry might have been shortened, but the expanded release limits do not give assurance that the shelf life first requested in the application can be met.

5.4.3 Example Checklist of Items to Complete Prior to Continued Process Verification

In conjunction with completed items from Stages 1 and 2, this functional checklist (Table 5.8) may be used to assess the readiness of the process to begin Stage 3.

Table 5.8: Example Checklist for Assessing Readiness for Stage 3

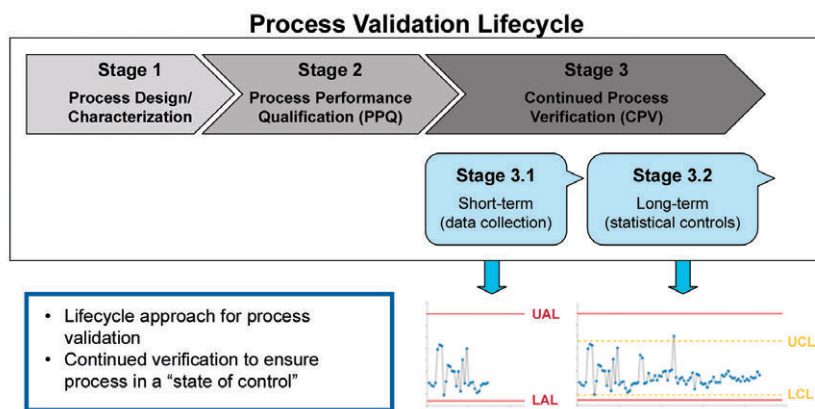
Readiness Prerequisites	Status
PPQ validation data evaluating intra and inter-batch variability using planned statistical analysis completed. Note: <i>use of graphical comparison is recommended.</i>	
Data from similar products/processes may be evaluated if leveraged to demonstrate process understanding	
Evaluation of test results for CMA to defined ranges conducted	
Assessment of operational variability across shifts, equipment sets, etc. performed	
Deviations related to process control reviewed and impact assessed	
Recommendations for process improvements and necessary revisions to documents such as batch records determined	
Assessment and identification of attributes for reducing heightened monitoring to routine levels conducted	
Summarize validated hold times and establish process times as applicable	
Expected conclusions identified and the expected confidence in the process and plan determined	
Conclusions from Stage 2 and the rationalization for proceeding to Stage 3 completed. Note: <i>data from some intermediate steps may not be available.</i>	

6 Continued Process Verification (Stage 3)

A successful PPQ (Stage 2) confirms the soundness of the process design and control strategy (Stage 1), and demonstrates that the commercial manufacturing process performs as expected and is capable of consistently delivering quality product.

The main purpose of the CPV (Stage 3) monitoring plan is to provide assurance that throughout the commercial phase of the lifecycle, the process remains in a state of control; however, a period of enhanced monitoring after completion of PPQ may be required for certain attributes or parameters to further increase the level of confidence in the process (see Figure 6.1).

Figure 6.1: Continued Process Verification Strategy



It is important to keep in mind that this stage is known by different names depending on the regulatory body in force. FDA and WHO call it Continued Process Verification [3, 26], while EMA uses Ongoing Process Verification [11]. Regardless of the terminology, the intent of the regulators is the same: manufacturers need to monitor the state of process control, verify the impact of variability, identify potential issues, and determine the best course of action to ensure that the process remains in control.

6.1 Determine the Continued Process Verification Plan

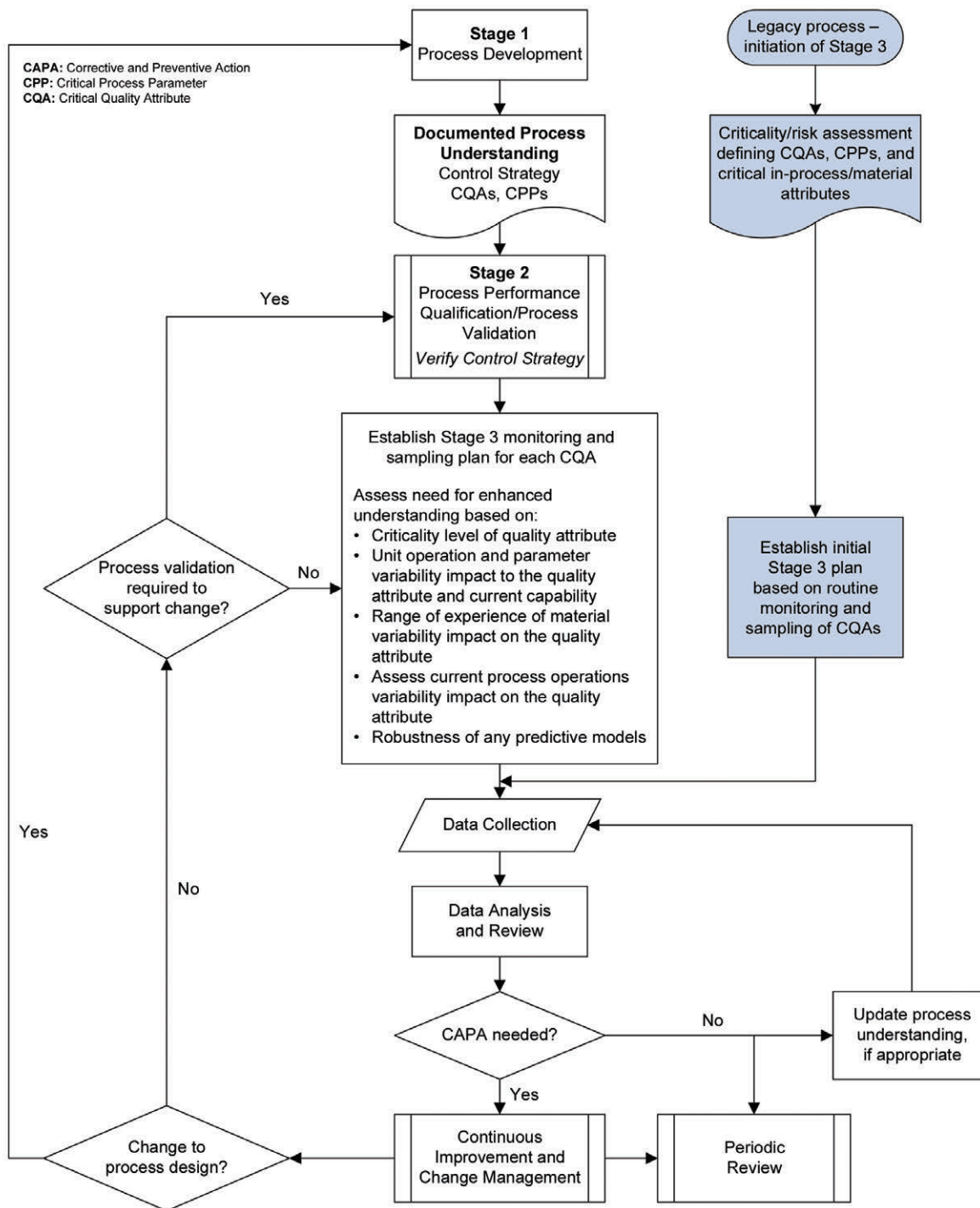
A CPV monitoring plan should be established to evaluate process capability and the ongoing impact of variability in process, materials, facility, equipment, or other inputs, continually increasing process understanding and generating variability estimates. These estimates can be used to establish long-term Statistical Process Control (SPC) limits and to adjust the levels and frequency of routine sampling and monitoring, as appropriate.

Control chart signals (e.g., statistical outliers, western electric rule violations), capability indices, and input-output relationships identified from continued process monitoring may trigger an investigation and the need for revisions to the control strategy, such as:

- Adjustments to extended testing levels and/or elimination/addition of monitoring parameters
- Revisions to the raw material sampling strategy
- Other process improvements, for instance optimization of analytical methods, process control, equipment, environmental, etc., that have been found to contribute to process variability

One approach to selecting parameters/attributes for the CPV plan and the overall process is summarized in Figure 6.2.

Figure 6.2: Flow Chart for Establishing a Stage 3 Monitoring Plan [35]



For all new products, it is recommended establishing a monitoring plan as early as possible to enhance process understanding. This may mean monitoring during manufacture of Stage 1 batches such as clinical supplies, engineering batches, and stability batch manufacture.

Minimally, a monitoring plan should be available following Stage 2 if full PPQ-level sampling and testing will not be continued.

The approach to analyzing and reviewing product and process performance data should be documented by procedure or protocol. The plan should be developed by SMEs (such as technical personnel, statisticians) and approved by the appropriate functional groups (QA/QC, Validation, Manufacturing, etc.). The monitoring plan should address, directly or by reference:

- Which input and output parameters and/or attributes will be monitored for each product
- How data will be collected
- Methodology that will be used to evaluate the data (e.g., statistical methods such as control charts, multivariate analysis)
- At what frequency the data will be evaluated

The plan could be product specific, covering all unit operations (raw materials, equipment settings, environmental conditions, and so forth) or products may be grouped (e.g., platform technology approach). Other elements to include in the monitoring plan or other associated documents (SOPs, VMP, etc.) are the roles and responsibilities of various functions, management reviews, and mechanisms to trigger changes requiring redesign and re-qualification.

The plan should be incorporated into the quality system at the manufacturing site to leverage the existing data collection and evaluation processes, including the annual/periodic review process. If the monitoring plan results are reviewed as part of commercial product release, approval of the plan by the quality unit (QA) at the manufacturing site is required by the EU [11], and recommended in other markets.

6.2 Determine which Variability to Include in the Continued Process Verification Plan

Data to be monitored is determined by the current understanding of the manufacturing process and systems (process, materials, components, equipment, facility, utilities, and environment) in relation to product quality attributes. This understanding may range anywhere from first principles, prior knowledge, and statistical models based on DoEs to empirical models, or even to understanding based on manufacturing experience.

Risk-based tools may be used for the selection of initial Stage 3 elements. The risk of an input (equipment parameter, raw material attribute, etc.) to impact the process may be ranked as well as the risk of the attribute (output) to impact the patient. For instance, the tablet appearance impact is a lower risk to the patient than tablet potency/stability. Risk scores may then be generated to prioritize the elements that are potentially most impactful to the process and ultimately the patient.

During Stage 3, estimates of long-term process variability are generated. Adjustments to the control strategy may be warranted as process experience and understanding of variability increases, including potential changes in the assignment of in-process/raw material attributes or a parameter criticality level. The criticality of finished product CQAs would only change based on new clinical data.

Initial Stage 3 monitoring plans, particularly for new products, may involve a greater number of parameters and/or heightened sampling and testing for certain parameters than during ongoing monitoring. Some CQAs (e.g., viral clearance for a biological product) may be confirmed through separate validation studies and not as part of the release of each batch; therefore, they may not need to be included in the Stage 3 plan.

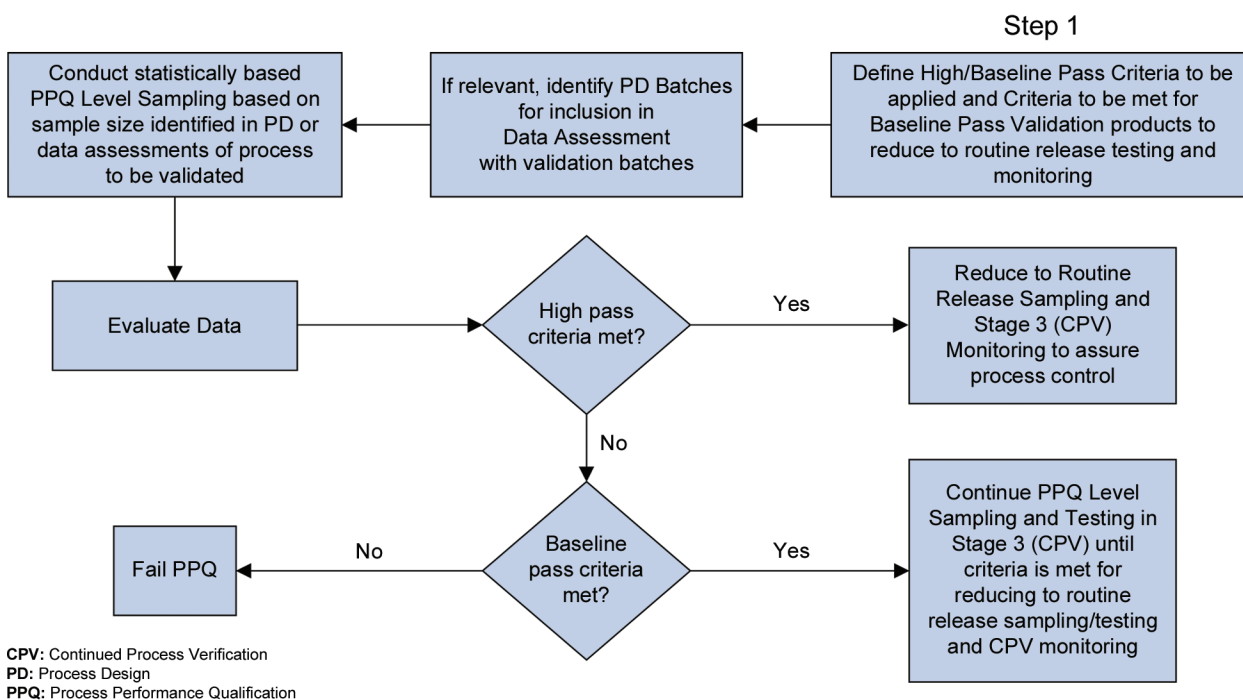
The number of parameters and/or extent of testing may increase or decrease as further knowledge is gained from the monitoring experience, as well as when specific residual risks are reduced or new risks are identified.

The decision to discontinue heightened/extended testing should be driven by the confidence achieved in the manufacturing process during Stages 1 and 2, and throughout Stage 3, based on the robustness of the control strategy and its ability to manage sources of variation.

To guide this process and define when PPQ-level sampling and testing may be reduced, decision trees may be used. They may be based on meeting various statistical criteria (e.g., prediction interval, tolerance interval, defect rate, or other statistical criteria met with a defined confidence) combined with an overall assessment of the process and the associated control strategy.

An example of a decision tree is provided in Figure 6.3. The rationale for the change or discontinuance of the monitoring should be documented and implemented through validation documentation, which may include change management systems.

Figure 6.3: Example Decision Tree for Moving from Process Performance Qualification to Stage 3 Sampling/ Testing



6.2.1 New Products [35]

For new products, the control strategy identified during development (Stage 1, Process Design) is based on process understanding and QRM, and provides the foundation for Stage 3 monitoring.

The parameters and attributes included in the enhanced sampling and testing in Stage 2 should be evaluated initially for continued monitoring in Stage 3. Consider both intra and inter-batch variability when establishing the monitoring plan.

Intra-batch variability is typically assessed during PPQ. If it has already been demonstrated that a smaller number of samples/values/data points represents the batch (that is, intra-batch variability data demonstrates that worst-case locations and time points are not significantly different than other points/locations, low defect rates have been demonstrated by the process with statistical rigor, etc.), then testing can be reduced to routine levels; however, this routine level should be scientifically and statistically justified.

Where it is not reasonable or practical to assess variability of input ranges of material quality attributes that may impact intra-batch or inter-batch variability during Stage 2, or if product quality attributes values are approaching the edge of an acceptance limit, then it may be prudent to continue to perform Stage 2 levels of sampling and testing during some portions of Stage 3 for those potentially impacted attributes.

With the appropriate risk-based analysis and documented justification, certain Stage 2 parameters may be eliminated or the level of sampling and testing could be reduced in the Stage 3 plan. An example of such a decision process is presented in Appendix 3 (Section 11.1).

One of the goals of initial Stage 3 monitoring for a new product is to finish establishing the capability of the process that began during Stage 1 and continued in Stage 2. That is, Stage 3 looks at process performance across many batches and continues to build the overall picture of inter-batch variability.

Where there is concern that the established control strategy may allow variability of the inputs that may impact output product quality, more batches may be needed to assess capability, and/or interim alert limits considered based on the current process understanding.

That is, if the input variability evaluated to date is limited compared to the input specification limits, more data should be compiled to assess the impact of variability closer to the specification limits. Alternatively, statistically-based alert/control limits could be established to facilitate evaluation of atypical variation in the input.

It should also be noted that a batch may yield one or more data points. In these cases, process capability analysis can be performed with groups of samples (e.g., six samples for each batch), taking into account the intra-batch variability.

Additionally, process capability may be calculated using batches from all three stages of PV. A statistician should be consulted when combining batches across stages for capability analysis to ensure that proper data pooling techniques are applied.

A criticality/risk assessment determines the level of impact each process variable or material attribute has on the CQAs; that is, where each variable falls in the continuum of criticality.

This criticality assessment typically was performed before the start of Stage 2 and may be revised on completion of Stage 2 based on increased process understanding. Cause and effect or correlations between inputs and outputs may or may not have been established.

Even after Stage 2, however, the impact of specific inputs (raw material properties and process parameters) may have not been fully assessed. Where the variability has not been fully determined, one of the objectives of the CPV plan will be to evaluate potential sources of variability for their impact on the CQAs or process performance and confirm or establish the inputs versus CQAs correlations.

This understanding may be achieved through the use of various statistical tools (e.g., multivariate analysis, principle component analysis, partial least squares, box plot/control charts) of the process database at defined points in time or observations of performance shifts associated with process changes (in inputs, outputs, or both).

6.2.2 Existing/Legacy Products [35]

Existing/legacy products developed traditionally (not by QbD) may not have critical attributes or parameters defined in their submissions; therefore, a criticality/risk assessment should be performed to identify those attributes and process parameters (including raw and in-process material attributes and manufacturing systems) that may impact patient safety, efficacy, and product quality.

The assessment should be based on current process understanding and relevant experience of the commercial process, including quality system events such as deviations and change controls, as well as product performance on stability. An example of such an evaluation is presented the ISPE Discussion Paper: "Topic 2 - Stage 3 Process Validation: Applying Continued Process Verification Expectations," Example 3 [35].

Stage 3 for existing/legacy products should begin with routine monitoring of the defined critical attributes and parameters. The initial evaluation may be based on a retrospective review of existing process performance data (i.e., from batches made before the decision to formally initiate Stage 3, APR). As with new products, when data is collected and analyzed, additional aspects that require evaluation may be identified.

One suggested action is to monitor additional parameters across batches or implement an intensive sampling plan of an output within a batch until the desired level of process understanding is achieved. Monitoring could provide the data to develop the correlations and cause and effect relationships, and help identify which inputs need better control to reduce output variability.

6.3 Determining Statistically-based Routine Sampling and Testing for Continued Process Verification

When selecting sampling plans and acceptance criteria for CPV, or blend uniformity and CU, one approach is to evaluate the OC curves for Stage 2, Stage 3.2, and the regulatory UDU test requirement [46]. A discussion of OC curves of sampling plans and acceptance criteria is given in the Appendix 6 Section 14.1

6.3.1 Example of Statistically-based Criteria: Content Uniformity

The purpose of statistically-based routine release sampling and testing is to provide a high level of assurance that dosage unit uniformity is high throughout the batch meeting patient needs and regulatory requirements and expectations.

The primary regulatory authority driving the use of statistically-based routine release criteria is the FDA [3]. However, given the harmonized UDU test requirements across the three ICH regions [56], the criteria established to meet FDA expectations may be applied to the other regions. Therefore, this section addresses the use of statistically-based routine release sampling and acceptance criteria applicable to the UDU tests USP <905> [46], European Pharmacopoeia 2.9.40 [51], and Japanese Pharmacopoeia 6.02 [52]. (Throughout the rest of this section, the use of “USP <905>” represents all three UDU tests.)

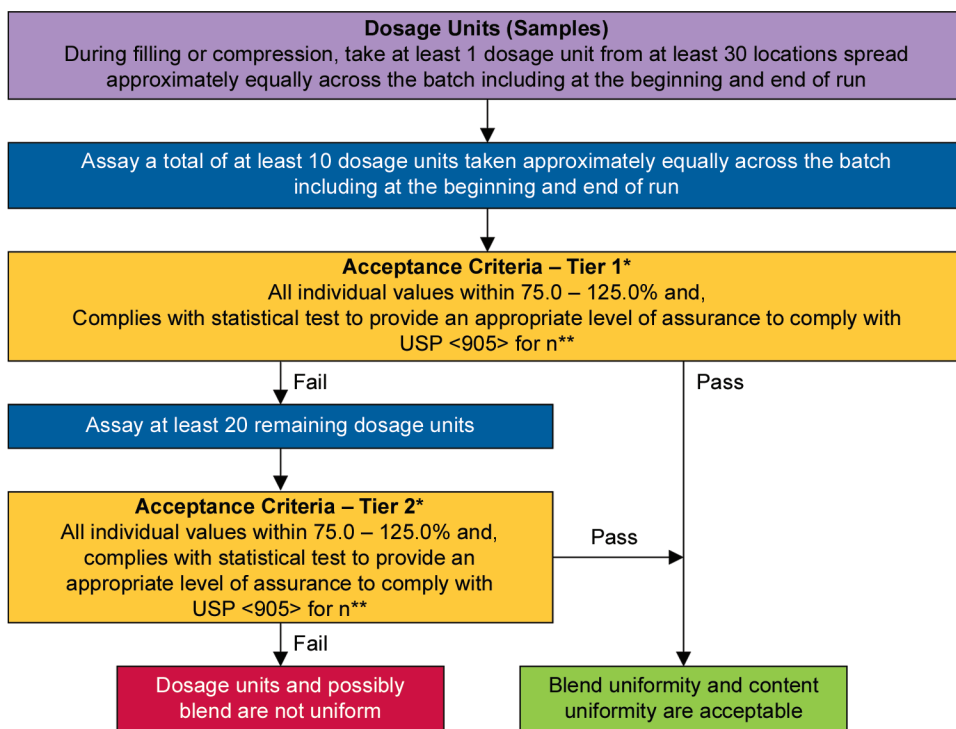
The USP UDU test [46] is a tiered test since it is comprised of two stages. The first stage consists of testing 10 dosage units. If the Stage 1 criteria are met, the sample passes the USP UDU test. If the Stage 1 criteria are not met, then another set of 20 dosage units are tested and the total set of 30 dosage unit CU results are compared to the Stage 2 criteria. If the Stage 2 criteria are met, then the sample passes the USP UDU test. Otherwise, the sample fails.

The same strategy can be used to show that with high confidence, a sample from the lot will pass the USP UDU test [46]. The strategy was published by the ISPE Blend Uniformity and Content Uniformity Technical Team [50].

An additional benefit of mimicking the sampling of USP <905> is that the results can also be analyzed against USP requirements, that is, the USP <905> AV value can be calculated [46]. While the statistical criteria established for CPV are tighter than USP <905> criteria (and therefore meeting these criteria logically provides the assurance to claim that the batch meets USP <905>), having the AV calculation available could be of value internally to the manufacturer and upon regulatory inspection while industry and FDA transition to applying statistically-based routine release criteria that demonstrate compliance with, and heightened assurance to meet, USP <905>.

A flow chart showing the ISPE Blend Uniformity and Content Uniformity Technical Team’s [50] recommended two-tiered approach is given in Figure 6.4, where at least 30 dosage units are sampled equally spaced throughout the tableting (or encapsulation) run. Then at least 10 of the 30 dosage units are tested in tier 1 against the desired statistical methodology criteria. If the tier 1 set of samples does not pass, then the remaining dosage units are tested and must meet the desired statistical methodology criteria for tier 2.

Figure 6.4: Process Flow Diagram for Assessment of Blend and Content Uniformity for Continued Process Verification (Stage 3.2) Batches [50]



*Acceptance criteria for Stage 3 Continued Process Verification may have reduced assurance to comply with USP <905> compared to that used for Stage 2 Process Qualification.

**n is the total number of assay results.

6.3.2 Statistically-based Acceptance Criteria

Note that the ISPE Blend Uniformity and Content Uniformity Technical Team's [50] recommendation in the previous section uses Sampling Plan 1 (one dosage unit tested from each of n locations) that is often used for routine release. The recommendation does not provide a specific statistical methodology.

An approach using ASTM E2709/E2810 standards was published by ISPE Blend Uniformity and Content Uniformity Technical Team [44]. There are several methods that can be used to evaluate CU data collected using Sampling Plan 1:

- ASTM E2709/E2810 standards [44] (See 5.3 for description)
- Two-Sided Tolerance Interval method that captures a specific proportion of the distribution
- "Exact" acceptance region corresponding to a variable acceptance sampling plan that assures results will fall within a specified interval (83.5% to 116.5%)

Another published method uses a Bayesian approach [57].

The following subsections provide more details on the Two-Sided Tolerance Interval and "Exact" methods. All of the methods provide an upper limit on the standard deviation for a given sample mean such that if the sample standard deviation is less than the upper limit, given the desired level of confidence, then the lot will have at least the desired probability of passing the USP UDU test [46].

For example, for a given sample mean, if the sample standard deviation is less than the upper limit and the sample passes, then with 90% confidence, there is at least a 95% probability that the lot would pass the USP UDU test [46].

When criteria are established and justified that demonstrate a high degree of confidence in meeting the USP <905> uniformity test [46], then from a statistical perspective, a company may consider that the USP UDU test need not be performed. Nevertheless, if a manufacturer intends to suspend the USP <905> test, this will need to be evaluated for compliance against their specific product registration.

6.3.2.1 *ASTM E2709/E2810 Method*

ASTM E2709 [58] provides a general methodology to assure compliance to a regulatory standard. E2810 [59] applies this methodology specifically to CU.

Assuming Normally distributed data, the lower bound on the probability of passing the UDU test for a specific “true” lot mean and standard deviation is calculated [60]. Based on the CU results generated using any of the three sampling plans above (Section 6.3.2), a confidence region with a specified confidence level is generated for the “true” lot means and standard deviations.

For each possible “true” combination of the lot mean and standard deviation in the confidence region, the lower bound can be calculated. With the specified confidence level, the probability of passing the USP UDU test [46] is greater than the minimum of all possible lower bound values in the confidence interval.

Figure 6.5 provides a pictorial of the ASTM method [44]. The x-axis and y-axis are the “true” lot mean and standard deviation, respectively. The solid line is the contour line where the lower bound for passing the USP UDU [46] test is at least 95%. Any combination of batch means and standard deviations below this curve has greater than a 95% chance of passing the USP UDU test. This is called the acceptable parameter region. A 50% contour would lie above the 95% contour and a 99% contour would lie below the 95% contour.

Based on statistics from a random sample or a systematic sample, the mean, $\bar{X}$, and standard deviation, s , are calculated and are shown in Figure 6.5. Based on the sample mean and standard deviation, a joint confidence interval [61] is generated for the lot mean and standard deviation that is represented by the triangle (Z is a standard normal critical value and ULS is the upper confidence limit on the standard deviation).

Therefore, if the confidence interval at the desired confidence level is completely contained under the solid line, then with the desired confidence (90% in this figure), there is at least a 95% chance that the batch will pass the USP UDU test [46].

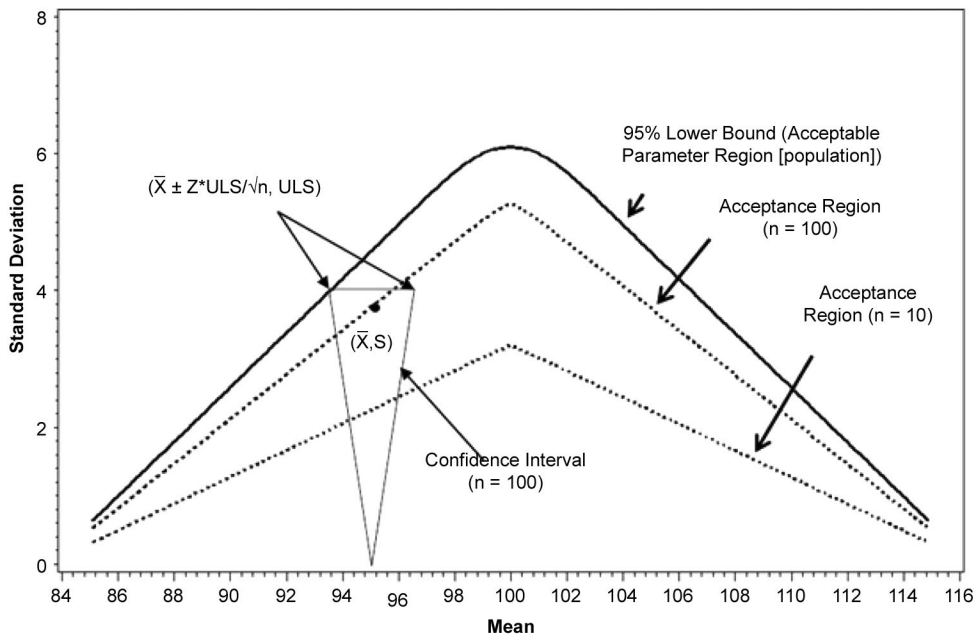
The point in the confidence interval with the lowest probability of passing the USP UDU test [46] is always at one of the vertices at the top of the triangle. The two dashed lines are the combination of sample means and standard deviations for $n = 10$ and $n = 100$ such that when the confidence interval is generated, one of the upper vertices falls on the solid 95% line. The set of all sample means and standard deviations for a given sample size lying below the dashed line forms the acceptance region.

As can be seen in the figure, the larger the sample size, the larger the acceptable standard deviation for a given sample mean. Any combination of sample mean and standard deviation in the acceptance region generates a confidence region at or below in the parameter region. So, with the desired confidence level, there is at least a 95% probability that the lot will pass the USP UDU test [46].

The points on the dashed line are the values that can be used to create an acceptance limit table.

Figure 6.5: Pictorial of the ASTM E2709/E2810 Methodology Applied to Content Uniformity [59]

Reprinted, with permission, from ASTM E2810 –11(Reapproved 2017) Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units, copyright ASTM International, 100 Barr Harbor Drive, West Conshohocken, PA 19428. A copy of the complete standard may be obtained from ASTM International, www.astm.org.



ASTM E2709/E2810 [44] can be applied to both Sampling Plan 1 (one result per location) and Sampling Plan 2 (more than one result per location). Sampling Plan 1 is more common for routine release whereas Sampling Plan 2 is often used for PV.

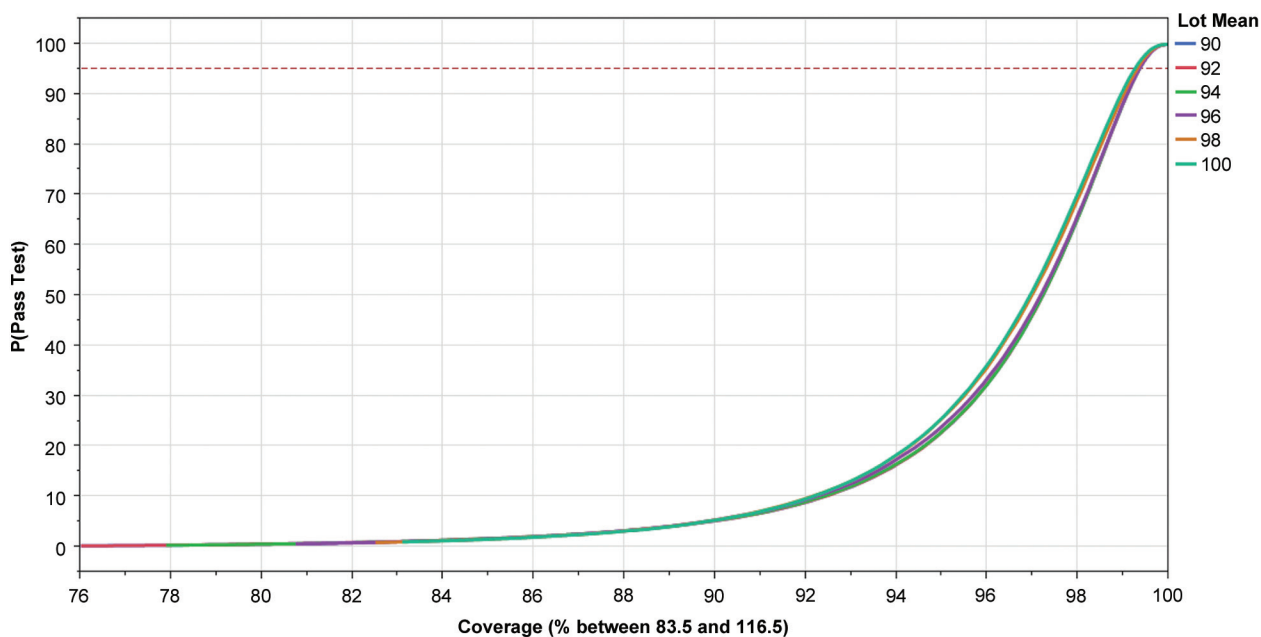
When one CU result is tested at each location, the standard deviation estimates the sum of the between and within location variability since it is not possible to estimate each variance separately. However, in Sampling Plan 2, the between and within location variability can be separated using VCA. Therefore, the standard deviation (s) and ULS in Figure 6.5 are calculated differently. (See reference [60] for more details.)

6.3.2.2 Tolerance Interval Approaches

Prior to discussing tolerance interval approaches, it is necessary to show the operating OC curve for passing the USP UDU test [46]. The USP UDU test allows the sample mean to fall as far from 100% LC as 83.5% to 116.5% LC.

If the coverage is defined as the probability of a result falling between 83.5% and 116.5% LC, then the USP UDU test [46] OC curves are as shown in Figure 6.6. A dashed reference line is shown at the 95% probability of passing the USP UDU test. The OC curves are based on simulation. The vertical axis is the probability of passing the USP UDU test and the horizontal axis is the coverage that is the probability that a single result will fall between 83.5% – 116.5% LC. A separate curve is shown for “true” lot means from 90% to 100% LC. The OC curves for 104% and 102% are the same as 96% and 98%, respectively (i.e., the OC curves are the same for lot means the same distance from 100% LC).

Figure 6.6: Operating Characteristic Curves for Passing USP Uniformity of Dosage Units [46] versus % Individuals Between 83.5% and 116.5% Label Claim for Lot Means between 90% and 110% Label Claim



There is a slight dependence on the lot mean. A zoomed in view of coverages between 95% and 100% LC is shown in Figure 6.7.

Figure 6.7: Operating Characteristic Curves for Passing USP Uniformity of Dosage Units [46] versus % Individuals Between 83.5% and 116.5% Label Claim for Lot Means between 90% and 110% Label Claim

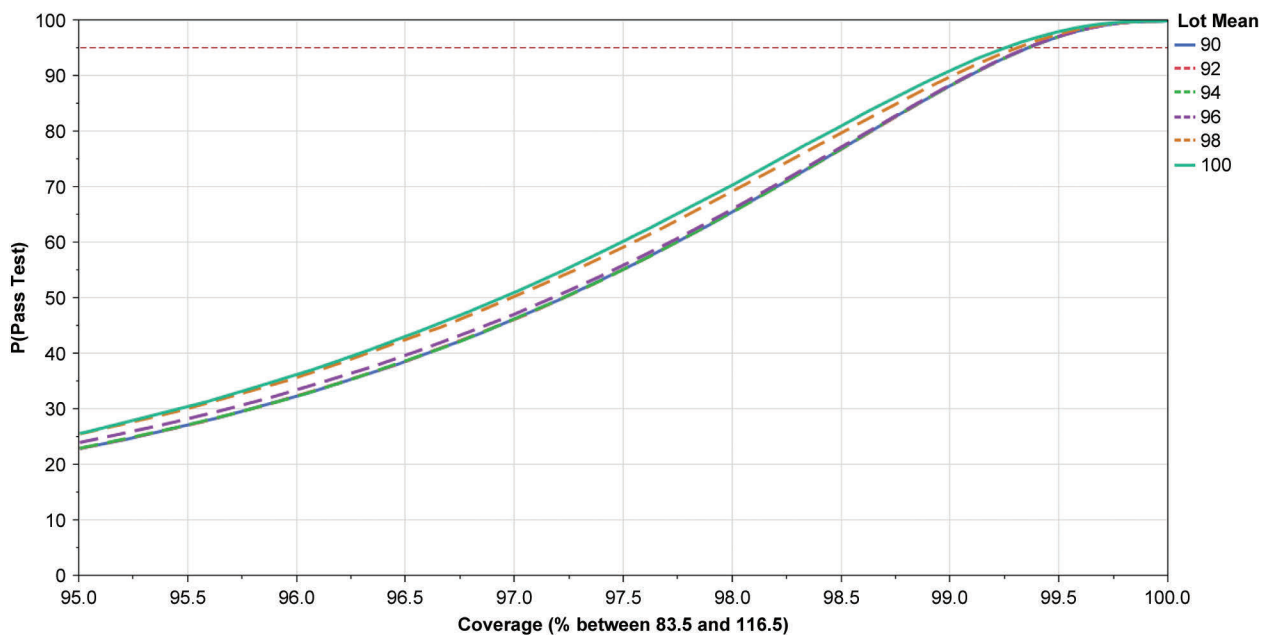


Table 6.1 shows the coverage required to achieve a 95% probability (dashed reference line) to pass the USP UDU test [46].

Table 6.1: Coverage (% Individuals between 83.5% and 116.5% Label Claim) to Achieve 95% Probability of Passing USP Uniformity of Dosage Units Test [46]

Lot Mean (% Label Claim)	Proportion of Individuals Between 83.5% and 116.5% Label Claim
100	0.9924
95	0.9934
90	0.9934
88	0.9934
86	0.9934
84	0.9934

Note that as the lot mean decreases from 100%, the coverage required to pass the USP UDU test [46] only very slightly increases from 0.9924 at a lot mean of 100% LC to 0.9934 for lot means of 95% LC to 84% LC. Therefore, if the coverage is at least 99.34%, then there is at least a 95% probability of passing the USP UDU test for all lot means.

The 99.34% serves one statistically valid quality standard where any methodology that can assure coverage greater than 99.34% would provide at least a 95% probability of passing the USP UDU test [46]. Tolerance intervals is a method that can satisfy this requirement since it provides an interval that captures a desired proportion of the distribution (coverage) with a specified confidence level. If at least 99.34% of the individual results (99.34% coverage is used throughout the rest of this document) are contained within 83.5% to 116.5% LC, then there is at least a 95% probability of passing the USP UDU test.

Since capturing 99.34% of the distribution requires estimation of percentiles in the tails of a Normal distribution, normality of the data is an important consideration and should be evaluated. The tolerance interval methods discussed in this Guide assume that the data was collected using a sampling plan that tests one dosage unit per each sampling location. This could be a random or systematic sample (i.e., samples taken from approximately equal locations throughout the lot based on time or lot size) taken from the lot.

The next two subsections describe two tolerance interval approaches: a Two-Sided Tolerance Interval and an “Exact” method.

Two-Sided Tolerance Interval

Given the sample size, confidence level, and coverage, a Two-Sided Tolerance Interval is constructed as follows:

$$\bar{X} \pm k \times s$$

Where:

$\bar{X}$ = sample mean

s = sample standard deviation

k = depends on the sample size, confidence level, and coverage

Table 6.2 shows the k values for confidence levels of 50%, 90%, and 95% to pass USP UDU [46] with 95% probability.

Table 6.2: *k* Values for Two-Sided Tolerance Interval with Coverage = 99.34%

Confidence Level (%)	n		
	10	30	60
50	2.95904	2.79344	2.75450
90	4.18636	3.34450	3.11626
95	4.68711	3.53363	3.23321

A very accurate approximation of *k* is given in the Appendix 6 (Section 14.2).

To meet the goal of having at least 99.34% of the individuals falling within 83.5% to 116.5% LC, a Two-Sided Tolerance Interval can be calculated using the desired confidence level and coverage of 99.34%. If the interval is completely contained within 83.5% to 116.5% LC, then with the desired confidence, there is at least a 95% probability of passing the USP UDU test [46].

As an example, let *n* = 30, sample mean = 98.60, and sample standard deviation = 3.42. The Two-Sided Tolerance Interval with 90% confidence is $98.60 \pm 3.34450 \times 3.42 = 87.16$ to 110.04; which is completely contained in 83.5 – 116.5, so the sample passes the acceptance criteria.

An acceptance limit table can be constructed by finding the maximum value of the standard deviation for a given sample mean such that either the lower endpoint is 83.5% or the upper endpoint is 116.5%. Plots of the tolerance interval acceptance limit tables are given in the Appendix 6 (Section 14.3).

A tolerance interval paper [62] was published that uses the interval from 85% to 115% instead of 83.5% to 116.5%. However, using 85% to 115% has a significant effect on the OC curves shown in Section 6.2 and 6.3 that gives the impression that the probability of passing the USP UDU test [46] increases as the lot mean gets further away from 100% LC. More details of this effect are in the Appendix 6 (Section 14.4).

Exact Acceptance Region [63, 64]

The Two-Sided Tolerance Interval approach shows that with the desired confidence, there is at least 99.34% of the distribution lies between the endpoints of the tolerance interval, which may be tighter than the entire range 83.5% – 116.5%; therefore, the probability of results falling between 83.5% and 116.5% is greater than 99.34%.

Another approach is to calculate the total probability of a result falling within the entire 83.5% to 116.5% LC interval. In acceptance sampling terminology, finding the maximum *s* for means over a specified range with a stated level of confidence is called an “acceptance region of a double-sided specification sampling plan.” The approach determines a set of sample means and corresponding maximum standard deviations such that the sum of individual probabilities of results falling below 83.5% and above 116.5% is held constant at 0.66% (i.e., 100.00 – 99.34). Plots of the acceptance limit regions are given in Appendix 6 (Section 14.5).

The set of ($\bar{X}$, *s*) defines the acceptance region boundary. Details of the “Exact” method are given in Appendix 6 (Section 14.5). An R program (not formally validated) that computes $\bar{X}$ and *s* for $\bar{X}$'s from 83.5% to 116.5% by 0.1% LC is given in Appendix 6 (Section 14.6).

A paper was published [65] that uses a polygon approach that approximates the “Exact” method and is easy to apply. Although the published method applies to passing the second stage of the USP UDU test, the method could also be modified for the overall USP UDU test [46]. More details are given in Appendix 6 (Section 14.7) for the “Exact” test and the polygon approximation.

Method Comparisons

Table 6.3 shows a portion* of the Acceptance Limit tables for the ASTM E2709/E2810 [44], Two-Sided Tolerance Interval and “Exact” approaches using overall confidence levels of 50%, 90%, and 95% to pass the USP UDU test [46] with 95% probability for n’s of 10, 30, and 60. A graphical representation of Table 6.3 is shown in Appendix 6 (Section 14.8).

Table 6.3: Acceptance Table for All Three Approaches (95% probability to pass USP Uniformity of Dosage Units [46])

Confidence Level	Sample Mean (% LC)		n = 10			n = 30			n = 60		
			ASTM E2709/E2810	Two-Sided Tolerance Interval	Exact Acceptance Region	ASTM E2709/E2810	Two-Sided Tolerance Interval	Exact Acceptance Region	ASTM E2709/E2810	Two-Sided Tolerance Interval	Exact Acceptance Region
50	100	100	4.825	5.576	5.893	5.485	5.907	6.018	5.704	5.990	6.047
	101	99	4.549	5.238	5.809	5.226	5.549	5.937	5.477	5.627	5.965
	102	98	4.260	4.900	5.576	4.903	5.191	5.706	5.150	5.264	5.735
	103	97	3.969	4.562	5.242	4.569	4.833	5.371	4.800	4.901	5.400
	104	96	3.677	4.224	4.865	4.234	4.475	4.987	4.449	4.538	5.015
	105	95	3.384	3.886	4.477	3.897	4.117	4.590	4.095	4.175	4.615
	106	94	3.091	3.548	4.088	3.560	3.759	4.191	3.741	3.812	4.214
	107	93	2.797	3.210	3.699	3.221	3.401	3.792	3.385	3.449	3.813
	108	92	2.502	2.873	3.309	2.883	3.043	3.393	3.029	3.086	3.412
	109	91	2.208	2.535	2.920	2.544	2.685	2.993	2.673	2.723	3.010
90	100	100	1.913	2.197	2.531	2.204	2.327	2.594	2.317	2.360	2.609
	100	100	3.211	3.941	4.210	4.479	4.933	5.052	5.002	5.295	5.363
	101	99	3.018	3.703	4.102	4.219	4.634	4.957	4.737	4.974	5.272
	102	98	2.824	3.464	3.865	3.949	4.335	4.713	4.438	4.653	5.031
	103	97	2.631	3.225	3.601	3.679	4.036	4.404	4.135	4.332	4.709
	104	96	2.436	2.986	3.334	3.408	3.737	4.079	3.831	4.011	4.364
	105	95	2.242	2.747	3.068	3.136	3.438	3.753	3.525	3.690	4.015
	105	94	2.047	2.508	2.801	2.864	3.139	3.427	3.220	3.369	3.666
	107	93	1.852	2.269	2.534	2.592	2.840	3.100	2.913	3.049	3.317
	108	92	1.657	2.030	2.267	2.319	2.541	2.774	2.607	2.728	2.968
95	109	91	1.462	1.792	2.001	2.046	2.242	2.448	2.300	2.407	2.619
	110	90	1.267	1.553	1.734	1.773	1.943	2.121	1.993	2.086	2.270
	100	100	2.810	3.520	3.770	4.190	4.669	4.788	4.790	5.103	5.174
	101	99	2.640	3.307	3.656	3.940	4.386	4.689	4.520	4.794	5.080
	102	98	2.470	3.094	3.433	3.690	4.103	4.446	4.240	4.485	4.837
	103	97	2.300	2.880	3.197	3.440	3.820	4.148	3.950	4.175	4.523
	104	96	2.130	2.667	2.960	3.180	3.537	3.842	3.660	3.866	4.190
	105	95	1.960	2.454	2.723	2.930	3.254	3.534	3.360	3.557	3.855
	105	94	1.790	2.240	2.486	2.670	2.971	3.227	3.070	3.248	3.520
	107	93	1.620	2.027	2.250	2.420	2.688	2.920	2.780	2.938	3.184
95	108	92	1.450	1.813	2.013	2.170	2.405	2.612	2.490	2.629	2.849
	109	91	1.280	1.600	1.776	1.910	2.122	2.305	2.200	2.320	2.514
	110	90	1.110	1.387	1.539	1.660	1.839	1.998	1.900	2.010	2.179

*In a full table, the increments for the sample mean would be 0.1% and the means would range from 85.1% to 114.9% LC

Note that the “Exact” method provides higher limits on the standard deviation than any other method.

Example

Suppose one dosage unit is tested at each of 30 locations with a sample mean of 97.3% LC and a standard deviation of 2.5% LC. Using a 90% confidence level and a 95% probability of passing the USP UDU test [46], the acceptance limit for the sample mean would be 3.679%, 4.036%, and 4.404% LC (rounding the 97.3 to 97.0 to be conservative) for the ASTM E2709/E2810 [44], Two-Sided Tolerance Interval, and “Exact” methods, respectively. Since 2.5% is less than any of these limits, the sample passes the acceptance criteria. Therefore with 90% confidence, there is at least a 95% chance that the lot would pass the USP UDU test.

Tiered Approach

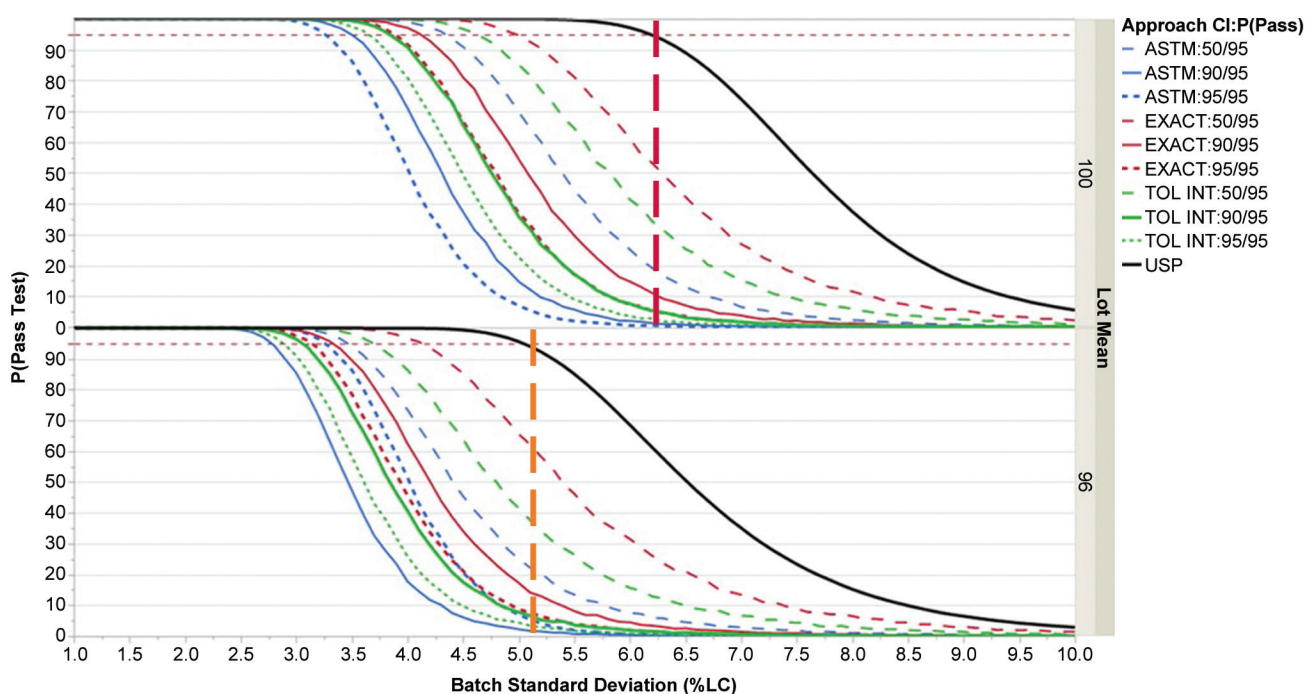
OC curves can be used to evaluate the three approaches using a single tier approach where there is only one set of test results. These curves are useful for choosing a sample size. OC curves and discussion are shown in Appendix 6 (Section 14.9).

Companies may want to use a two-tier sampling plan that mimics the USP <905> test [46], that is, $n = 10$ units in tier 1 and if the tier 1 criteria are not met an additional $n = 20$ units are tested in tier 2 for a total of $n = 30$ dosage units.

Figure 6.8 shows the probability of passing each method for lot means of 100% and 96% LC based on the 2-tiered plan. The x-axis is the lot standard deviation and the y-axis is the probability of passing each approach. Solid, dashed, and dotted lines are at the 50%, 90%, and 95% confidence levels.

For example, the probability of passing the USP UDU test [46] is 95% (vertical reference line) when the lot mean is 100% and the lot standard deviation is about 6.25% LC. The corresponding probability of passing the ASTM E2709/E2810 tiered approach [44] is about 1% using the 90% confidence level. At the 50% confidence level, it would be about 19%. All three approaches are assuring that in the “worst” case, there is at least a 95% probability of passing the USP UDU test.

Figure 6.8: Operating Characteristic Curves for ASTM E2709/E2810, Tolerance Interval, and “Exact” Methods at 50%, 90%, and 95% Confidence Level



Conclusion

The purpose of statistically-based routine release sampling and testing is to provide a high level of assurance that dosage unit uniformity is high throughout the batch, meeting patient needs and regulatory requirements and expectations. The sampling plan(s) and criteria can be established considering:

1. OC curve relationships between PPQ, CPV, and the UDU test [46]
2. Whether a single tier or two-tier sampling plan should be performed
3. Which acceptance criteria should be used for evaluation of CU data

The ASTM E2709/E2810 [44], Two-Sided Tolerance Interval, and the “Exact” acceptance limits can all be used to evaluate CU data. All methods can provide a desired degree of assurance that a sample from a lot will pass the USP UDU test [46].

The ASTM E2709/E2810 method [4] is a standard, the Two-Sided Tolerance Interval acceptance table is the easiest to create, and the “Exact” method provides the largest acceptance limits. The ASTM E2709/E2810 and “Exact” methods require a computer program unless the table has been generated. The acceptance polygon approximation approach is also simple to use.

Although not included in the discussion or OC curves for the three methods, it is recommended that an additional criterion be included: that no CU result can fall outside 75% to 125% LC.

6.4 Dissolution

The specification for immediate release dissolution contains a value of Q and dissolution time point (e.g., $Q = 80$ at 30 minutes). The USP Dissolution <711> test [53] criteria are all relative to the value of Q and are provided in Table 6.4.

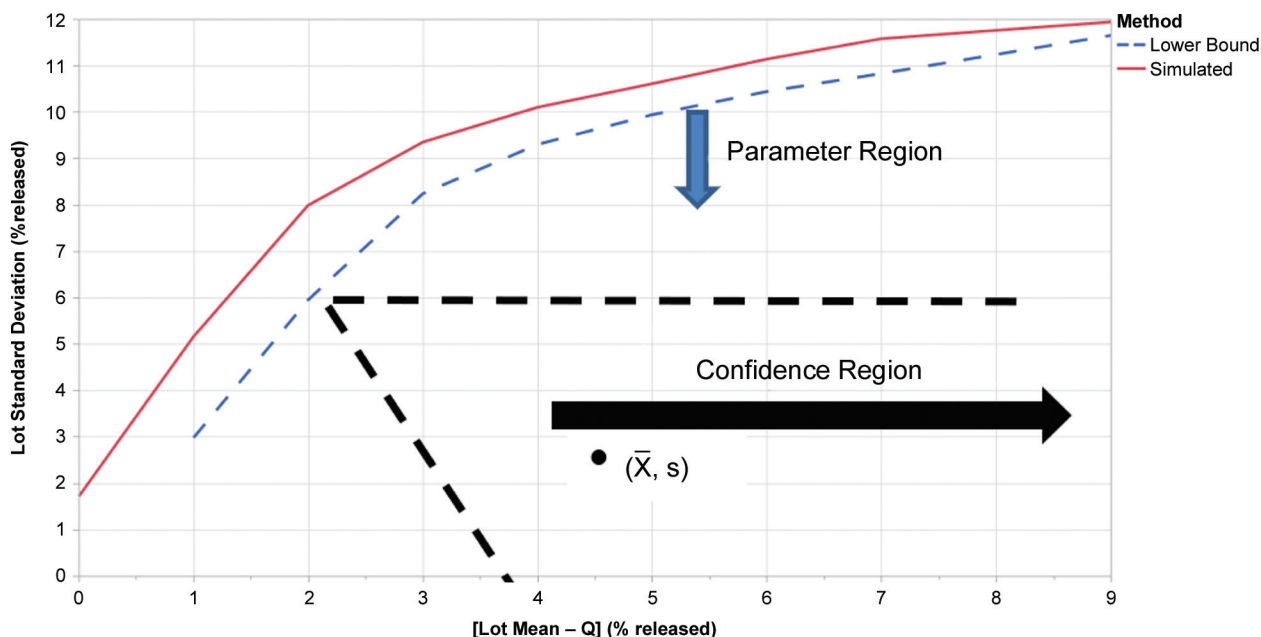
Table 6.4: USP Dissolution Criteria

Stage 1	Test 6 units (Result = % released at specified dissolution time point) <i>Pass if all 6 results $\geq Q + 5$</i> <i>Otherwise go to Stage 2</i>
Stage 2	Test 6 additional units <i>Pass if for all 12 units the following criteria are met:</i> 1) <i>Mean result $\geq Q$</i> 2) <i>No result $\leq Q - 15$</i> <i>Otherwise go to Stage 3</i>
Stage 3	Test 12 additional units <i>Pass if for all 24 units the following criteria are met:</i> 1) <i>Mean result $\geq Q$</i> 2) <i>No more than two results $\leq Q - 15$ with no results $\leq Q - 25$</i> <i>Otherwise fail</i>

ASTM E2709/E2810 [44] can be applied to dissolution immediate release. However, since the criteria for the dissolution test is different from the UDU test [46], all of the mathematics to obtain the lower bound to pass the test must be performed and therefore, the acceptance limit tables change.

The strategy is the same as with CU with one exception. The confidence interval for the lot mean is a lower one-sided interval instead of two-sided since the only way to fail the test is to have low results. A pictorial is given in Figure 6.9 showing the 95% contours for passing the USP Dissolution test based on simulation (thin solid red line) and by calculating the lower bound (thin dashed blue line) on passing the USP Dissolution test [53].

Figure 6.9: Pictorial of the ASTM E2709/E2810 Methodology Applied to Dissolution



Since the probability of passing the USP Dissolution test [53] only depends on how far the “true” lot mean is above Q , the x-axis is the difference between the lot mean and Q . The y-axis is the “true” lot standard deviation. The thin solid red line is the contour line where the probability of passing the USP UDU test [46] is at least 95%. Any point below the thin solid red line is in the parameter region meaning that any point in the region has greater than a 95% probability of passing the USP Dissolution test. The thin dashed blue line is the lower bound on passing the USP Dissolution test.

Any combination of batch means and standard deviations below this contour has at least a 95% chance of passing the USP Dissolution test. A 50% contour would lie above the 95% contour and a 99% contour lie below the 95% contour.

Based on statistics from a random sample or a systematic sample using Sampling Plan 1, the mean, $\bar{X}$, and standard deviation, s , are calculated and are also shown in Figure 6.9. Based on the sample mean and standard deviation, a joint confidence interval [61] is generated for the lot mean and standard deviation that is represented by the bold dashed black line.

Therefore, if the confidence interval at the desired confidence level is completely contained under the thin dashed blue line, then with the desired confidence, there is at least a 95% chance that the batch will pass the USP Dissolution test [53].

The point in the confidence interval with the lowest probability of passing the USP Dissolution test [53] is always at the vertex. The set of all sample means and standard deviations for a given sample size whose vertex fall on the thin dashed blue line forms the boundary for the acceptance region.

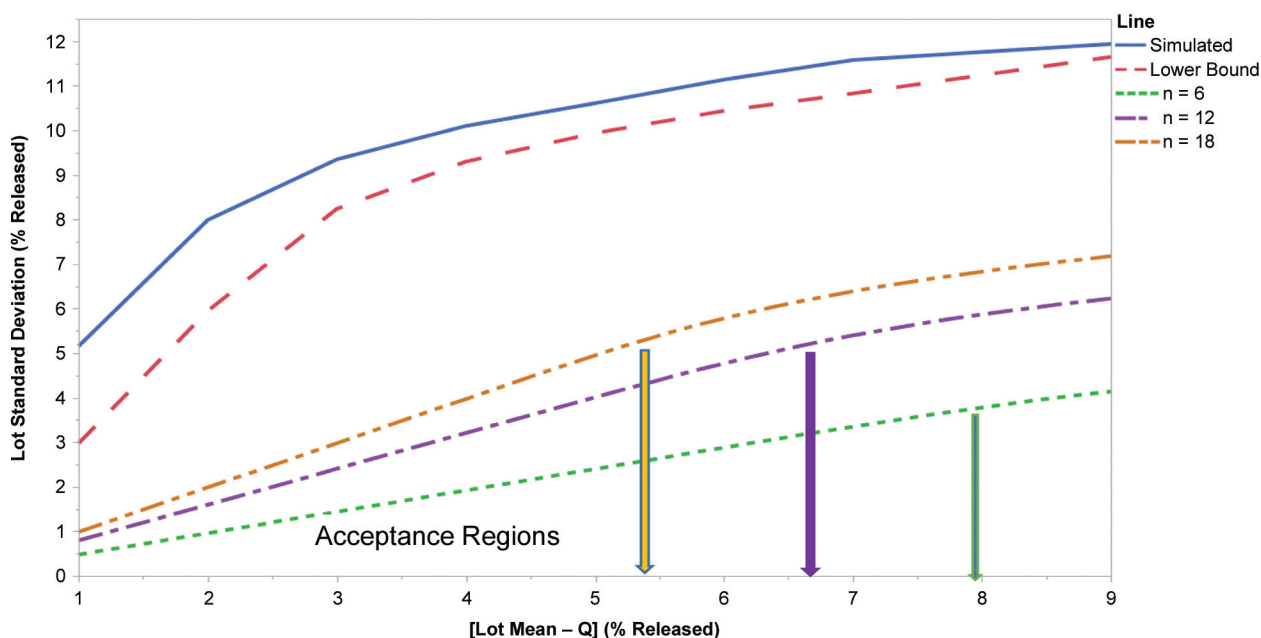
Any combination of sample mean and standard deviation on the acceptance region boundary generates a confidence region at the parameter region boundary. Acceptance regions for $n = 6, 12$, and 18 are shown in Figure 6.10. Any point falling in the acceptance region has, with the desired confidence level, at least a 95% probability of passing the USP Dissolution test [53].

The points on the acceptance region boundary are the points used to construct an acceptance limit table. An acceptance limit table for various sample sizes is given in Appendix 6 (Section 14.11).

The acceptance limits for dissolution are very conservative; therefore, other methods may provide wider limits. One approach is to simulate the probability of passing the USP Dissolution test [53] based on the vertex values for the lot mean and standard instead of using the lower bound calculation. A Bayesian approach may also provide an improved set of acceptance limits.

Acceptance Limit tables for Sampling Plan 2 can be constructed but are not included in this document.

Figure 6.10: Acceptance Regions for Dissolution Sampling Plan 1 (n = 6, 12, and 18)

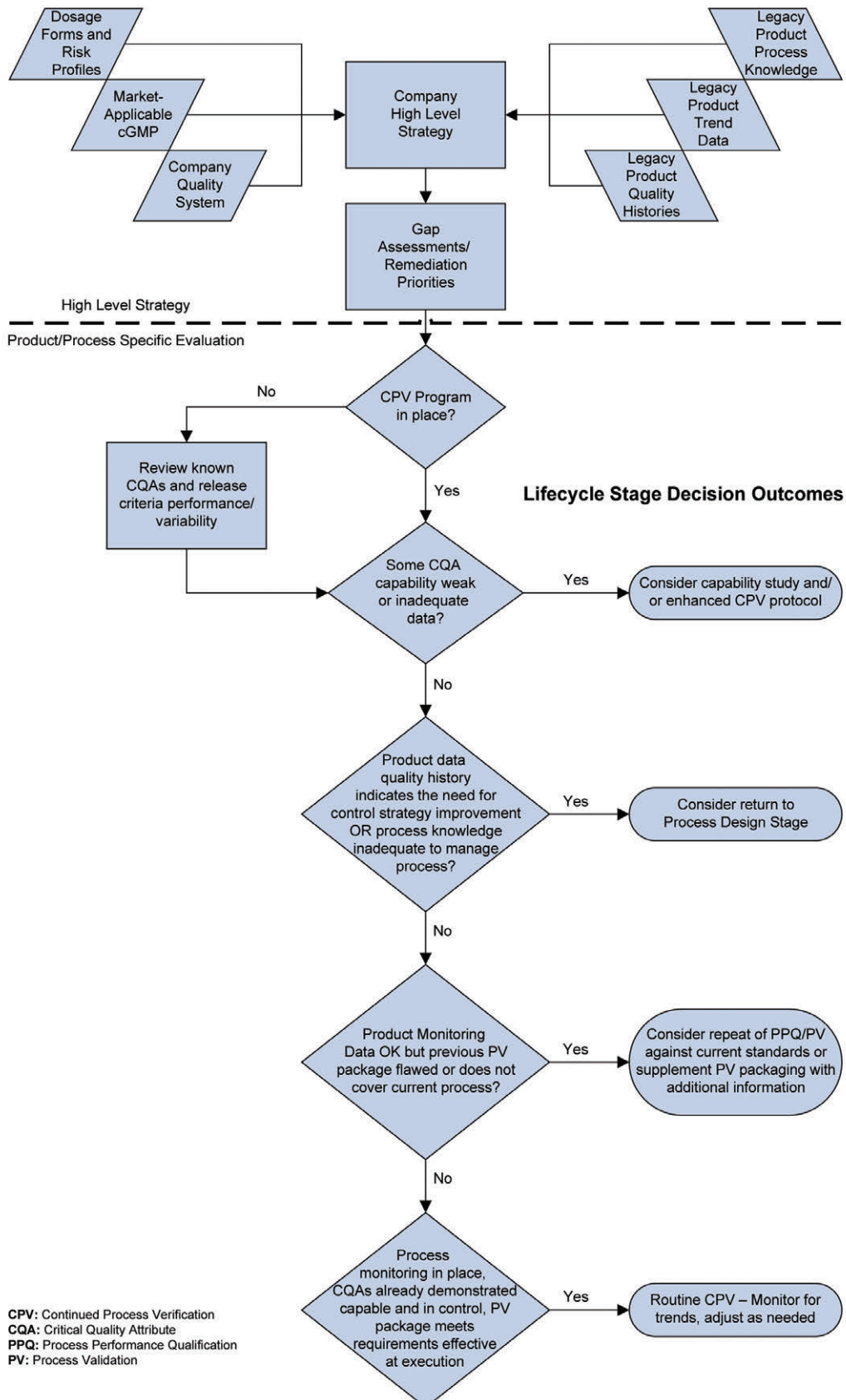


Acceptance tables may also be developed for extended release using ASTM E2709 [58] but are not included in this document.

6.5 Evaluate Legacy Products for Heightened Monitoring/Testing Need

Legacy products require a completed PV to ensure processes have the appropriate level of control to provide customers with products that comply with specifications. The steps to evaluate legacy products' need for heightened monitoring/testing are shown in Figure 6.11.

Figure 6.11: Heightened Monitoring Evaluation Steps for Legacy Products [33]



Step 1 – Create/review company high-level strategy for legacy products.

Step 2 – Perform a gap assessment of the legacy products list to determine remediation priorities.

Step 3 – Begin product-specific evaluation by checking the legacy control strategy against the CPV to confirm process/data is in place so that CQA and release criteria can be evaluated against product process performance and variation. If not, establish a CPV program.

Step 4 – Perform capability test to check CQA data against CPV requirements. If insufficient data exists, perform product process capability study or execute a CPV protocol to gather data and ensure process control.

Step 5 – If the data shows that process is not capable, go back to process design phase data and evaluate CPP/CQAs. Identify process steps/equipment that may cause increased process variation.

Step 6 – Evaluate monitoring/sampling system to determine if data collection steps are sufficient to provide a true view of critical process step capabilities and controls. Add increased monitoring/sampling to PV plan to remediate gaps.

Step 7 – Check designed process against actual process to confirm current process represents what is filed. Meet with regulatory team to discuss impact of changes and revise PV plan to include process changes and evaluate effect on control strategy. Execute PV if there is insufficient data to demonstrate control.

Step 8 – Move to routine CPV once CQA data demonstrates process control and process monitoring sufficiently demonstrates that effective controls are in place.

6.6 Periodic Review and Revalidation

The principles contained in FDA PV Guidance [3] and Annex 15 [11] are consistent with enhanced process understanding, increased use of risk management in the pharmaceutical industry, and continual improvement as outlined in ICH Q8(R2), Q9, and Q10 [1, 2, 6].

Additionally, technology available for process monitoring and control has significantly advanced in recent years. While ongoing monitoring and periodic heightened testing represents a superior approach by assessing process health in a timelier fashion, periodic revalidation should still be considered.

Frequency of revalidation should depend on the rigor of the CPV program, including the frequency and thoroughness of within and between batch variability evaluation. While a between batch variability assessment likely occurs much more frequently than annually, heightened within batch testing should occur at least annually and be coordinated in advance of the APR, within which a statement of validation status should be made.

Even with a thorough CPV program, challenging of the process with worst-case extended control strategy variables such as different operators and shifts, worst-case hold times, worst-case material variabilities (as feasible) and laboratory variabilities at least once every three to five years is recommended.

Following evaluation of challenge batch results, the validation package should be updated with yearly evaluations back to the last full revalidation and the results of the challenge batch.

In determining whether or not revalidation is warranted, statistically-based routine results should also be considered. Where rigorous statistical standards are applied for within batch variability prior to the release of each batch, heightened within batch testing may not be periodically required when batches meet routine batch tier-one criteria. If batches regularly require additional testing and/or application of second-tier criteria, then revalidation should be considered.

It is also recommended that in the decision to revalidate or conclude a validated state is being maintained, a risk assessment be completed annually and the results and associated priorities updated in the VMP.

These risk assessments can be completed by use of an excel-based risk assessment (see Figure 6.12), and should include:

- Age of the validation packages
- Number of process-related deviations that year
- Product volume
- Number of equipment changes
- Type of dosage form
- Product strength
- Whether or not the existing validation package meets contemporary standards
- Batch rejections
- Assay qualification status
- Data trends

The risk tool should include the rationale for the categories included and the scoring system. Process risk assessment results should be considered in conjunction with the results from the within batch heightened testing results and the inter-batch variability assessment.

It should be noted that revalidation never solves any process control issues; remediation needs to take place prior to revalidation.

Figure 6.12: Example of a Validation Risk Ranking Assessment Tool

Validation Criteria	Risk Level	Risk Points	Rationale	Product 1		Product 2		Product 3		Product 4		Product 5	
				Score		Score		Score		Score		Score	
Age of validation < 5 years?	H	No = 5	A	No	5	Yes	0	No	5	No	5	Yes	0
Manufacturing in last 18 months?	H	No = 5	B	No	5	Yes	0	Yes	0	Yes	0	No	5
Yearly confirmation batch (or validation less than one year old)?	M	No = 3	C	No	3	No	3	No	3	No	3	Yes	0
Dose > 5 mg/dosage unit?	M	No = 3	D	No	5	Yes	0	Yes	0	Yes	0	Yes	0
Dosage form?	H	Oral = 0 Parenteral = 5	E	Parenteral	5	Oral	0	Oral	0	Parenteral	5	Oral	0
Volume < 12 batches/year?	M	No = 3	F	No	3	No	3	Yes	0	No	3	Yes	0
< 3% batches produced have level 2 – 3 (process related) deviations?	H	No = 5	G	No	5	Yes	0	No	5	Yes	0	Yes	0
Batch rejection rate < 0.5% (process related)	H	No = 5	H	No	5	Yes	0	No	5	Yes	0	Yes	0
Process validation meets key elements of contemporary standards?	H	No = 5	I	No	5	Yes	0	Yes	0	Yes	0	Yes	0
Assay method qualification meets current standards?	L	No = 1	J	No	1	Yes	0	Yes	0	Yes	0	Yes	0
Number of equipment change requests since last validation?	0 to 2	L = 0	K	> 5	5	0 to 2	0	0 to 2	0	3 to 5	3	0 to 2	0
	3 to 5 = M	M = 1											
	> 5 = H	H = 5											
Score = overall process risk (not additive)		Total		Score	23.5	Score	3	Score	9	Score	9.5	Score	2.5
Validation Priority:	No Action (0 – 3)			High		No Action		Medium		Medium		No Action	
	Low Priority (4 – 6)												
	Medium Priority (7 – 14)												
	Moderate Risk (15 – 19)												
	Intermediate Revalidation (20 – 25)												
Suggested Priority					1		4		3		2		

6.7 Report: Frequency, Recommendations for Further Actions, Relevance with Annual Product Review

A key element of CPV is that the routine product reviews occur in as “real time” a basis as possible. The review discussions should include process performance evaluations, potential process-related customer complaints, stability performance, and deviation-prevention effectiveness, with action plans and follow-up for any mid to high-level concerns. Rapid awareness of product concerns helps to ensure timely resolution of potential issues prior to impacting patient supply.

Both the events and actions from routine product reviews should be captured in a documented form that ensures awareness of any issues, actions, or both by key stakeholders such as quality and operations.

Depending on production volumes, formal documentation of these reviews and action endorsement could vary from the issuance of periodic reports (possibly bi-annual for mid to high-volume products) summarizing performance, to approval of meeting minutes by key stakeholders where CPV reviews and discussions take place, with more formal documentation via reports issued only as part of the APR.

As mentioned earlier, it is recommended to leverage CPV data analysis and trending for the process performance review portions of the APR. The occurrence and conclusions of any statistical trend outliers identified as part of CPV and periodic team reviews should be tracked and recorded for use as part of the APR. Maintaining a summary of this information eliminates the need for rework in this area and avoids conducting the same process investigations significantly after the event has occurred.

7 Contract Manufacturing

Many companies are turning to Contract Development Organizations (CDOs), CMOs, and/or Contract Packaging Organizations (CPOs) to develop and manufacture their products. One site may provide all services (CDMPOs), or several contract sites may be used to produce one product. The type of companies who are contracting work range from virtual companies (with all of their manufacturing and development activities outsourced) to large companies that use CDMPOs to augment their internal capacity, or as a risk mitigation strategy.

CDMPOs may be responsible for a portion of the product lifecycle or be involved from initial development to commercial launch. As PV in the current paradigm encompasses development of the design space through demonstration of process control throughout the product lifecycle, the CDMPO industry should be active participants in the PV process no matter what portion of the product lifecycle they directly impact. These organizations need to be knowledgeable in all aspects of the PV lifecycle so they can meet their client's long-term goals.

While the license holders are ultimately responsible for the products' adherence to the current regulatory expectations surrounding PV, it is important that CDMPOs have well-defined programs and the skills and knowledge to execute.

Example case studies are described in Appendix 4.

7.1 Contract Development, Manufacturing, and Packaging Organizations and License Holder Relationship

The significance of the relationship between the CDMPO and license holder(s), including partners, cannot be understated. Creating a partnership between all parties ensures that everyone is working toward a common goal with the end user, the patient, always in mind. It is essential to establish clear expectations at the beginning of a project. This may include exchanging procedures and templates, and both parties should be able to freely share information to maximize the potential for success.

When using multiple contracting organizations, it is important to consider how the different organizations will communicate. The ability to have multi-party confidentiality agreements to maximize communication is a best practice. It is particularly important that information from Stage 1, usually generated by a CDO or at an internal site, is clearly communicated to those who will be responsible for later stages of manufacturing. In addition, knowledge of small scale and clinical batch manufacturing is very helpful when determining the number of batches to be manufactured in Stage 2 and determining the potential enhanced sampling required in Stage 3.

7.2 Maintaining Compliance while Ensuring Flexibility

One of the most important attributes of a successful CDMPO with respect to PV is the ability to be flexible enough to meet the needs of all clients while maintaining the ability to have a consistent and defensible program. CDMPOs should have policies in place that outline the minimum requirements for performance at all stages of PV but should allow flexibility within the bounds of regulatory expectations to ensure that they best meet the needs of their clients.

7.3 Best Practices in Stage 1

During Stage 1, the process design is defined. The difficulties that many contract organizations face is that the expectations for defining design and developing products can vary widely by their clients. Some clients will expect a significant number of experiments, stability data, and documentation, while some may have very little to no data and are not able to invest significant resources to generate this data.

For example, when manufacturing generic or legacy products, the amount of data available may only be a batch record from a previous manufacturing site. However, the products are still important to the patient population relying on them, and a minimum standard needs to be defined related to how much data is required to ensure the manufacturing process will produce a consistent product.

If a CDO is used to generate Stage 1 data, this contracting organization should have general knowledge about the planned manufacturing site. Some of the important attributes to consider include what equipment will be used, the basic process flow at the manufacturing site, and the planned technical capabilities of that site. If this information is understood up front, then the development organization can generate experimental designs that provide relevant data to the future manufacturing process.

However, the commercial manufacturing site is often not defined at the start of development. One approach is to have a product-specific control strategy that outlines the CQAs, process parameters (all classifications), and in-process and final product controls required to effectively manufacture the product, and then match these requirements with the manufacturing site. If this approach is taken, then it is important to understand the common equipment and technical capabilities of most manufacturing sites to ensure that the design will not limit manufacturing site choice.

Another approach is to utilize a Contract Development and Manufacturing Organization (CDMO) that would develop the process and manufacture the product at the same site. In this scenario, the development scientists generally have systems designed with the manufacturing process in mind. It is also important, in this case, to document the development activities and define how the developed process will ensure the product manufactured meets all desired quality attributes.

Using a control strategy or Quality Target Product Profile (QTPP) document, the CDO or CDMO should clearly articulate all process steps, the critical attributes of each step, and how control is achieved to the CMO and CPO. A review of raw material requirements and expected controls (including excipients, containers, and disposables) should also be included in the control strategy.

This control strategy should reference all studies performed in support of the product design. Having a single document that references all data related to product development is helpful during subsequent regulatory audits to demonstrate that the process and product knowledge has been captured and that an adequate design was determined.

For new products, performing process-specific risk assessments before manufacturing batches for PPQ is useful to ensure that the manufacturing process is capable as designed to meet the parameters determined in development and documented in the control strategy.

For site transfers, performing a process-specific risk assessment is also appropriate to augment the control strategy and demonstrate how the local process compares with the product being transferred. If the product is a technical transfer or is being manufactured at another site, generating a comparability report at this stage can also help with later regulatory filing.

While transferred products may already be developed, it is important to perform some development studies during site transfer that could impact the product at scale. For example, product hold or mixing studies at scale should be considered prior to moving into Stage 2 at scale at each site of manufacturing. The CDO and CMO sites, as applicable, should have procedures in place that describe how these types of studies are performed and should be able to provide evidence that the program is ready to incorporate this data into the control strategy.

Analytical development and method qualification should be completed prior to proceeding to Stage 2. Mapping the testing sites and documenting a list of sampling requirements plus shipping and storage requirements prior to starting Stage 2 is considered a best practice.

In cases where clinical manufacturing, initial registration, and stability batches are done at one facility and validation and commercial launch at another facility, attention to detail when documenting data in Stage 1 and any other batches prior to validation will increase the chance of success after site transfer.

7.4 Best Practices in Stage 2

The expectations of Stage 2 PV are generally the same for CMOs, CPOs, and internal site manufacturing organizations. However, contract organizations have some unique challenges as they are often manufacturing a greater number of different processes on the same equipment than an internal manufacturing site, providing services to clients with different expectations and procedures.

A VMP summarizing all the activities to be performed and a high-level rationale for strategy decisions is often helpful. This document can describe bracketing, matrixing, or family approaches and the rationale for the total number of batches to be manufactured. In the situations where concurrent activities are being performed, such as completing filter validation, PPQ batch manufacturing, packing qualification, and shipping studies simultaneously, the VMP is a good tool to wrap all of these activities together and provide one consolidated overview of the product qualification approach.

All PV activities should be summarized in a report. For complicated strategies in which multiple protocols and reports are generated, it may be useful to generate a master validation report summarizing all completed activities in addition to the process report. For large validation exercises it may also be appropriate to have multiple validation plans. For example, in an oral solid dosage process there could be a plan for granulation, one for compression, and one for coating. The site-specific procedures or VMP should define the requirements for reporting.

Robust documentation confirming site readiness prior to PPQ batches is a best practice and is especially important at a contract manufacturing site where customers may not have ready access to non-client specific documentation.

The readiness document should include an evaluation of the qualification status of all equipment, facilities, utilities, and methods to ensure all product-specific and non product-specific items are in a qualified state in alignment with the product's requirements, in addition to the general requirements in place from the contract manufacturer. As CMOs often have many activities going on at the same time, it is important to confirm that a comprehensive review of a product's requirements is performed considering all other ongoing activities, including any product change-over requirements, as CMOs are almost always processing multiple products on the same manufacturing lines.

One of the unique challenges faced by a CMO is protocol generation, given the different requirements, terminology, and expectations from each client. The operators performing the tasks are less likely to make errors if documentation is consistent, but clients are often looking for customized solutions. A best practice is defining a template protocol that can present consistent information to operators, while allowing flexibility in content to support clients.

The completion of PPQ batches is often a prerequisite to filing the product, so it can be an activity that is requested to be expedited. A best practice is defining a consistent project schedule that can be used for planning as well as providing the contracting site with sufficient time for report generation and review. Quality of information and robust evaluation of data to ensure conclusions are logical and based on fact cannot be risked in an effort to achieve a timeline; therefore, up-front planning is critical.

Another best practice when writing PPQ reports includes referencing the Stage 3 plan.

PPQ is most frequently used to describe the process of ensuring the consistency of product manufacturing and placement into a primary container. When the primary container is then further processed to include a device, performing PPQ of the packing process is also considered a best practice, in which case a CPO should have a documented strategy to support their customers.

While the CPO may not need to complete a formal PPQ process for a manufacturing process that only requires the primary container to be cartoned, the CPO should have a strategy that defines when PPQ is required for packaging activities.

7.5 Best Practices in Stage 3

Stage 3 PV is an important tool for ensuring that product manufacturing remains in control.

The role of contracting organizations, specifically CMOs and CPOs, in the CPV process may not be well defined; however, best practices include sharing information across sites (for example, CMO and internal site, multiple CMOs, separate CDO, CMO, and CPOs). This allows for appropriate actions to be taken to ensure the process remains in control and the product continues to consistently meet all defined quality attributes.

One best practice related to CPV is to make certain that the CMO includes specific information in the quality agreement as to who is responsible for execution of the CPV program.

The CMO should have a defined program that specifies how they will administer a CPV program if responsible, and if not responsible, how they will respond to information provided by the responsible party.

The quality agreement should require that information related to trends is shared.

The contracting organization (CMO or CPO) should have the ability to include additional sampling to support Stage 3.1, if required. It should have a defined mechanism for removing this additional sampling when no longer needed and to tighten control parameters as the data demonstrates that this is desirable.

The contracting organization should understand what is critical to a process, what should be monitored, and how the data should be analyzed. The CPV system should allow flexibility in the reporting period and the types of data to be collected, while having defined minimum standards. Additionally, the CMO or CPO should have qualified professionals on staff to support statistical analysis of data.

The CPV program should be designed to be proactive and have mechanisms by which to facilitate interaction with other sites in the product's supply chain that may contribute to the findings or benefit from the information.

APRs should also be performed either by the Contract Manufacturing and Packaging Organization (CMPO) or the license holder in partnership with the CMPO, and a best practice would include a description in the quality agreement of how the CPV and APRs work together. APRs may cover multiple sites and facilities as well and the CMO should have processes in place to support multisite APRs if needed.

7.6 Stage Gate Processes

One useful tool when working with a CDMPO is to have a stage gate process in place where the responsibilities for specific deliverables are defined. These deliverables should encompass all stages of the PV that will be performed at the CDMPO and ensure that specific time-bound reviews of progress occur.

As a part of the stage gate process, the first step is to agree on roles and responsibilities. An example RACI is provided in Figure 7.1.

Figure 7.1: Example Stage Gate Process RACI (Responsible, Accountable, Consulted, Informed)

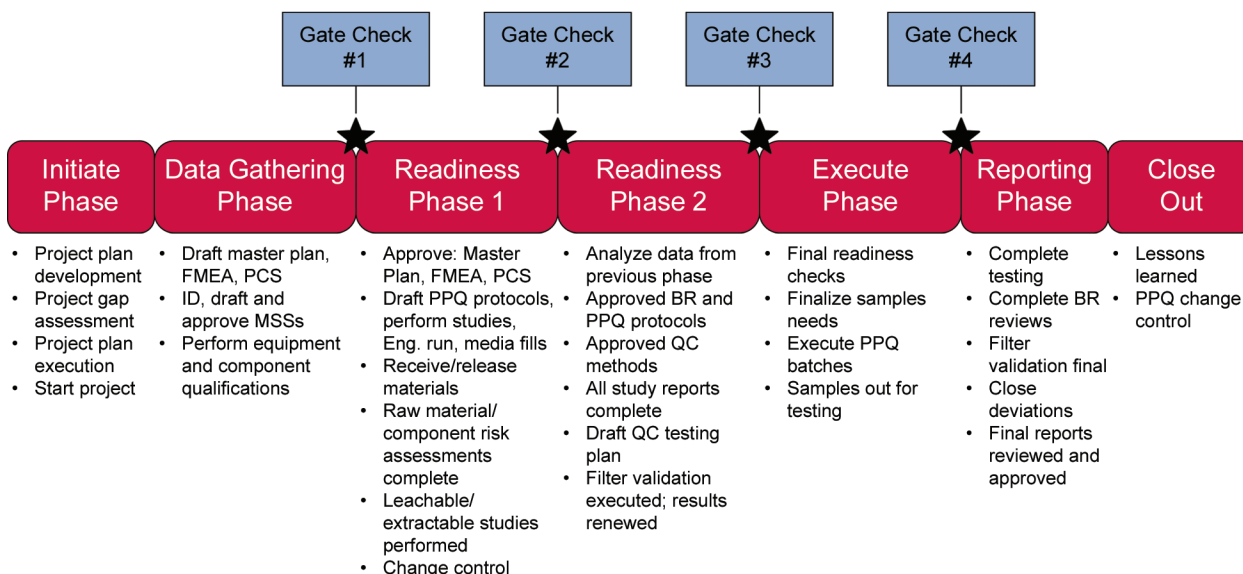
		Project Leadership (Management)										Project Team Members (CDMO-execution team)										Project Team Members (CDMO-execution team)					External Resources						
Project Deliverable (or Activity)	Role	Executive Sponsor	Project Management	Technical Services	PD Management	Operations Management	Validation Management	QA	Regulatory	BD	QC	Project Manager	PD	Technical Services	Process Validation	Operations	QA	Regulatory	Process Engineering	QC	Project Manager	Executive Team	QA Rep	Ops Rep	Analytical Lead	Technical Lead	Client Consultant	Third Party	Partner Consultant	Contract Lab	Role #5		
Plan Phase Activities																																	
Development Studies		I		I	A		I	I				I	R	I	I			I				A	I	I		I	I						
• Validation Master Plan (general)		I	I	C	I	C	A	C	C	I	C	I	I	I	R	I	I	I	I	I	I	I		I	I	I	I	I					
• Business Risk Assessment (strategy)		A	R	I	I	I	I	I	I	R	I	R										A	A	I	I	I	I						
• Client. Specif. Validation Master Plan		I	I	C	I	I	A	C	I		C	I	I	I	R	I	I	C	I	I	I	I	I	C	I	I	C						
• Technical Hand-Off Package 1		I	I	A	I	C	C	C	I		C	I	R	R	R	I	I	I	I	I	I	I	I	C	C	C	A						
- Gap Analysis		I	I	A	I	I	I	I	I	I	I	I	I	R/C	C	R/C	C	I	C	C	C	I	I	C	R	C	R						
- Leachable/ Extractable Survey/RA														R	I				C		A	I				R							
- Leachable/ Extractable Study												I		I	I		I	I	I		A	I						R					
- Technical Risk Assessment/ Control Strategy (summary of CPP/CQA)/ Process Description Flow Diagram		I		A		C	C	C	C		C	R	I/R	R	R	R	C	I	C	I	I	I	C	R	C	A							
- Filter Validation												I		I	C	I	I				A	I				C		R					
- Develop/Clinical study data				I	I	I	I	I	I		I	I									A	I											
Execute Phase I Activities																																	
• Verification Study Protocol Generations (lab scale)					A							I	R	C	I			I	I	I	I		C	C	C	R							
• Verification Study Protocol Generations (production scale)						I	A					I	I	C	R	C	C	C	C	C/I	I		C	C	C	R							
• PPQ Protocol Draft 1						C	A	C	I		C	I		I	R	I	I	I	C	C	I		C	C	C	R							
• ENG Batch Records				A		C	I	I	I		I	I		I	R	I	C	I	C	C	I		C	C	C	A							
• Clinical Batch Records				A		C	I	C	C		I	I		R	C	C	C	C	C/I	C	I		C	C	C	A							
• Technical Hand-Off Package 2		I	I	A		C	C	C	C		C	R	I/R	R	R	R	I	I	C	I	I	I	C	R	I	A							
• Readiness Protocol						C	A	I	C		I	I		C	R	I	C	I	C	C	I		I	I	I	I							
R = Responsible = person who performs an activity or does the work (number indicates which item area is responsible for) A = Accountable = person who is ultimately accountable and has Yes/No/Veto. Try to limit the "A"s for one activity to one role. C = Consulted = person that needs to provide feedback and contribute to the activity I = Informed = person that needs to know of the decision or action (communication with this group is usually 1-way in nature, "Need to know")																																	

Figure 7.1: Example Stage Gate Process RACI (Responsible, Accountable, Consulted, Informed) (continued)

		Project Leadership (Management)								Project Team Members (CDMO- execution team)								Project Team Members (CDMO-execution team)					External Resources										
Role		Executive Sponsor	Project Management	Technical Services	PD Management	Operations Management	Validation Management	QA	Regulatory	BD	QC	Project Manager	PD	Technical Services	Process Validation	Operations	QA	Regulatory	Process Engineering	QC	Project Manager	Executive Team	QA Rep	Ops Rep	Analytical Lead	Technical Lead	Client Consultant	Third Party	Partner Consultant	Contract Lab	Role #5		
Project Deliverable (or Activity)		Execute Phase II Activities																															
		• Engineering Batch Execution			C		A					I		R	I	R	I		C	C	I		C	I	I	A							
		• PPQ Protocol Final Draft			C		C	A	C	C		C	I		I	R	I	I	I	I	I	I		C	I	I	C						
		• Technical Hand-Off Package Final	I	I	A		C	C	C	C		C	R	I/R	R	R	R	I	I	C	I	I	I	C	R	I	A						
		• Concurrent at scale Study Protocol			I		C	A	I	I		C	I		C	R	I	C	C	I	I/C	I		C	I	I	C						
Pre-Execution Phase Activities																																	
• Readiness Protocol Execution	I	I	I		C	A	C	I		C	I		R	R	R	R	I		R	I	I	I	I	I	I								
• Pre-PPQ batch Dry-Runs/Ops walk throughs			I		A	I	C	I		C	I		R	I	R	R	I	C	I	I		C	C	I	C								
• Concurrent at scale Study Execution			I		A	I	C	I		C	I		C	C	R	C	I	C	I	I		C	C	I	C								
• PPQ batch Execution	I	I	I		A	I	C	I		C	I		C	C	R	C		I	R	I	I	C	C	I	A								
Close Phase Activities																																	
• Create Lessons Learned	I	I	I		I	I	I	I	I	I	A		C	C	C	C	I	I	C	A	I	I	I	I	I								
• PPQ Report	I	I	I		C	A	C	C		C	I		I	R	I	I	I	I	I	I	I	C	C	C	C								
• CPV Plan	I	I	C		C	A	C	C		C	I		I	R	I	I	I	I	I	I	I	C	C	C	A								
R = Responsible = person who performs an activity or does the work (number indicates which item area is responsible for) A = Accountable = person who is ultimately accountable and has Yes/No/Veto. Try to limit the "A"s for one activity to one role. C = Consulted = person that needs to provide feedback and contribute to the activity I = Informed = person that needs to know of the decision or action (communication with this group is usually 1-way in nature, "Need to know")																																	

Next, the specific deliverables are often outlined in a product schedule with predecessor and successors clearly identified. Highlighting specific deliverables that are critical to the project's success can then be translated into a formal stage gate process where strategic check-ins occur. An example of a stage gate process for a product being transferred to a new manufacturing site after the development work has been completed is provided in Figure 7.2.

Figure 7.2: Example Stage Gate Process for Product Transfer



Following a stage gate process will ensure that nothing is missed and that the project teams are on track. Ensuring project documentation is complete early, data analysis from previous batches are effectively studied, and robust operator training is complete increases the chance of success and reduces misses throughout the process.

Contracting organizations often have significant experience with PV as they frequently manufacture many different products. Using RACI and stage gate tools makes sure that any complexity in the supply chain, which is inherent when working with multiple organizations, is well managed. Each contract manufacturer should define the activities required at each gate based on site-specific procedures.

7.7 Regulatory Audit Expectations

Once Stage 2 activities are completed successfully, often there is a period of time when all parties are jointly preparing for filing and eventual commercial launch. While the license holder is ultimately responsible for the product filing, it is an expectation that during the Prior Approval Inspection review, the CDMPO can clearly articulate information related to all stages of PV, even if they are only responsible for one piece.

This is specifically true for CMOs, which most frequently own the Stage 2 process. Ensuring that all development activities are clearly documented, linked to the final production process, and understood at the manufacturing site is an important aspect of audit preparedness.

7.8 Contract Development, Manufacturing, and Packaging Organizations – Specialized versus One Source Models

Contracting organizations can specialize in one attribute of the manufacturing process or provide services to meet the needs of some or all manufacturing activities. This is applicable to the PV design as the more product transfers that occur, the more carefully knowledge transfer should be planned.

The benefit of a specialist may be added capabilities and/or increased focus on a particular attribute of the product lifecycle.

An organization that is able to develop, manufacture, and package provides the ability to streamline processes and improve communication. This can result in reduced supply chain complexity and the ability to share data more freely.

8 Change Management

8.1 Change Management Principles

The principles of an effective change management system apply regardless of the stage within the product lifecycle.

In the development phase, a change management system is necessary to evaluate and implement changes, for example, from resolution of troubleshooting exercises.

Where a pharmaceutical system is required to support products and processes developed using an enhanced, QbD approach and the principles described in ICH Q8(R2) [1], an effective change management system is essential. Section 3.2.3 in ICH Q10 [6] describes items for inclusion in the change management system in relation to the stage in the lifecycle, such as:

- The potential impact of the change using QRM tools
- Evaluation of the proposed change by SME
- Evidence that the change objectives were achieved

The GMP requirements must be met regardless of the stage of the lifecycle or whether the product and processes have been developed using minimal or enhanced, QbD approaches. GMP requirements usually include:

- An SOP that describes the approach to evaluation, approval, and implementation of the proposed change, and confirmation that the change was effective and did not have negative consequences
- Clear accountabilities for all change management activities
- Prioritization of urgent and important changes (e.g., a corrective or preventive action)
- With regard to change management, the quality unit should:
 - Ensure that a change management system is established
 - Approve or reject proposed changes
 - Audit the impact of changes post implementation

The change management process requirements become more defined as products move from development to qualification and lifecycle continued verification stages. The process needs to assure the safety, efficacy, and quality of the product that results from the change.

The extent and depth of the application of the change management principles can vary according to the stage in the lifecycle where the change is proposed. For example, there may be less rigorous application of these principles during development, particularly during early stage development, than in commercial manufacture.

8.1.1 Change Management System Model

ICH Q10 [6] defines change management as:

“A systematic approach to proposing, evaluating, approving, implementing and reviewing changes.”

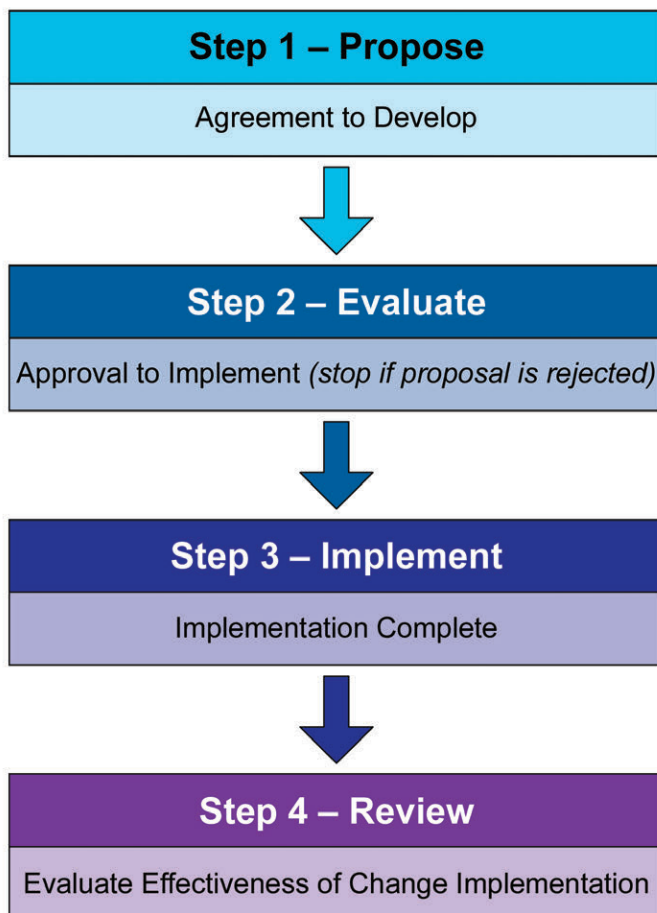
This description makes clear that the scope of change management is broader than the scope of change control, which is described in ICH Q7, Section 13 [66]. “Change control” often refers to the execution step of an individual change, whereas “change management” is a more systematic holistic approach to the review and management of a portfolio of changes and the change process, including all components of “change control.”

In an ICH Q10-based [6] Pharmaceutical Quality System, change management applies to the entire product lifecycle. Additionally, if an organization chooses to operate an ISO 9001 system [67], the change management system could include elements not covered under ICH Q10 [6] or GMP, for example, changes to business processes.

The high-level model described in this section is adapted from the definition of change management and the four steps described in ICH Q10 [6] (see Figure 8.1). Each step ends with either a gate or a decision point, which should be completed before proceeding. This section also provides further information on each step within the model.

Following these steps is considered an effective way to ensure that proposed changes are evaluated and implemented effectively. It may be necessary to return to an earlier stage, for instance, if the benefits of implementation are not fully realized. The level of formality of application of these steps can vary depending on the stage in the lifecycle, see below.

Figure 8.1: Step and Gate Model for Change Management [9]



8.1.2 Change Management in the Product Lifecycle

Change management needs to be utilized throughout the product lifecycle process as a way to communicate and manage changes in a documented manner. The initial step during this process is to define a product control strategy, including raw materials, utilities, facilities, equipment, and procedural controls. As the process evolves, the control strategy should be refined.

The control strategy will act as a way to identify which developmental data can be used to determine the process control state. For example, certain facilities implement design control early in the process, which allows data to be utilized later. Other sites do not utilize change control until after the process is qualified, and therefore development data is suspect and probably will not be allowed.

Changes in the control strategy may affect the state of process and product control.

8.1.3 Change Management of Design Space and Control Strategy

It is important to use change management in the development phase to facilitate knowledge transfer and ensure appropriate controls are in place. Each step identified as part of the control strategy needs to be defined as early as possible so team members know what changes were tested and how they were developed.

At a minimum, process changes during development need to be recorded in a development notebook. A better approach is to utilize protocols or batch records that define what process controls are implemented during the design phase as well as the status of raw materials used.

QA review and approval of records may be required if batches are used in a GMP environment.

8.2 Changing Manufacturing Sites

The steps for changing a manufacturing site, such as expansion to another site within the company or performing a transfer to a CMO, are detailed the *ISPE Good Practice Guide: Technology Transfer* [41].

The steps for identifying the effect of changing manufacturing sites on the validated state begins with initiating a change control as indicated in Section 8.1.2. The change control process should include a process risk assessment to determine the impact to the CPPs and CQAs of any process step changes.

Typically manufacturing site changes include component or raw material changes that need to be reviewed. It is recommended to keep changes to a minimum at first to demonstrate equivalency. Steps to consider are utilizing the current manufacturing site's components, raw materials, and process steps for the initial transfer, and then implementing changes after the process transfer has demonstrated control.

All steps should be documented as part of the change control including an overall assessment, testing, results, and a final report. A risk analysis should provide a review of process changes, environmental changes, personnel training, and equipment assessment with input from engineering, manufacturing, regulatory, purchasing, and quality.

A review of design development (Stage 1) design space, and Stage 2 equipment qualification and process qualification information, will provide insights into the level of risk and required corrective action. Each of the assessments should be recorded in protocols, assessments, white paper studies, or meeting minutes. This data will provide the framework for the decision on risk level and consequently the type of testing required to implement the change.

Gaps identified as part of the risk assessment need to be remediated. The remediation typically includes specification updates, engineering/water runs (including data gathering with sampling plans), procedural updates, and test method updates. After data gathered from engineering/water runs demonstrate that the process performs consistently, and maintains or reduces process variability, the team can proceed to revalidation.

The number of revalidation runs is based upon the level of residual risk from the risk assessment and the number of batches (Section 5.1) required to demonstrate that the process will maintain a state of control and identify opportunities for improvement.

One approach to revalidation is to utilize CPP and CQA data from a statistically-significant number of manufacturing batches from the primary manufacturing site to define control limits and to define acceptance criteria for both C_{pk} and P_{pk} data of transfer batches. Increased sampling should be instituted based upon risk levels until the level of control attained by the new site is equivalent or greater than that achieved by the primary manufacturing site.

It is important to note that no product should be released to the market until all assessments, studies, and reports have been reviewed by the regulatory group and released by the quality unit. Often material component changes will result in changes to CQAs, and therefore may be considered adulterated if released for sale.

9 Appendix 1 – Case Study: Legacy Products

Appendices 1 to 4 provides a series of case studies consisting mainly of real products produced at companies utilizing approaches deemed compliant at the time. The authors of the case studies did not have the benefit of this *ISPE Good Practice Guide: Practical Implementation of the Lifecycle Approach to Process Validation* when validating their processes, and some regulatory inspectors were early in the knowledge curve when these products were approved.

9.1 Executive Summary

This chapter presents a PV lifecycle case study wherein a legacy solid oral dose manufacturing process in the US was scaled from a 40 ft³ (1.13 m³) bin blender unit operation to an 80 ft³ (2.27 m³) bin blender unit operation. The case study outlines an overview of good practices for systematically assessing and managing risk in the lifecycle approach for PV Stage 1 (Process Design), Stage 2.2 (PPQ) and Stage 3.1 (CPV).

Historical data from the 40 ft³ blending process was reviewed and assessed. Comparable product and manufacturing processes at the 80 ft³ scale were evaluated to ascertain expected manufacturing variability. Following the Stage 2 PPQ study, additional commercial lots were produced. The data was statistically evaluated to demonstrate an exceptionally robust process.

This case study combines qualitative and quantitative assessments of product risk, using statistical tools that quantify process understanding and illuminate process robustness. The sampling plan philosophy reviewed past knowledge and experience to estimate the sampling required to obtain the desired assurance. The process was successfully scaled from a 40 ft³ bin blender to an 80 ft³ bin blender without introducing any measurable additional process variation.

9.2 Case Study Overview and Background

The examples and data provided in this case study were derived from the modification of an approved manufacturing process.

The product was an immediate release film coated tablet manufactured in a 40 ft³ bin blender based on ICH Q8(R2) QbD principles [1]. The original process underwent a Stage 2.2 PPQ study and was monitored as part of the firm's Stage 3.2 CPV program.

Per current FDA SUPAC-IR guidance [68], changes in the batch size from the pivotal/pilot-scale bio-batch material to larger or smaller production batches requires submission of additional information in the application. The change to an 80 ft³ bin blender unit operation was classified as a Level 1 change requiring [68]:

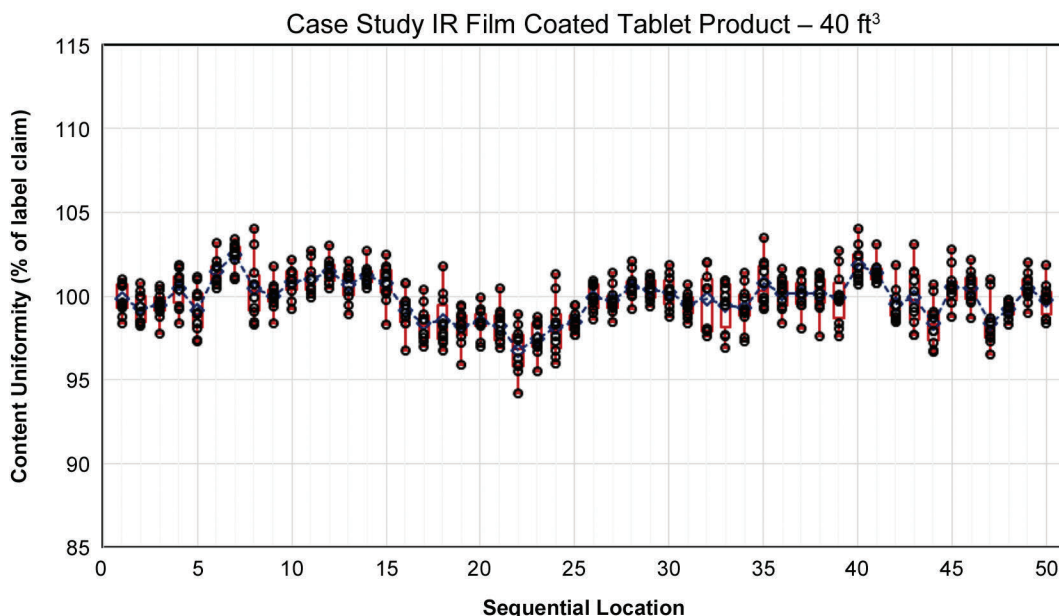
- Notification of change and submission of updated batch records in the annual report.
- One batch on long-term stability reported in annual report.
- All scale-up changes properly validated.

The proposed Stage 2.2 strategy met all regulatory requirements. Note that products that underwent QbD-based product development may apply tools such as a comparability/post-approval change management protocol.

Fifty successful batches of this product at the 40 ft³ scale were manufactured without any process deviations or failures. A run chart for the CU attribute (50 lots) of the produced batches is shown in Figure 9.1.

For each commercial batch, 10 tablets were randomly sampled and assessed for CU following USP <905> Uniformity of Dosage Units [46] and submitted specifications.

Figure 9.1: Content Uniformity Run Chart



A summary of the CU statistics of the displayed 50 lots derived using a VCA is provided in Table 9.1. In this table, the “Overall StDev” represents the standard deviation of the pooled individual CU results. This data provides a dosage uniformity capability index (D_{pk}) greater than 2.0 for Stage 1 testing, which signifies an exceptionally robust process that is expected to continue meeting all CU requirements.

Note: D_{pk} is a comparable statistic to C_{pk} but applicable to the stage-wise USP <905> testing method [46]. See Section 9.3 for definition and description.

Table 9.1: Summary of Content Uniformity Statistics

Statistic	Value	Lo 95%	Hi 95%
Mean	99.82	99.60	100.04
Within StDev	1.14	1.07	1.22
Between StDev	1.11	0.93	1.38
Overall StDev	1.58	1.49	1.69
Number of Lot/Locations	50		

The manufacturing process for this product (40 ft³ process) involved a dry mix and direct compression followed by a non-functional film coating. To improve operational efficiency, scale-up to an 80 ft³ bin blender was desired. In addition to the larger scale bin, it was identified that a vacuum transfer system was required for raw material transfer so that the product could be effectively scaled.

The validated process used an optimal bin fill of 47% for the 40 ft³ bin.

The firm has considerable experience with comparable products manufactured in 80 ft³ bin blender. During the initial investigation of the scale-up operations, a detailed assessment of similar product/process performance was performed.

FDA PV Guidance allows for evaluation and use of previous credible experience with sufficiently similar products and processes [3]. Information on comparable products with similar formulation and bin batch size was collected. Products and processes with comparable formulations (e.g., percent active, MCC/lactose ratio, magnesium stearate level, talc, croscarmellose sodium level), raw material physical attributes, powder rheology characteristics, blend batch size, bin fill, blend bulk density, and blend uniformity results were identified.

A summary of similar formulations manufactured at the 80 ft³ bin blender scale and the associated CU data statistics, each derived from a VCA of the specific product/process, are provided in Table 9.2.

Table 9.2: Summary of Similar Formulations Produced in 80 ft³ Bin

Product	Drug Load (%w/w)	Batch Size (kg)	Bulk Density (g/cc)	Bin Fill Level (%)	API Particle Size	BU Status	Reviewed Lots	Within Batch CU StDev	Between Batch CU StDev
Prod A	5.03	900	0.61	56	Similar	Conforms	25	2.28	1.20
Prod B	6.65	900	0.65	57	Similar	Conforms	53	1.42	0.68
Prod C	5.15	900	0.62	58	Similar	Conforms	29	1.74	1.33
Prod D	5.00	900	0.65	56	Similar	Conforms	45	1.73	0.54

The blend process parameters are similar for each of the four formulations. Qualitatively, because of extensive experience with comparable products at this scale, the risk of adapting the same process parameters for the scale-up verification study (Stage 1) is low.

A bin fill level of 58% was chosen for the 80 ft³ bin, which is close to the optimal recommended level of 60%. This bin fill level improves shear among particles in addition to axial/radial mixing, and improves mixing dynamics. The blending processes with kinematic (same number of revolutions) similarity were adopted.

A preliminary qualitative assessment created a scientific review of past experience (by application of knowledge management tools as an enabler) and potential issues, and provided guidance for appropriate settings and conditions, thus negating the need to develop and determine blend process parameters from scratch (see Table 9.3).

The scientific review and assessment eliminated the need to acquire raw materials for multiple full-scale batches and saved valuable manufacturing floor time and other associated resources for more productive operations. The approach provided qualitative assurance that proper blend process parameters were identified prior to a full-scale verification at PV Stage 1.

Stage 1 demonstration batches were manufactured to primarily characterize the bin parameters. Other processes/equipment (i.e., compression and coating parameters) were verified during demonstration batch manufacturing.

Table 9.3: Process Capability Targets

Compression	
IP Hardness	$C_{pk} > 1.0$ or $P_a > 99.7\%$
IP Weight Variation	$C_{pk} > 1.0$ or $P_a > 99.7$
Press Speed	All batches at $> 80\%$ of maximum
% Yield	Meet limits per SOP
Finished Product (FP) Critical Quality Attributes	
FP Dissolution	$D_{pk} > 1.0$ or P_a at Disso S1 $> 99.7\%$
FP Assay	$D_{pk} > 1.0$ or $P_a > 99.7\%$
FP Content Uniformity	$D_{pk} > 1.0$ or $P_a > 99.7\%$ and $AV < 10$

Prior to initiating Stage 2.2 studies, a comprehensive technical risk assessment that qualitatively determined the impact of individual material attributes, process parameters, and finished product quality attributes, was performed. This assessment concluded that the scale up to an 80 ft³ blender bin was low risk.

9.3 Critical Quality Attributes Operating Characteristic Curves

A break from the case study story is now made to express a more detailed description of statistical tools applicable to understanding product risk.

A basic objective of many statistical analyses is to provide assurance that the product will consistently and reliably meet the quality attributes for each CQA. A limited number of samples are removed from the process and the analyses of these samples are used to infer the characteristics of the entire population. If the population follows a Gaussian distribution (i.e., the distribution is Normal), the overall characteristics can be reasonably described by two variables, the mean and the standard deviation.

Specific CQA acceptance criteria transform the data distribution into the probability of passing the test for the particular CQA. The acceptance probability provides assurance that samples removed from the described distribution will meet the defined requirements (that is, the acceptance probability is a measure of the process capability).

For simple attributes, such as assay, wherein a single measurement is compared to specification limits, it is reasonable to apply statistical tools such as traditional capability measures to provide this assurance.

However, the acceptance criteria for most CQAs in the pharmaceutical industry pose a challenge for a direct application of traditional capability approaches. For example, immediate release dissolution requirements, per USP <711> guidelines [53], follow a stage-wise acceptance; thus, a direct application of a capability approach becomes complicated.

While the acceptance criteria appear to pose daunting complications to the analysis process, the defined acceptance rules (i.e., specification requirements) can be analytically resolved through the use of an OC curve. The OC curve analytically transforms the “true” population statistics (mean and standard deviation) into the probability of meeting or passing the acceptance criteria. As an example, the transformation for assay can be determined analytically using the following equation that uses the Normal distribution function:

$$\text{Prob of Passing} = \text{NORM.DIST}(\text{'True Pop'n Mean'}, \text{USL}, \text{'True Pop'n StDev'}, \text{TRUE}) - (\text{NORM.DIST}(\text{'True Pop'n Mean'}, \text{LSL}, \text{'True Pop'n StDev'}, \text{TRUE}))$$

Figure 9.2 provides an example set of OC curves derived using the above equation for assay with specification limits of 90.0 – 110.0%.

Figure 9.2: Operating Characteristic Curves for Assay

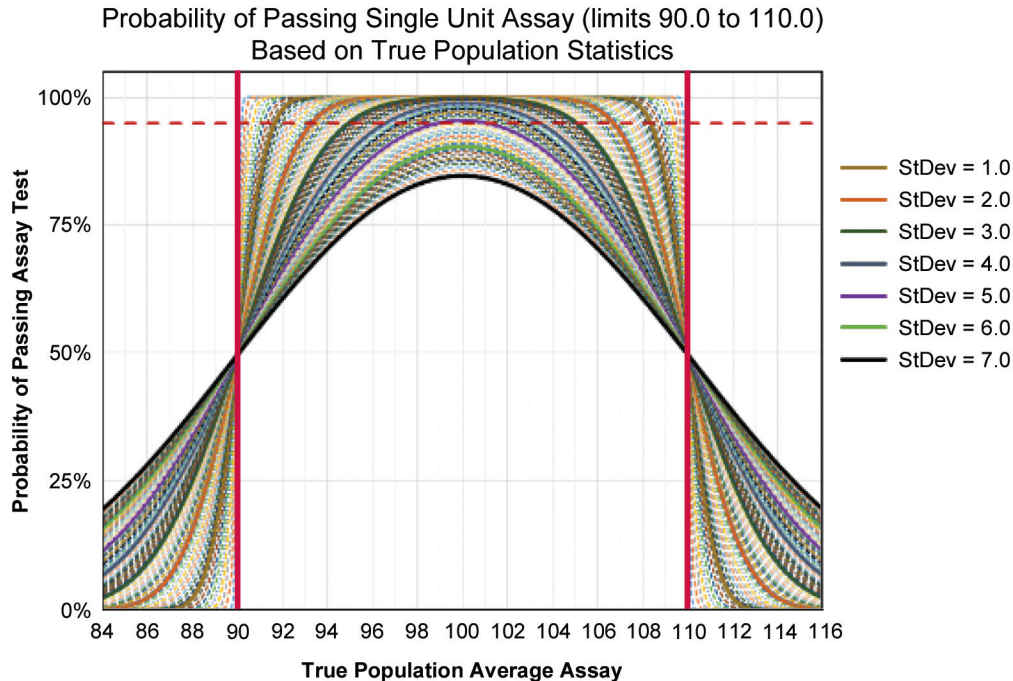


Figure 9.2 plots a series of True Population Standard Deviations curves along a True Population Average Assay on the x-axis. The standard deviation is provided in 0.1% increments with solid curves representing unit standard deviation values. These curves are analytically derived based on the probabilities of meeting the specification requirements for an associated Normal distribution with denoted statistics (mean and standard deviation).

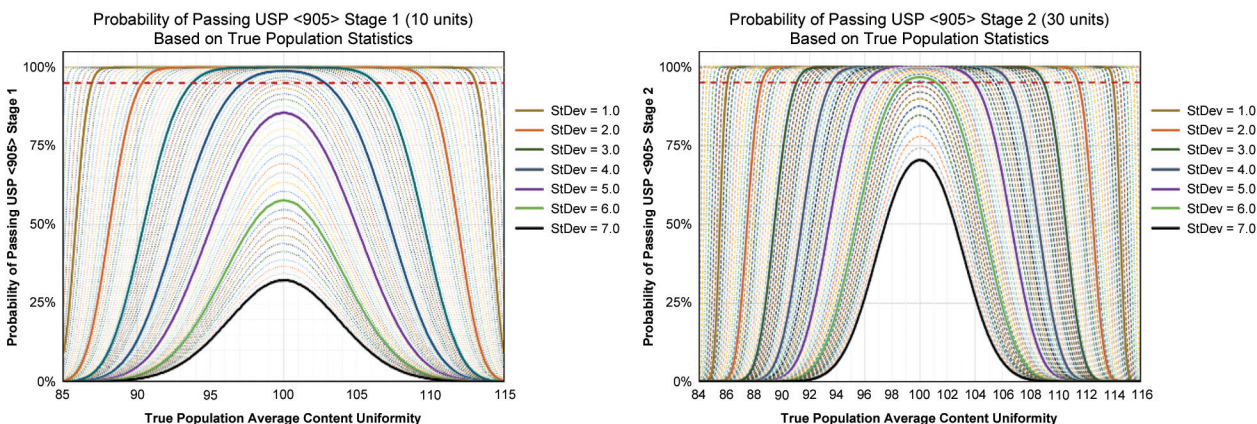
Solid vertical lines represent the 90.0% and 110.0% specification limits. The curves relate the probability of meeting the specification requirements if the population statistics were precisely known. Note that if a population had a 90.0% average, then a single sampled unit pulled for an assay analysis has a 50% chance of meeting the specification.

A similar set of curves can be derived for both Stage 1 and Stage 2 acceptance of the CU specification requirements outlined in USP <905> [46]. The Stage 2 curves presented here represent the cumulative probability and thus effectively provide the overall probability of meeting the USP <905> guidelines. Because the specification rules for CU are more complex than for assay, the derivations of the OC curves are more intricate than for the assay CQA.

Note that the USP <905> acceptance criteria [46] for CU are based on both the mean and variance of a small randomly derived sample set of the entire population. Once appropriately developed, the OC curves properly transform the true population statistics into the probability of meeting or passing the defined requirements.

OC curves for CU based on the requirements of USP <905> [46] are provided in Figure 9.3. The Stage 2 curves (representing the overall test requirements) are directly comparable to Sampling Plan 1 and, when properly used in conjunction with measures of the within and between variation of a stratified sampling process, will provide a similar assessment as offered by Sampling Plan 2.

Figure 9.3: Operating Characteristic Curves for Content Uniformity



Determining the Assurance Probability (P_a and P_{ai}) and the Capability (D_{pk})

The above OC curves theoretically define the transformation of the detailed CQA requirements into the probability of passing the specific CQA test. Two terms (P_a and P_{ai}) that describe the assurance of meeting CQA testing are used herein.

Based on the sampled statistics, the acceptance probability (P_a) provides the chance that a test result derived from the same population will meet the CQA test requirements. P_a relates the expected performance based on the observed sample statistics.

P_a is related to standard statistical process capability terms (C_{pk} and P_{pk}); however, for Content (Dosage) Uniformity, the USP stage-wise acceptance specifications [46] distort a direct application of these process capability measures. A comparable capability measure, D_{pk} (based on the P_a computation), is used that provides a measure similar to the standard statistical terms. D_{pk} provides a capability measure based on the probability of producing a defect (assuming a Normally distributed data set).

Using the OC curves, P_a (and subsequently) D_{pk} capability can be determined for each stage in the USP method [46], and relates the capability of the process to meet the requirements for that specific stage. Table 9.4 expresses how P_a and D_{pk} are related.

Table 9.4: Relationship of P_a and D_{pk}

Determined P_a (%)	Comparable D_{pk}	Approximate "Sigma" Process
90 %	0.55	1.6
95 %	0.67	2.0
99 %	0.86	2.6
99.7 %	1.00	3.0
99.99 %	1.33	4.0
99.9999 %	1.66	5.0
> 99.99999998 %	> 2.0	> 6.0
Key: P_a = Acceptance probability D_{pk} = Dosage uniformity capability index		

A lower limit of P_a , termed P_{al} , provides a confidence bound on how well sampling defines the P_a measurement. P_{al} provides a measurable assurance, based on a desired confidence, that the process will meet the specification requirements. It provides an assurance similar to that provided by a tolerance interval except where a tolerance interval only provides an assurance of meeting a defined bound at a given confidence, P_{al} provides a measurable bound for a given confidence. Where a tolerance interval only provides a “pass/fail” indication (e.g., the process will meet a 95/95 criteria), P_{al} relates a *continuum* that indicates how close the process is to an acceptable assurance level. For example, P_{al} may indicate 95% confidence that 99.8% of future tests will meet the requirement, which clearly passes a 95/95 criterion by a reasonable margin.

There are four possible confidence interval combinations, though only the upper (or High StDev) combinations provide practical relevance to the limiting concern.

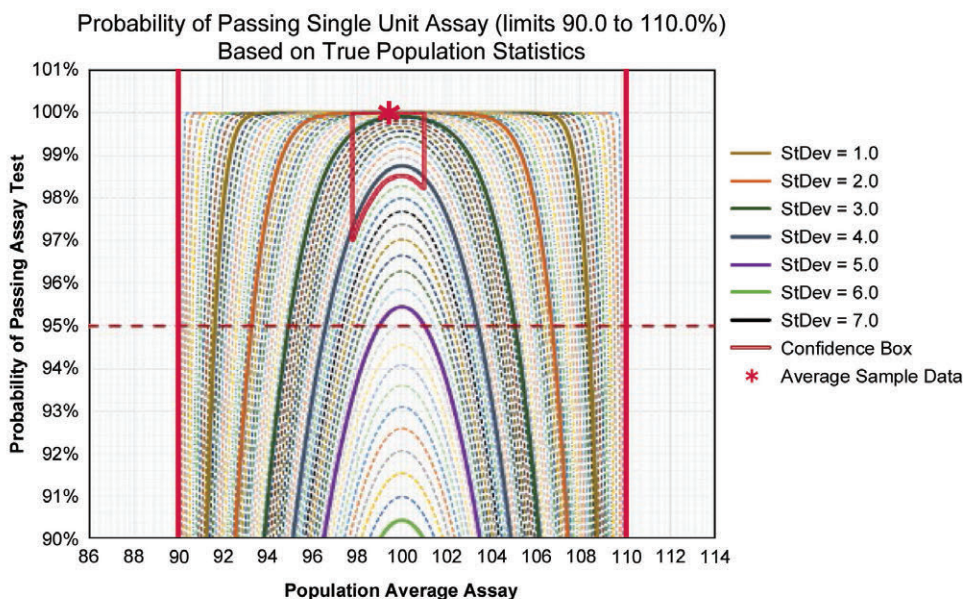
1. Low mean and Low standard deviation
2. Low mean and High standard deviation
3. High mean and Low standard deviation
4. High mean and High standard deviation

These confidence interval combinations, when applied to the OC curve, generate a confidence interval “box”. Recall that the OC curve provides a theoretical transformation of the CQA acceptance criteria of the true population distribution into the probability of passing or the acceptance bound. Confidence intervals describe how well the sampled statistics capture the true population statistics.

Figure 9.4 graphically presents an example of a confidence interval box applied to the assay OC curve. In this example, a set of 10 units was removed from the population and tested for assay. The sampled average and standard deviation were determined and plotted as an asterisk (*). This point defines the expected assurance probability (P_a).

The four confidence interval combinations are determined (with $\alpha = 0.05$) and represented by a lined box. One can now infer, with the desired (95%) confidence, that the true population statistics reside within this confidence box. The lowest probability of passing point on this box represents the highest risk and is defined as the Lower Assurance Probability (P_{al}). In this specific example, one can state with 95% confidence that 97.4% of possible assay tests removed from this population will meet the 90.0 to 110.0% specification requirements.

Figure 9.4: Confidence Interval Box



9.4 Estimate the Number of Samples for the Process Validation Stage 2.2 Protocol

Returning to our case study example, a review of historical data provided a perspective of the statistical capability of the current 40 ft³ process, as well as the capability of the production operations experience with comparable 80 ft³ processes.

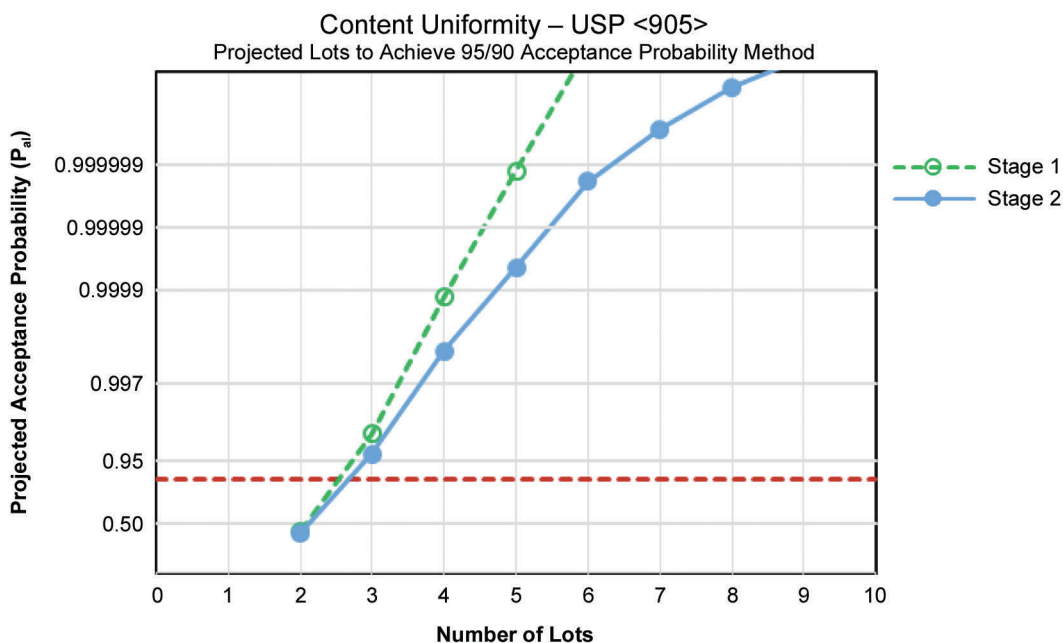
The qualitative risk assessment indicated that the scale-up presented a low-risk situation. For the current study of the scale-up between 40 ft³ and 80 ft³ bin blenders, data from the long history of 40 ft³ production batches was used to estimate the average CU of the process (average CU = 100.69). A VCA of data from the comparable 80 ft³ processes (averaging the variance from across the 50 produced batches of four comparable processes) was used to project the estimated variability of the process (providing an estimated within lot standard deviation = 1.71 and between lot standard deviation of 0.85). These products evaluated showed low variability, achieved by implementing robust product control strategies throughout the lifecycle.

An assessment of the historical data projected that three Stage 2.2 PPQ batches would be sufficient to assure that the blend process at the 80 ft³ scale could consistently produce uniform powder blends per defined process parameters.

Three Stage 2 PPQ batches were manufactured and the data demonstrated with 95% confidence that greater than 90% of future lots (with consistent materials, a stable, constant manufacturing environment, and robust test methods) would meet the desired specification requirements.

Applying the lower acceptance probability method (P_{al} – see detailed description in Section 9.3) with the estimated statistics derived for this case study example, and a sampling plan that includes 60 units for each batch, a projection of anticipated P_{al} was generated for a successive number of produced lots (shown in Figure 9.5).

Figure 9.5: Projection of Anticipated P_{al}



If the estimated statistics properly represent the scaled-up process, these computations project the number of lots required to achieve a 95% confidence that 90% of tests will meet the USP <905> CU requirements for both Stage 1 and Stage 2 (recall that Stage 2 represents the overall test requirement) [46]. In this particular case, three produced batches should be sufficient to achieve the desired assurance.

Note that this assessment concludes that if a PPQ validation study were completed with just two lots of data and if the observed statistics were as expected from the projection (mean = 100.69, within standard deviation = 1.71, and between lot standard deviation = 0.85) then there would be 95% confidence that only about 50% of lots would meet the USP requirements. Using the same statistics with the quantity of data from a third lot projects that there will be 95% confidence that at least 90% of the lots will meet the USP requirements indicates that three PPQ lots should be sufficient to satisfy the protocol conditions. A fourth produced lot would increase the lower 95% confidence level of assurance above 99.7%.

9.5 Assess Stage 2.2 Data

In the specific instance of this case study, three batches of the process using the 80 ft³ bin blender were produced. Samples were removed according to the described protocol, which included a standard 20 × 3 (60 units total) stratified CU assessment for each batch produced.

Recall again that the basic objective of the statistical analysis of Stage 2.2 data is to provide assurance that the product will consistently and reliably meet the quality attributes for each CQA. The basic P_a method provides this assurance; however, the analysis can be complicated by the effect of within and between batch variation.

There are two general scenarios related to variation sources:

- Those scenarios where the between batch/location variation is small and insignificant compared to the within batch/location variation
- Those scenarios where the between batch/location variation is significant when compared to the within batch/location variation

In Scenario (a), it is reasonable to pool individual data for the acceptance probability analysis as the between location variation is insignificant (this is comparable to Sampling Plan 1), but in Scenario (b), care must be taken to determine the effect of batch-to-batch variation (an assessment comparable to Sampling Plan 2).

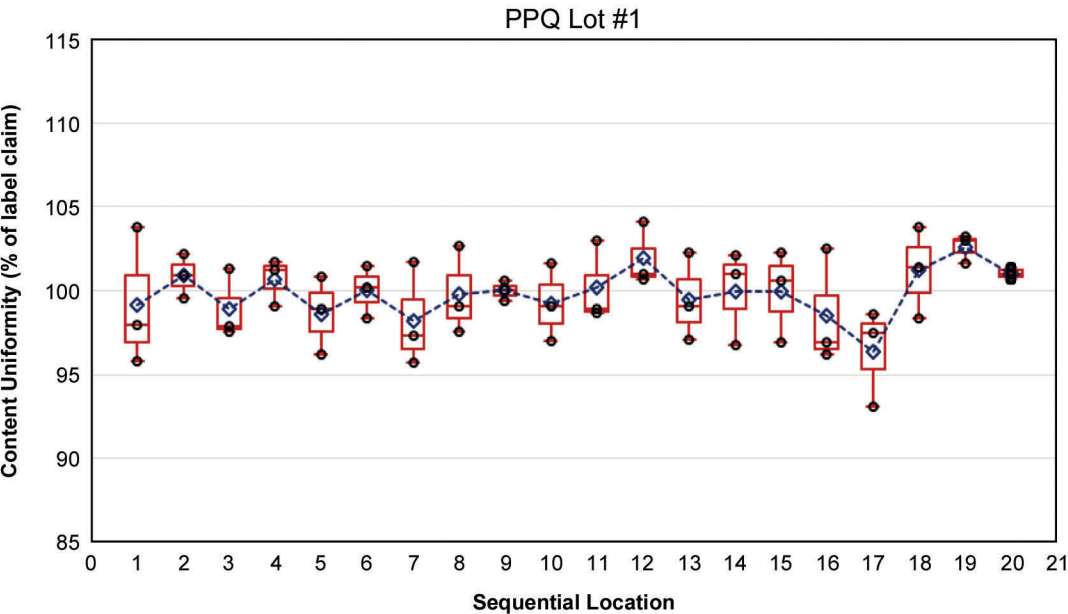
An Analysis of Variance (ANOVA) provides a statistical hypothesis test that assesses, at a rudimentary level, if the variation between the means of several groups (e.g., between batches/locations) are statistically significant when compared to the within batch/location variation. Table 9.5 provides an example ANOVA for 20 locations of CU data (3 units were assessed for each location) acquired from the first 80 ft³ scale-up Stage 2.2 PPQ batch.

Table 9.5: Example Analysis of Variance (ANOVA) Content Uniformity Data

ANOVA – PPQ Lot #1					
Source	DF	SS	MS	F Ratio	Prob > F
Between	19	109.78	5.78	1.00	0.478
Within	40	230.41	5.76		
Total	59	340.19			

A run chart for this data is provided in Figure 9.6.

Figure 9.6: Example Analysis of Variance (ANOVA) Content Uniformity Data Run Chart



The p-value for the CU data collected in Stage 2.2 PPQ Lot 1 was greater than 0.05, which indicates that the between location variation is not statistically significant when compared to the within location variation. In this scenario, where the between location variation is not significant when compared to the within location variation, a P_a computation can be reasonably completed by using the overall mean and standard deviation (and associated confidence intervals) of all pooled batch data with the OC curve (essentially a Sampling Plan 1 assessment).

This was accomplished as described earlier in assurance probability determination (Section 9.3). The computed P_a and P_{al} for this specific batch indicates with 95% confidence that this lot should meet the CU acceptance value requirements described in USP <905> [46] more than 99.99% of the time if repeatedly tested. This conclusion is consistent with the result derived using the ASTM E2810/E2709 method [44].

A similar analysis was completed for each of the three distinct Stage 2.2 PPQ batches and indicated that each batch, assessed independently, had a high probability of routinely meeting the USP requirements [46].

The above analysis (comparable in practice to the assurance provided by ASTM E2810/E2709 [44]) reviewed each lot distinctly and independently and provided the desired assurance that each specific lot would routinely meet the USP <905> requirements [46]. From a PPQ perspective, it is also important to assess the effects of batch-to-batch variation and provide an assurance that the process, if maintained, is robust and will continue to meet the desired requirements.

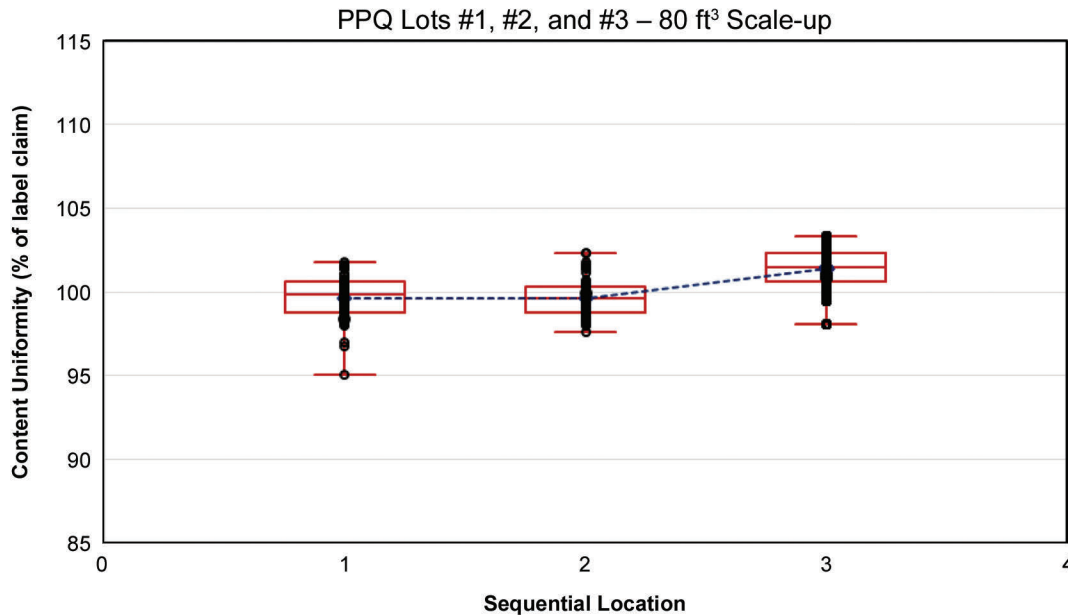
For this case study assessment, three lots, each with 60 units, were manufactured and measured. Note that since the individual lot assessment concluded that the between location was not significant when compared to the within location, each lot of 60 data points was pooled for the between batch assessment. Table 9.6 contains an ANOVA that compares the within batch and between batch variation.

Table 9.6: Analysis of Variance (ANOVA) Comparison of Within Batch and Between Batch Variation

ANOVA – PPQ Lots #1, #2, and #3 – 80 ft ³ Scale-up					
Source	DF	SS	MS	F Ratio	Prob > F
Between	2	119.72	59.86	44.11	< 0.001
Within	177	240.21	1.36		
Total	179	359.94			

In this multi-batch analysis, the ANOVA hypothesis indicates that the variation between batches is statistically significant when compared to the within batch variation (as evidenced by the p-value being less than 0.05). A graphical representation of the three Stage 2.2 PPQ batches CU data is provided in Figure 9.7.

Figure 9.7: Content Uniformity Run Chart



Since the between batch variation is statistically significant when compared to the within batch variation, a more comprehensive statistical analysis was warranted, as it is not reasonable to assume that the data can be combined into one large pool.

The first step in this more comprehensive analysis is to complete a variance component analysis to derive estimates of both the within and between batch standard deviation, as well as the associated confidence intervals. The variance component analysis for this assessment is provided in Table 9.7.

Table 9.7: Variance Component Analysis

Statistic	Value	Lo 95%	Hi 95%
Mean	100.23	99.93	100.53
Within StDev	1.16	1.06	1.30
Between StDev	0.99	0.51	6.21
Overall StDev	1.42	1.29	1.58

The process used to determine the expected assurance probability (P_a) is similar to that previously described, but with an added step of integrating the contributing fraction of each expected “between” batch segment.

Conceptually consider that multiple batches are produced that have a varying (Normally distributed) between lot variation that dictates the average CU for that batch, and that each conceptual lot is produced with a consistent within lot variability. The overall acceptance probability is provided by an integration of these conceptual lots.

Using this method, it is expected that $> 99.9999\%$ ($D_{pk} > 2.0$) of 10 unit CU samples removed (per USP <905> [46]) from any of these three batches will meet the Stage 1 AV requirements described in USP <905> and minimum of 96.13% (P_{al}) will meet the requirements with 95% confidence. Although the between batch variation was statistically significant, this assessment provides reasonable assurance that the observed between batch variability is not of practical significance; it has a medium-low risk potential (the slight risk is associated with batch-to-batch uncertainty) for the CU CQA. The batch-to-batch uncertainty will diminish as more batches are produced and tested.

9.6 Product Risk Evaluation and Enhanced Controlled Strategy for Continued Process Verification (Stage 3.1)

The statistical results for each CQA from the Stage 2.2 PPQ studies were compiled using the appropriate OC curves to derive both P_a and P_{al} . As mentioned, acceptance probabilities (P_a) are comparable to a process capability index measurement (D_{pk}). This capability measure is used to provide a quantitative assessment of process understanding and risk. Table 9.8 shows an example of risk associated with each CQA.

Table 9.8: Example of Risk Associated with Each Critical Quality Attribute

Low Risk Critical Quality Attribute	Medium Risk Critical Quality Attribute	High Risk Critical Quality Attribute
$P_a > 99.99\%$	$99.7\% < P_a < 99.99\%$	$P_a < 99.7\%$
$P_{al} > 99.7\%$	$95\% < P_{al} < 99.7\%$	$P_{al} < 95\%$
$D_{pk} > 1.33$	$1.0 < D_{pk} < 1.33$	$D_{pk} < 1.0$
$D_{pk} \text{ (low)} > 1.0$	$0.67 < D_{pk} \text{ (low)} < 1.0$	$D_{pk} \text{ (low)} < 0.67$

A low risk CQA is associated with a process with a comparable process capability greater than 1.33 and a lower confidence assurance of a process capability greater than 1.0. This indicates good confidence that the process for that CQA is statistically robust.

In contrast, a high risk CQA is associated with a process that has demonstrated either marginal capability (i.e., capability less than 1.0) or has insufficient data collected to assure with reasonable confidence that the process is robust.

After the three-batch Stage 2.2 PPQ assessment for the 80 ft³ bin scale-up, the CU attribute displayed a $P_a > 99.9999\%$ ($D_{pk} > 2.0$) and a P_{al} of 96.13% ($D_{pk}\text{-low} = 0.69$). This indicates that the process should be quite robust, but insufficient evidence is available to conclude this with high certainty.

It was thus decided that a comprehensive statistical monitoring assessment would be completed after two additional commercial batches were produced (total of five batches) to re-evaluate the product risk. The philosophy here is that compiling data from a few more batches will substantially increase the confidence in the overall process robustness. A summary of the CU data is provided in Figure 9.8 and Table 9.9.

Figure 9.8: Graphically Presented Content Uniformity Data for Process Performance Qualification (PPQ) plus Two Batches

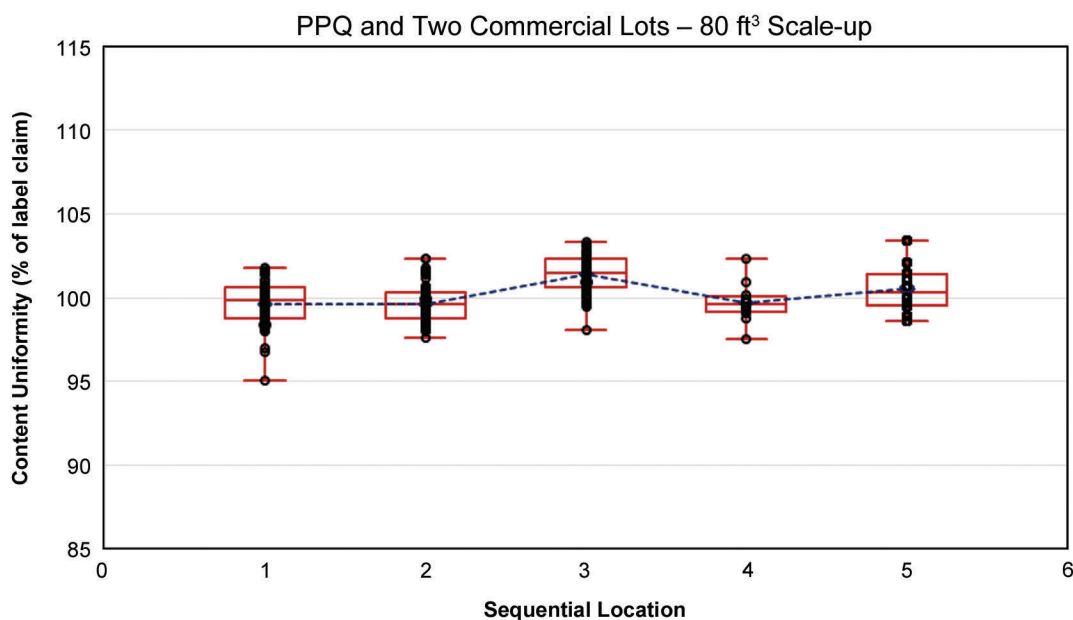


Table 9.9: Content Uniformity Data for Process Performance Qualification Plus Two Batches

Risk Assessment	Stage 1	Stage 2
Expected P_a	> 99.999%	> 99.999%
95% P_{al}	> 99.999%	> 99.999%
Capability (D_{pk})	> 2.0	> 2.0
95% Capability (D_{pk-low})	1.88	> 2.0

As demonstrated by the capability statistics, a very high assurance that the process is capable and robust was achieved after the production of five commercial batches.

As part of CPV, further confirmatory assessment was attained after a total of 10 batches were produced (see Figure 9.9 and statistical summary in Table 9.10).

Figure 9.9: Graphically Presented Content Uniformity Data for First 10 Commercial Lots in 80 ft³ Bin

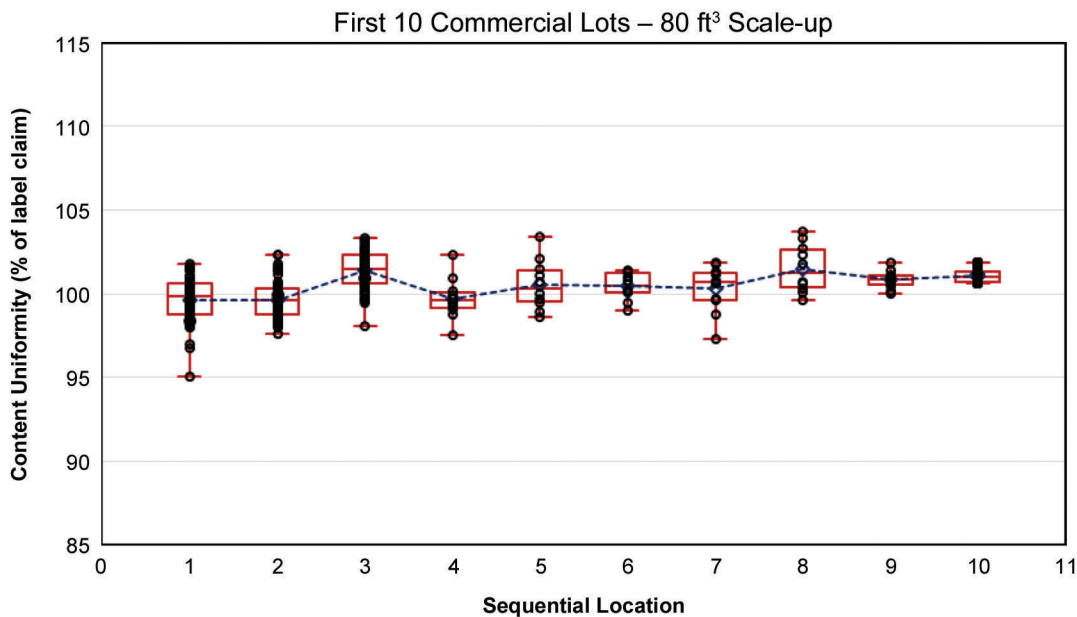


Table 9.10: Content Uniformity Data for First 10 Commercial Lots in 80 ft³ Bin

Risk Assessment	Stage 1	Stage 2
Expected P_a	> 99.999%	> 99.999%
95% P_{al}	> 99.999%	> 99.999%
Capability (D_{pk})	> 2.0	> 2.0
95% Capability (D_{pk-low})	> 2.0	> 2.0

After ten 80 ft³ bin blender lots were produced, the process clearly demonstrated a high capability to routinely meet the requirements for CU. Further, the initial 10 lots of data for this 80 ft³ process appear to provide comparable, if not improved, uniformity than the 40 ft³ process.

Recall from the earlier discussion that the 40 ft³ process demonstrated an average CU of 99.82% with a within standard deviation of 1.14 and between lot variation of 1.11. The 80 ft³ process compared favorably, demonstrating a within lot standard deviation of 1.16 and between lot standard deviation of 0.68.

Overall, a potential minor improvement in the consistency between lots for the product and a successful scale-up of this legacy product from a 40 ft³ blender to a more commercially efficient 80 ft³ process was achieved.

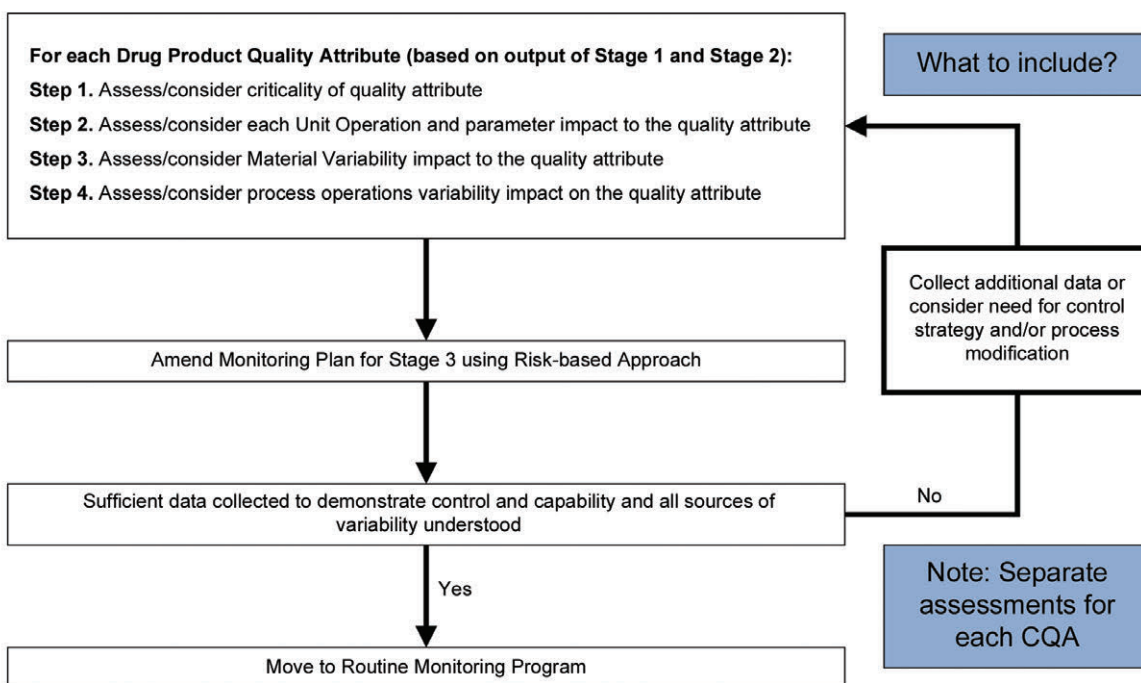
10 Appendix 2 – NDA Products Case Studies: Small Molecules

10.1 Case Study 1: Selection of CQAs and PPs for CPV – Applying Risk-based Approach to CPV Determination to a New Small Molecule Drug Product, Utilizing Data from the *ISPE PQLI® Guide Part 2 – Illustrative Example* [35]

The *ISPE PQLI® Guide Part 2 – Illustrative Example* [35] describes the model product PaQLInol Tablets [8]. Based on the data and development knowledge presented in the PQLI Guide, a science- and risk-based approach is used to determine which subset of CQAs and parameters are subject to heightened monitoring and sampling in Stage 3 (CPV). In this case, heightened monitoring is the same or at a similar level of monitoring and sampling as conducted in Stage 2, which is increased or enhanced compared to the eventual routine situation.

The flowchart shown in Figure 10.1 outlines the decision-making process.

Figure 10.1: Heightened Monitoring Assessment Decision Making Process [35]



This assessment is performed separately for each CQA of the output drug product or drug substance.

For each CQA, questions (Steps 1 to 4 in Figure 10.1) are applied taking into account formulation and process development studies, as well as manufacturing information obtained from using this formula and process (e.g., manufacture of clinical batches or scale-up/technology transfer batches). Data generated during Stage 2 is also reviewed.

If sufficient data has been collected to demonstrate control and capability, and the impact of all sources of variability is understood, these CQAs do not need to be included in a heightened monitoring and testing plan during CPV.

Being capable means a statistically-based estimate of process variability is determined, and meets product/process performance requirements with a sufficient level of confidence. It should be noted that the impact of variability is defined as variability within the acceptable range of values and acceptance criteria that were justified as part of product submission.

10.1.1 Step 1 – Assessment of Drug Product Critical Quality Attributes to Monitor

Criticality ranking of PaQLInol Tablets CQAs from the ISPE PQLI® Guide Part 2 – Illustrative Example [8] is determined. A section from the relevant table is presented in Table 10.1.

Table 10.1: Some Drug Product CQAs with Criticality Ranking [35]

Critical Quality Attribute	Criticality Rating	Rationale and Comments
Assay	High	Overdose – side effects; under dose – lack of efficacy; however, dose response curve is not precipitous
Uniformity of Dosage Units	High	Variability in plasma levels may lead to side effects or poor clinical response; however, dose response curve is not precipitous
Dissolution	High	Poorly soluble (BCS class 2) drug substance – dissolution characteristics important for bioavailability; however, linkage of dissolution to bioavailability is not known
Water Content	High	Moisture may affect degradation of dosage form performance, i.e., dissolution. API stable; however, API in drug product requires further investigation. Could also impact microbiology.

In the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8], PaQLInol Tablets are dosed orally at 30 mg daily. This example focuses on two of the CQAs that are assigned high severity, UDU and dissolution. There is no change in criticality ranking based on Stage 2 PV data.

10.1.2 Step 2 – Assessment of Each Unit Operation and Parameter Impact on the Critical Quality Attributes

The cause and effect matrix for the PaQLInol Tablet process after formulation development and before process development is given in Table 10.2.

Table 10.2: Cause and Effect Matrix for PaQLinol Tablets before Process Development Studies [35]

	Drug Product					
CQA/Unit Operations	Dispense	Blend	Lubricate	Compress	Coat	Package
Appearance	L	L	L	L	M	L
Identity	M	L	L	L	L	M
Assay	M	M	L	M	L	L
Impurities	L	L	L	L	L	L
Uniformity of Dosage Units	L	H	M	M	L	L
Dissolution	L	L	H	H	L	L
Microbiology	L	L	L	L	L	L
Key:	L = Little or no impact		M = Indirect impact/Medium Risk		H = Direct impact	

Concentrating on dissolution and UDU is justified in Stage 3 CPV as these quality attributes are highest risk before process development studies are conducted (Table 10.2). Additionally, development/PV Stage 1 studies to understand and reduce and/or monitor homogeneity of the drug substance lead to an understanding of assay CQA since these values can be calculated from the mean of the individual tablet assay values. Extensive studies resulted in:

- Introduction of in-line NIR testing for blend homogeneity and at-line testing of UDU as important elements of the control strategy
- Identification and use of an algorithm as an important element of the dissolution control strategy

The cause and effect risk matrix for PaQLInol Tablets after process development studies is given in Table 10.3.

Table 10.3: Cause and Effect Matrix for PaQLInol Tablets after Process Development Studies and Application of the Control Strategy [35]

	Drug Product					
CQA/Unit Operations	Dispense	Blend	Lubricate	Compress	Coat	Package
Appearance	C	C	C	C	C	C
Identity	C	C	C	C	C	C
Assay	C	C+E	C	C+E	C	C
Impurities	C	C	C	C	C	C
Uniformity of Dosage Units	C	C+E	C+E	C+E	C	C
Dissolution	C	C	C+E	C+E	C	C
Microbiology	C	C	C	C	C	C

Key: C = Cause E = Effect

Note: all risk assignments are now **Low** (see Table 4.4 in *ISPE PQLI® Guide Part 2 – Illustrative Example* [8] for risk assignments before application of control strategies).

Types of Control Strategy Elements Applied:

- C: Conventional Control Strategy Elements including cGMP
- C+E: Conventional Control Strategy Elements including cGMP and Elements of Enhanced QbD Approaches

The risk assessment criteria applied during development studies shows that the impact on all drug product CQAs is Low risk when a comprehensive control strategy is applied.

As part of Step 2 in building a CPV program, the residual risk in the control strategy is evaluated.

The residual risk assessment, using a different risk assessment tool more suitable for the evaluation of routine manufacturing (e.g., the FMECA risk ranking guide given in Appendix 3 of *ISPE PQLI® Guide Part 2 – Illustrative Example* [8]), confirms that PaQLInol Tablets have a Low level of residual risk, leading to an appropriate number of batches, for example three, being manufactured satisfactorily to support Stage 2.2. For further discussion, see Section 5.7 of *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

Introduction of Real Time Release Testing (RTRT), as proposed in *ISPE PQLI® Guide Part 2 – Illustrative Example* [8], requires continued monitoring during the initial part of Stage 3 (Stage 3.1), at the same level as during Stage 2.2.

In Step 2 of building a CPV program, the residual risk in the control strategy is evaluated. Theoretically, all of the unit operations have been mitigated to the predicted green or low-level risk for each unit operation's impact on each CQA, but low variability across a wide range of input material attributes in combination with operational conditions may not have been demonstrated.

Regarding robustness, there could be some residual risk. For the purpose of this example, the focus is on the impact of compression on dissolution and CU. A summary of the control strategy risk assessment for UDU and dissolution after Stage 2 is shown in Table 10.4, leading to propose the PV Stage 3 monitoring plan elements.

Table 10.4: Control Strategy Assessment Summary after Stage 2, Process Qualification [35]

Uniformity of Dosage Units	Dissolution
- Acceptance criteria applied to drug substance particle size - Extensive studies performed to understand homogeneity during blending and lubrication unit operations - In-line NIR applied to blending and lubrication unit operations - At-line NIR individual tablet assay for UDU provides a high level of confidence (PAT tool) using stratified sampling - Each tablet indirectly evaluated for weight (pressure monitoring) Control strategy established and confirmed Consideration for Stage 3.1 based on Step 2 Consideration of reduced testing compared to Stage 2 for routine monitoring based on control strategy - Reduced frequency of at-line testing of individual tablet assay for UDU	- Understanding of the process to produce and acceptance criteria applied to drug substance particle size - Prediction algorithm developed from DoEs dependent on: - Drug substance particle size - Specific surface area of lubricant - Lubrication mixing time - Tablet crushing force - Model developed at small scale and limited confirmation during Stage 2 - Stratified sampling applied for testing of tablet cores Control strategy established and confirmed Consideration for Stage 3.1 (based on decision process Step 2 and control strategy) Continue stratified sampling at the same level as above for a defined number of batches, as well as measurement of material attributes of drug substance particle size, specific surface area of lubricant and tablet crushing force, and the process parameter of lubrication time. Maintain end product testing. Verify multivariate model and demonstrate robustness, and provide comparative data between prediction and measurement to support movement to RTRT.

10.1.3 Step 3 – Assess Material Variability Impact

Table 10.5: Summary Output of Risk Evaluation after Formulation Development and IVIVC Studies Using FMEA [35]

CQA (Severity)/ Failure Mode	Appearance Friability Hardness	Impurities	Water	CU	Dissolution	Microbiology
Magnesium Stearate Surface Area	M	L	L	L	H	L
PaQLInol Particle Size	M	L	L	L	H	L
Key: L = Little or no impact M = Indirect impact/Medium Risk H = Direct impact • CU: Low level of risk remains for the API particle size. • Dissolution: A high level of residual risk remains for magnesium stearate specific surface area and PaQLInol particle size.						

There are two raw materials used in PaQLInol Tablets with the potential to have a significant impact on dose uniformity and dissolution. Based on prior knowledge, it was theorized that API particle size could have significant impact on content and dose uniformity; however, tablet strength and testing during development have provided enough data to downgrade this risk to a Low level (see Table 10.5).

Conversely, due to the feed forward control strategy model, limited development data, and the desire to eliminate routine testing of dissolution as part of batch release testing, the CQA of dissolution is considered an excellent candidate for heightened testing as part of a CPV plan.

The variability of within batch results should be considered in determining the number of samples tested and sampling locations for each batch.

Although the powder blend is designed to be free-flowing, variability is estimated during early phases of production with different batches of excipients. Continued monitoring of dissolution along with material attributes and process parameters impacting dissolution is justified during the first part of CPV to confirm that the model and predictions are acceptable.

10.1.4 Step 4 – Assess Operational Practices Impact

The following operational practices could impact CU or dissolution of product:

- Multiple operators
- Multiple shifts
- Multiple equipment sets
- Process interruptions (breaks, lunches, weekends, equipment malfunctions, etc.)

A review of the level of process understanding and the design of the control strategy for PaQLInol Tablets indicates that these factors are very low risk. For example, for UDU, there are many control strategy elements that are operator-independent, such as in-line monitoring of blend homogeneity linked either to an automatic system to stop blending, or an easy-to-read revolution counter. Homogeneity is confirmed after the lubrication unit operation; therefore, reduced testing is justified during Stage 3 CPV.

Decision Process Risk Assessment Summary

Dissolution is largely dependent on three material attribute properties for PaQLInol Tablets: drug substance particle size, magnesium stearate surface area, and tablet crushing force, and one process parameter, lubrication time.

Operators can have an impact on the equipment set up and the resulting process parameters and crushing force. Although the powder blend is designed to be free-flowing, variability is estimated during early phases of production because of the different excipient batches used and use of operations personnel.

Continued monitoring of dissolution plus material attributes and process parameters impacting dissolution is justified during the first part of CPV to confirm that the model and predictions are acceptable.

Table 10.6 shows a summary of the science and risk-based evaluation for the four step CPV risk assessment as applied to CU and dissolution for PaQLInol.

Table 10.6: Summary of PV Stage 3.1 Evaluation [35]

Risk \ Quality Attribute	Content Uniformity	Dissolution
Patient Risk Level	H	H
Unit Operations Risk	M	H
Material Risk	L	H
Operations Practices Risk	L	M
Residual Overall Risk	L	M
Key: L = Little or no impact M = Indirect impact/Medium Risk H = Direct impact - CU: Based on the analysis, no additional monitoring is required post PPQ. - Dissolution: Based on the analysis, further evaluation is needed.		

Additional sampling and testing for dissolution should be included for a period of time until control and capability have been established.

10.1.5 Process Validation Stage 3.1 Monitoring Plan Summary and Criteria

Criteria could be set, such as a defined confidence interval of process capability (e.g., $C_{pk} > 1$, with 99% confidence per USP <905> utilizing greater than 30 samples [46]) that, when achieved, would drive a review to decide if and what testing could be reduced to the routine monitoring level, and which elements of the control strategy could be considered for change.

A summary of the monitoring plan for Stage 3 CPV is given in Table 10.7, with dissolution testing at a heightened level. **Note:** the table focuses on product (output) CQA testing, but the monitoring plan also could include heightened material CQAs testing, process parameter monitoring, and frequent trending of any and all results.

Table 10.7: Monitoring Summary for CPV – Example [35]

CQA	HMP	Rationale	Sampling	Acceptance Criteria	Target min C_{pk}	# of Batches	Rationale
Appearance	No	Routine sampling and inspection use AQL acceptance sampling	Routine	Meets Release Criteria	NA	NA	NA
Identity	No	Identity confirm by multiple tests (assay, dissolution, UDU)	Routine	Meets Release Criteria	NA	NA	NA
Impurities	No	Impurities controlled in API formulation and process produce stable drug product	Routine	Meets Release Criteria for Degradation Products	> 1.0	NA	NA
Friability	No	Adequate In-process control	Routine	Meets In-Process Criteria	NA	NA	NA
Hardness	No	Adequate In-process control	Routine	Meets In-Process Criteria	NA	NA	NA
Assay	No	In-process NIR provides confidence in assay	Routine	Meets Release Criteria	> 1.0	NA	NA
Uniformity of Dosage Units	No	At-line NIR for individual tablet assay and In-line weight control data provides high level CU will meet quality requirements	Routine	Meets Release Criteria	> 1.0	NA	NA
Dissolution	Yes	Complex multivariate relationship requires more data to assess robustness	60 tablets/ batch using stratified sampling	Mean > 85%; RSD 8.5 max ^{Note 1} MAs for API particle size, magnesium stearate surface area and crushing force and lubrication time monitored	>1.0	As needed to assess/ achieve C_{pk}	*MA, *CS, *CAP
Microbiological Quality	No	Oral ingestion and low water activity of the drug product formulation mitigates microbial quality issues	Routine	NA Annual Verification	Routine release requirements	NA	NA

Note 1: acceptance criteria follow ASTM E2709 [58] using 90% confidence interval

Key: AQL = Limiting Quality Level CS = Control Strategy MA = Material Attribute
CAP = Capability Analysis HMP = Heightened Monitoring Plan RSD = Relative Standard Deviation

10.1.6 Proposed Routine Monitoring Program

When the defined capability measures are achieved as part of Stage 3.1 CPV, the levels of testing may be adjusted to statistically-appropriate routine levels, which in the case of dissolution, involves RTRT. This level of testing is applied as part of the process performance and product quality monitoring system, which is likely to lead to the application of statistical evaluation, for example, capability. If RTRT is implemented, frequent monitoring of some of the direct process measurements, such as blender revolutions, should be considered.

Criteria could be set, such as a defined confidence interval of process capability (e.g., $C_{pk} > 1$, with 99% confidence), which when achieved, would drive a review to decide if and what testing could be reduced to the routine monitoring level, and what elements of the control strategy could be considered for change.

10.2 Case Study 2: Batch Size Reduction Process Performance Qualification

This case study describes the PPQ for reducing the batch size for an oral suspension drug product from the qualified batch size of 1892 L (499.8 US gal) to 946 L (249.9 US gal). This represents a 50% batch size reduction, which will allow greater flexibility with respect to product demand.

The manufacturing process for 946 L batch size consists of blending pre-weighed quantities of the formulation ingredients in a stainless steel process vessel according to the master batch record. A flow diagram depicting the compounding process is provided in Figure 10.2. Following QC release, the tank containing the blended formulation is transferred to a multi-head filling line where the blended product is dispensed into plastic containers.

Figure 10.2: Process Flow Diagram for Oral Suspension Drug Product

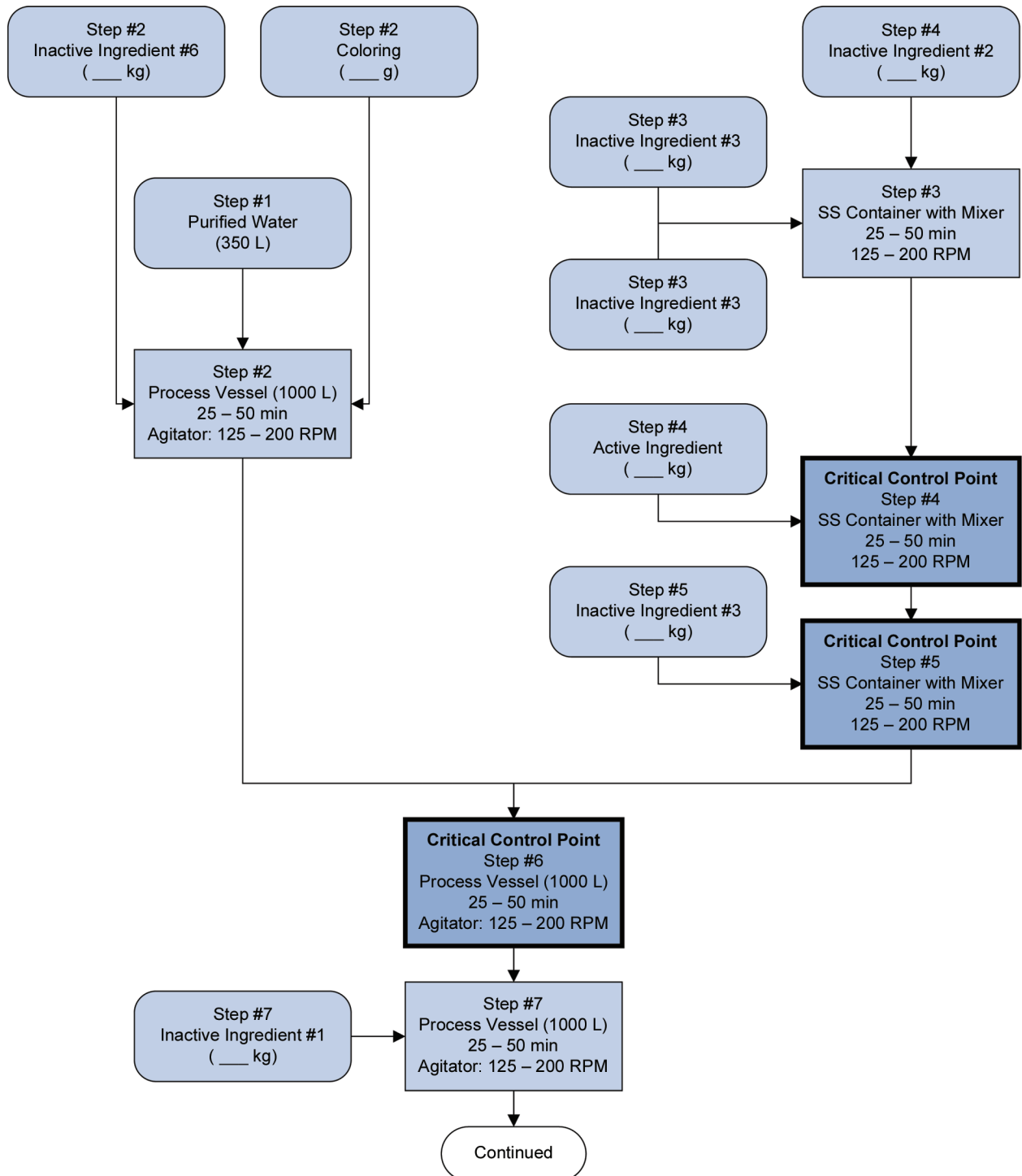
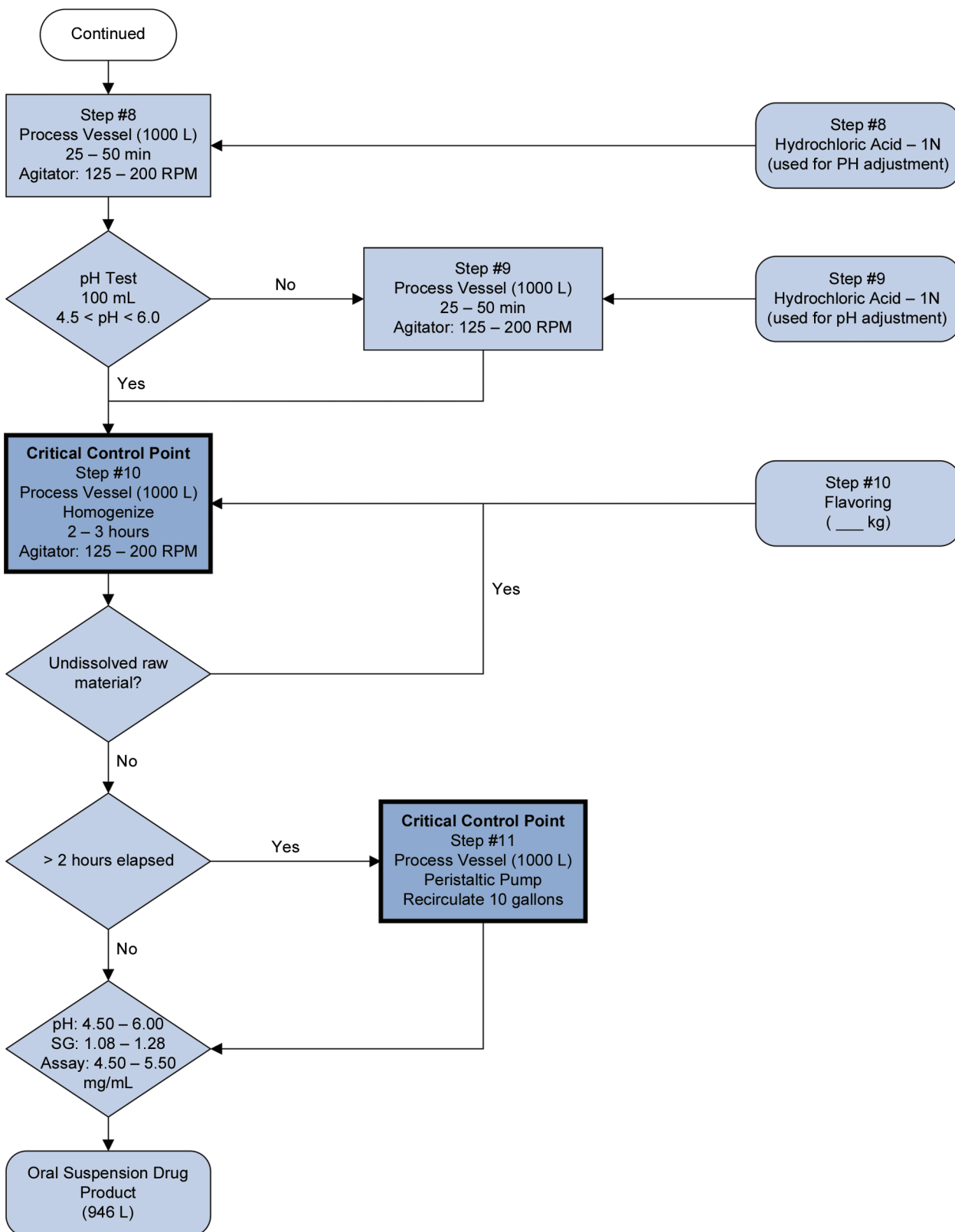


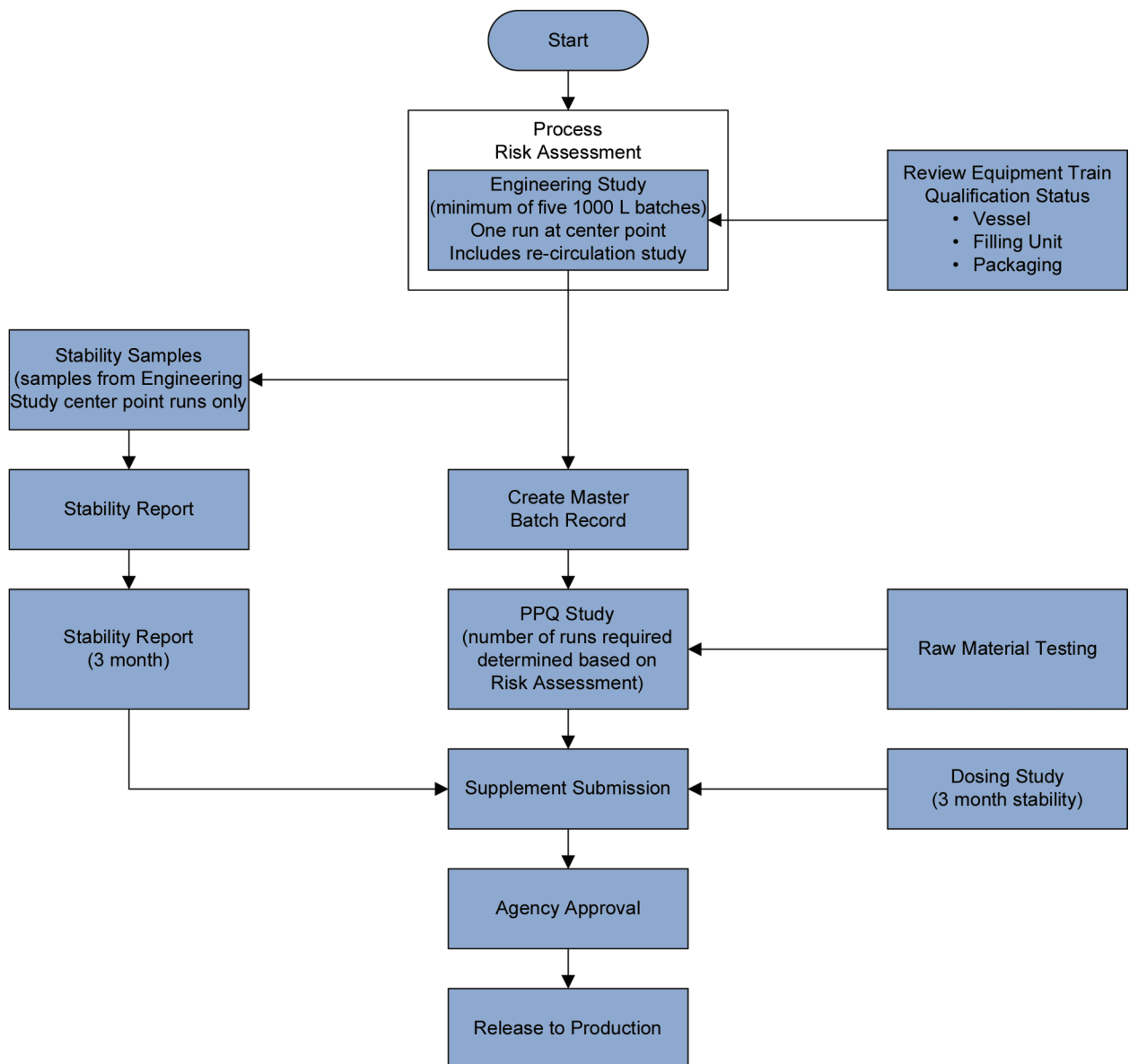
Figure 10.2: Process Flow Diagram for Oral Suspension Drug Product (continued)



10.2.1 Prerequisite Work

Prior to PPQ, a number of prerequisite activities were completed, including engineering studies to determine the blending process design space, and risk assessments to determine the criticality of each process step. A schematic overview of the batch rescale plan is provided in Figure 10.3.

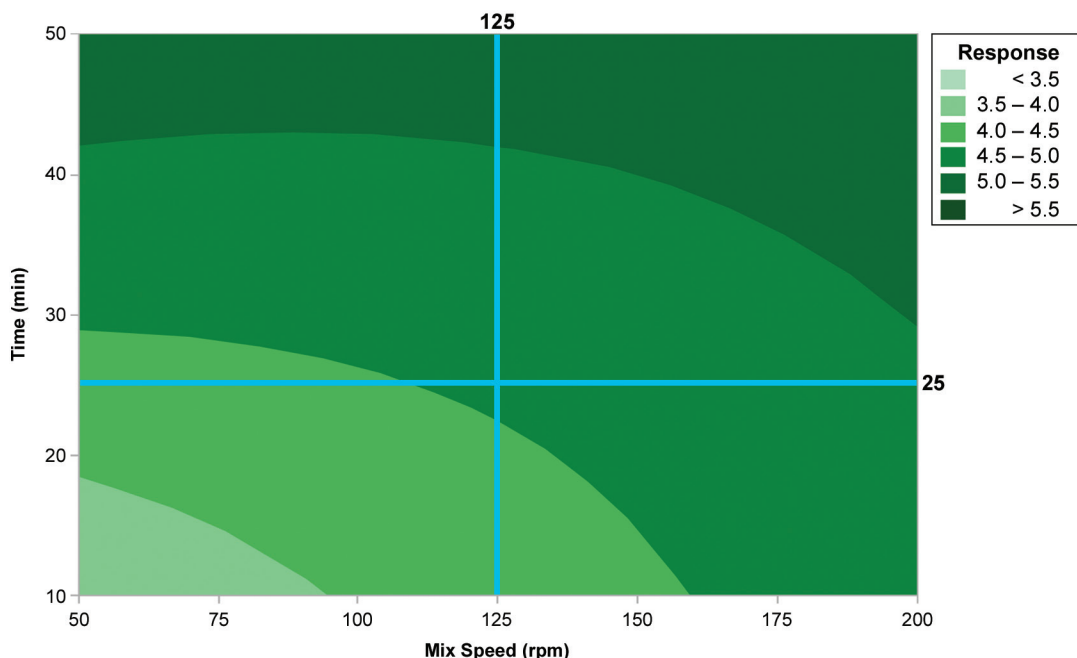
Figure 10.3: Oral Suspension Drug Product Batch Size Rescale Plan



The engineering study consisted of operating the blender at a variety of mixing speeds and times to determine the optimal parameter settings and the limits at which acceptable product can be produced.

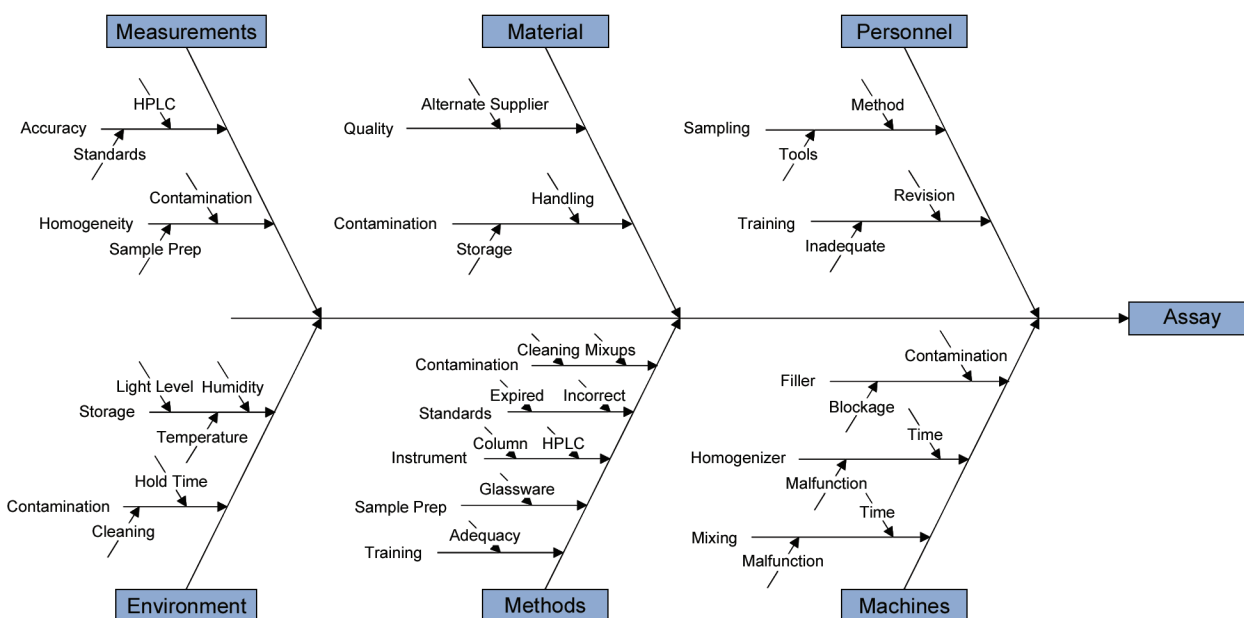
The experimental design also included one center point run in order to detect any curvature in the process response. Samples drawn from the center point run were placed on stability. Figure 10.4 is a contour plot of assay versus mix time and speed. In this case study, the knowledge space with respect to assay, mix time, and mixing speed is represented by the entire graph. The design space is defined as the area in the graph representing acceptable assay results. The design space required to achieve batch homogeneity in this example was defined as mixing times greater than 25 minutes and mixing speeds greater than 125 rpm.

Figure 10.4: Contour Plot of Assay versus Mix Time and Speed



A cross-functional team consisting of representatives from manufacturing, engineering, QC chemistry, and validation was assembled to conduct a risk assessment of the process using a process FMEA (PFMEA). To start, Ishikawa (fishbone) diagrams were prepared to identify potential sources of variation affecting each CQA. An example Ishikawa diagram for product assay is provided in Figure 10.5.

Figure 10.5: Ishikawa Diagram for Oral Suspension Drug Product Assay



After completing the Ishikawa diagrams, a PFMEA was completed (see Table 10.8) and each failure mode prioritized according to a defined risk priority scheme. The prioritization (Risk Priority Number – RPN) assigned to each failure mode was then used in conjunction with the risk associated with each CQA to determine an overall risk level (Table 10.9).

Table 10.8: Example Process Failure Mode and Effect Analysis for Oral Suspension Drug Product Manufacturing Process

Item Number	Process	Function	Failure Mode	Effects	Cause	Controls in Place	OCC	SEV	DET	RPN
	Description of process.	List all the process functions.	List all the specific failure modes that could occur for each process.	List all the effect(s) of each failure mode. Include downstream in-process effects as well as end product effects.	List all the causes for each failure mode.	List all of the controls currently in place to mitigate the probability of occurrence for each failure mode.	1 – 3	1 – 5	1 – 5	1 – 75
1. Raw Materials										
1.1.1	Active Ingredient	Active Ingredient and Suspensoid	Active forms a compact cake upon settling	Product cannot be readily dispersed on shaking	Particle size too small	Raw Material QC Testing	1	1	1	1
1.1.3			Assay out-of-spec	Bulk and Finished product does not meet spec	Different Supplier	Raw Material QC Testing	1	5	1	5
1.2.1	Inactive Ingredient #1	Sweetener/ Laxative/ Suspending agent	Crystallization	Crystals stick to bottom of drum	Storage Temperature	Container Inspection	3	1	2	6
2. Compounding Part I										
2.1.1	Weighing Step	Quantity of Ingredients	Under/Over Weigh	Distort product analytical characteristics	Scale Calibration	SOP 1-033 Scale verification checks	2	5	2	20
2.1.2					Vendor weight incorrect	SOP 3-083 Drums are weighed prior to using	2	5	1	10
3. Filling										
3.1.1	Recirculate 10 gallons prior to fill	Maintain batch uniformity	Active not fully dispersed	Product not uniform	Incorrect recirculation volume (operator error)	None	3	5	5	75
4. Packaging										
4.1.1	Capping	Induction Seal	Incomplete Seal	Product Leakage	Incorrect Cap	Inventory Control	1	3	1	3
4.1.3					Inadequate torque of pre-heat seal cap	QA Capping Checks	2	3	1	6
4.1.4					Line speed too fast	SOP for Induction Seal Set Up	3	3	3	27

Table 10.9: Process Overall Risk

		CQA Risk Level		
		1	2	3
PFMEA Risk Priority Number	1 – 25	Low	Low	Medium
	26 – 50	Low	Medium	High
	51 – 75	Medium	High	High

The overall risk level was used to determine appropriate statistical risk levels for sample size and process capability calculations. Table 10.10 shows the statistical risk level matrix applied to this process qualification.

Table 10.10: Statistical Risk Level Matrix

Overall Risk Level	Confidence (1- α)	Test Power (1- β)	Population Coverage (P)
Low	0.90	0.90	0.90
Medium	0.95	0.99	0.99
High	0.99	0.99	0.99

After successfully completing the prerequisite engineering studies and risk assessments, and assigning appropriate statistical risk levels for each CQA, the process was deemed ready for PPQ. The PPQ of the new batch size had the specific objectives to:

- Verify that the blending procedure as described in the production batch record using a 1000 L process vessel was adequate to provide a uniform product
- Verify that the filling equipment/procedure was appropriate to provide uniform content in the filled bottles to support the label claim
- Verify that the finished product consistently met requirements specified in the finished product specifications

10.2.2 Validation Methodology

A minimum of three validation batches or runs were executed for PPQ. The PPQ study was performed in two phases:

Phase 1 established the preliminary estimate of the process capability. During Phase 1, no PV batches were released until a long-term process capability (Ppk) of at least 1.0 was demonstrated for each CQA. Upon successful completion of the PPQ Phase 1 study, an interim report was written and approved allowing release of the PPQ batches to distribution. A minimum of three consecutive successful Phase 1 PPQ batches needed be completed prior to graduating to PPQ Phase 2.

In Phase 2, PPQ batches were released for distribution; however bulk and finished product sampling and testing continued at PPQ-established levels until the lower capability confidence interval bound calculated for each CQA was demonstrated to be at or above 1.0 and a state of statistical control demonstrated.

10.2.3 Sampling Plan Rationale

The sample size chosen for finished product testing in any individual validation batch or run is eight. This sample size is based on the acceptable assay range of 4.50 – 5.50 mg/mL and worst-case standard deviation of 0.13 mg/mL obtained from engineering study bulk-product test data. The sample size was calculated using the one-sample t test sample size formula:

$$n = (t_{\alpha/2} + t_{\beta})^2 \left(\frac{s}{\delta} \right)^2$$

Where:

n = Required sample size

α = Risk of rejecting a true hypothesis

β = Risk of accepting a false hypothesis

s = Sample standard deviation (historic)

δ = Difference to be detected

The α and β risk values used in the sample size calculation were obtained from the PFMEA. According to the PFMEA, the highest RPN value for any process step in the manufacture of the oral suspension drug product following mitigation is 45. Any maximum RPN value within 26 – 50 indicates that the sampling plan chosen must provide a minimum confidence ($1-\alpha$) of 0.95 and a minimum test power ($1-\beta$) of 0.99.

The sample size calculated provides 95% confidence ($\alpha = .05$) that true assay differences of 0.25 mg/mL or greater will be detected with a probability of at least 99% ($\beta = .01$). The 0.25 mg/mL assay difference is approximately 1/4 of the acceptable range for the API content in the oral suspension drug product.

The number of validation runs was determined based on the number of runs required to demonstrate a lower capability confidence interval bound ($1-\alpha = 0.95$) greater than or equal to 1.0. The minimum number of runs in any case was not less than three.

The confidence level ($1-\alpha$) used to calculate the capability confidence interval was based on the output of the PFMEA previously developed for the oral suspension drug product manufacturing process. According to the PFMEA, the maximum RPN value determined for a process step following mitigation is 36. Any maximum RPN value within 26 – 50 indicates that the long-term process capability calculated must provide a minimum confidence ($1-\alpha$) of 0.95.

Upon successful completion of the PPQ Phase 2 study, a final report summarizing the protocol testing and results for both Phase 1 and Phase 2 was written and approved qualifying the use of the 1000 L process vessel for 946 L of the oral suspension drug product. Approval of the PPQ final report indicated that sampling and testing of subsequent product batches at normal production levels as indicated in the master batch record was appropriate.

Assay data for the finished drug product is provided in Table 10.11. Capability statistics were used to assess the performance of the process.

The capability index chosen was the P_{pk} , which is calculated based on the overall process variation. Because of the limited amount of data available at the beginning of PV, the standard 3-sigma tolerance band used to calculate capability was replaced with a tolerance factor multiple of sigma calculated to cover the desired population proportion at the given confidence level.

The value of the tolerance factor (k_2) was determined based on the total number of data available from all batches collectively. The value for k_2 was updated at the completion of each batch to reflect the additional data available. Figure 10.6 contour plot shows the PV assay results depicted graphically.

Table 10.11: Process Validation Assay Results for Oral Suspension Drug Product

Oral Suspension Drug Product Process Performance Qualification Assay Results (mg/mL)								
Batch	Sample Number							
	1	2	3	4	5	6	7	8
1	5.081	4.728	4.915	5.080	4.850	5.310	4.972	4.769
2	4.804	4.900	4.822	4.862	4.684	5.200	5.151	4.856
3	5.126	4.875	4.870	5.011	4.848	5.016	5.093	5.069
4	4.710	5.094	4.943	4.940	4.979	5.141	5.018	4.977
5	4.757	4.997	4.782	4.724	5.040	5.020	4.836	5.041
6	4.846	5.035	5.216	4.949	4.965	5.027	4.984	4.947
7	4.934	5.090	5.167	4.981	4.880	4.904	5.050	4.913
8	4.770	5.142	4.841	5.037	5.005	4.958	4.749	5.031
9	5.135	4.910	5.101	4.999	5.114	4.920	4.836	5.070
10	4.804	4.907	5.012	4.887	4.891	4.981	4.730	4.891
11	4.848	4.927	5.036	5.098	4.979	5.017	5.072	4.934
12	5.075	5.034	4.873	4.809	5.083	5.092	5.057	4.830
13	5.005	5.058	4.802	5.010	5.154	5.082	5.045	4.904
14	4.866	4.997	5.015	5.156	4.810	4.898	5.005	5.007
15	4.923	4.839	4.944	5.026	4.932	4.752	4.839	4.977

Figure 10.6: Graph of Process Validation Assay Results for Oral Suspension Drug Product

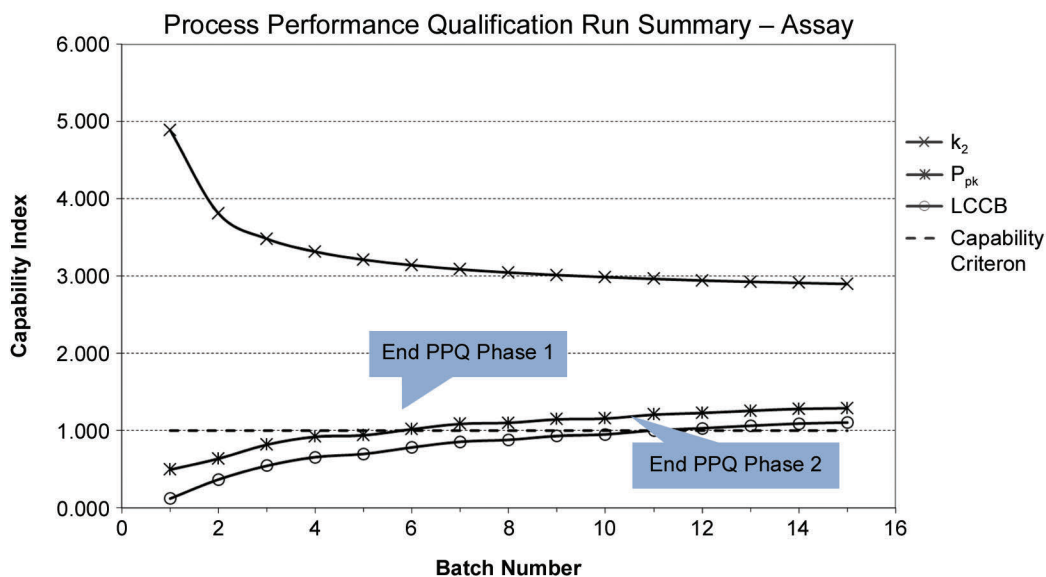


Figure 10.6 shows the P_{pk} , Lower Capability Confidence Bound (LCCB), and k_2 values for each batch plotted on the same chart. The minimum capability criterion chosen for the PPQ study was 1.00.

As can be seen in Figure 10.6, k_2 decreases asymptotically as more PV batches are added to the data set. This decrease is roughly mirrored by the simultaneous increase in P_{pk} and the LCCB. The gap between the capability estimate and the LCCB also decreases as the chart progresses to the right. This narrowing is the result of increasing sample size as more PPQ runs are added, which in turn yields improved estimates of P_{pk} .

Additionally, Figure 10.6 shows that assay capability reached the minimum capability criterion at PPQ run 6. To demonstrate that significant variability estimates had been achieved, additional runs were monitored at the PPQ-established sampling and testing levels until the LCCB also rose above the minimum capability criterion. At run 11, the LCCB rose above the minimum capability criterion, thus completing the second PPQ phase.

11 Appendix 3 – NDA Products Case Studies: Large Molecules or Bio-derived Products

11.1 Case Study 1: Large Molecule Example Column Chromatography Step – Parameter Selection for CPV [35]

The greatest challenge for demonstrating continuation of the validated state for a biological product (i.e., CPV) is often the limited amount of data that a manufacturer has at the commercial scale prior to the commencement of both PPQ and CPV.

Since biological manufacturing processes are typically very expensive and time consuming, sponsors will often run a limited number of engineering batches at the commercial scale prior to the initiation of PPQ, and may complete a relatively low number of commercial batches before submitting a regulatory application. FDA suggests [3]:

“...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...”

It is clear that there is regulatory concern about reducing the testing plan prematurely (i.e., with a lack of statistical confidence in the process).

That said, there are a considerable number of parameters assessed during the PPQ exercise that are not subject to variability estimates. They may be subject to some type of trending, but it was determined that SPC methods are not needed because the results are below an analytical method's Limit of Quantitation and/or Limit of Detection, or they are not subject to Normal distribution, or are Pass/Fail results.

In addition, most statistical tools require a minimum number of batches before trend limits/control limits/variability estimates can be applied. This creates a bit of “grey area” between PPQ and when a manufacturer can objectively apply statistical tools for assessing maintenance of the validated state.

In light of the comments above, Table 11.1 shows an example of a bridging strategy between PPQ and CPV. The parameters included in the table represent those parameters that were defined in the control strategy as requiring inclusion in the PPQ exercise (including all critical operating parameters, IPCs, In-Process Acceptance Criteria (IPAC), and additional sampling).

From that starting point, parameters were assessed for whether or not they needed to be included in the formal CPV effort. The Action/Rationale column contains a justification for the decision reached by a multi-functional project team.

Just as it is important during PPQ to state clearly that “All parameters matter, but some more than others,” so it is with CPV, where it should be understood that “All parameters matter, but only a subset are subject to statistical assessment and/or trending.”

It may be unnecessary to trend certain parameters during CPV, but that does not mean they are insignificant to demonstrating the validated state. It just means that there are existing quality systems that should be leveraged to ensure the validated state.

While specific parameter determinations will vary by sponsor, this example of product “AEX” should provide some guidance with regard to the types of discussion necessary prior to the initiation of the CPV program.

Table 11.1: Example Bridging Strategy between PPQ and CPV [35]

Critical Operating Parameter	Normal Operating Range	Include in CPV	Action/Rationale
None			
In-Process Control	Limit(s)	Include in CPV	Action/Rationale
Packed Bed Height	32.0 ± 2.0 cm	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
Number of cycles since last passing HETP test	< 5	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
Total Number of Previous Uses on Resin	< 32	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
Column Backpressure during Equilibration, Load, Wash, and Elution	≤ 25 psig	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
Outlet pH (offline) at End of Equilibration	5.0 ± 0.2	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
Protein Load per Volume of Resin	≤ 20 g/L	No	Not subject to normal distribution; failures addressed under existing quality system (i.e., deviation investigation)
In-Process Acceptance Criteria	Acceptance Criteria	Include in CPV	Action
Eluate Endotoxin	Alert Limit: ≥ 5 EU/mL Action Limit: ≥ 10 EU/mL	Yes	Compare to historical commercial data for assurance of consistency of environmental, water, and equipment microbial control.
Eluate Bioburden	Alert Limit: ≥ 10 CFU/10 mL Action Limit: ≥ 50 CFU/10 mL	Yes	Compare to historical commercial data for assurance of consistency of environmental, water, and equipment microbial control.
Step Yield (A ₂₈₀)*	≥ 75%	Yes	Control chart to continuously verify that desired unit operation output is consistently met.
Eluate Purity (RP-HPLC)	≥ 85%	Yes	Control chart to continuously verify that desired unit operation output is consistently met since PV batches had downward trend.
Additional Sampling	Acceptance Criteria	Include in CPV	Rationale
Eluate Host Cell Protein Content	< 500 ng/mL	No	Adequately demonstrated removal during PV batches; consecutive PPQ batches were all > 10× lower than the acceptance criterion
Eluate DNA Content	< LOQ	No	Adequately demonstrated removal during PV batches; consecutive PPQ batches were all < LOQ

**While step yield is not a product quality measurement, it is an important indicator of process performance and shows that the desired product quality can be achieved in a consistent manner.*

The four parameters identified as requiring inclusion in the formal CPV exercise were:

- Eluate endotoxin
- Eluate bioburden
- Step yield
- Eluate purity by RP-HPLC

Data from 10 batches (including 2 representative engineering batches as well as the 3 PPQ batches) were collected and assessed on an ongoing basis, but summarized for the purpose of this example. It is assumed that testing/monitoring would be ongoing until the defined number of batches is achieved, at which time the CPV acceptance criteria may be reassessed.

Eluate endotoxin is a routine IPAC with an associated alert limit of ≥ 5 EU/mL and an action limit of ≥ 10 EU/mL.

Eluate bioburden is a routine IPAC that has an associated alert limit of ≥ 10 CFU/10 mL and an action limit of ≥ 50 CFU/10 mL.

As stated in Table 11.2, neither eluate endotoxin nor bioburden are subject to Normal distribution since results are frequently at or near the limit of detection for the respective analytical methods. Consequently, the data cannot be control charted or subjected to Cpk, but they can be tabulated and subjectively assessed for observable trends.

While there is a defined quality system in place that would identify an IPAC failure, for example a deviation investigation, such an investigation may not include an assessment for data trending upward toward the alert or action limit. In this case, it is valuable to include this parameter in the formal CPV assessment to ensure that such a trend would be detected and any problems with associated systems like environmental control, water quality, and equipment cleaning could be identified early and addressed prior to impacting product quality.

From the individual data sets in Table 11.2, the conclusion could be drawn after each lot that there are no observable trends; therefore, the process is in a state of control with regard to AEX eluate endotoxin and bioburden.

Table 11.2: Eluate Data Sets [35]

<i>AEX Eluate Endotoxin Data</i>			
Lot Number	Result (EU/mL)	Lot Number	Result (EU/mL)
Engineering #1	< 0.5	004	2
Engineering #2	1	005	< 0.5
001 (PPQ #1)	2	006	1
002 (PPQ #2)	< 0.5	007	1
003 (PPQ #3)	< 0.5	008	< 0.5

Table 11.2: Eluate Data Sets [35] (continued)

<i>AEX Eluate Bioburden Data</i>			
Lot Number	Result (CFU/10 mL)	Lot Number	Result (CFU/10 mL)
Engineering #1	4	004	0
Engineering #2	0	005	1
001 (PPQ #1)	1	006	2
002 (PPQ #2)	0	007	1
003 (PPQ #3)	0	008	0

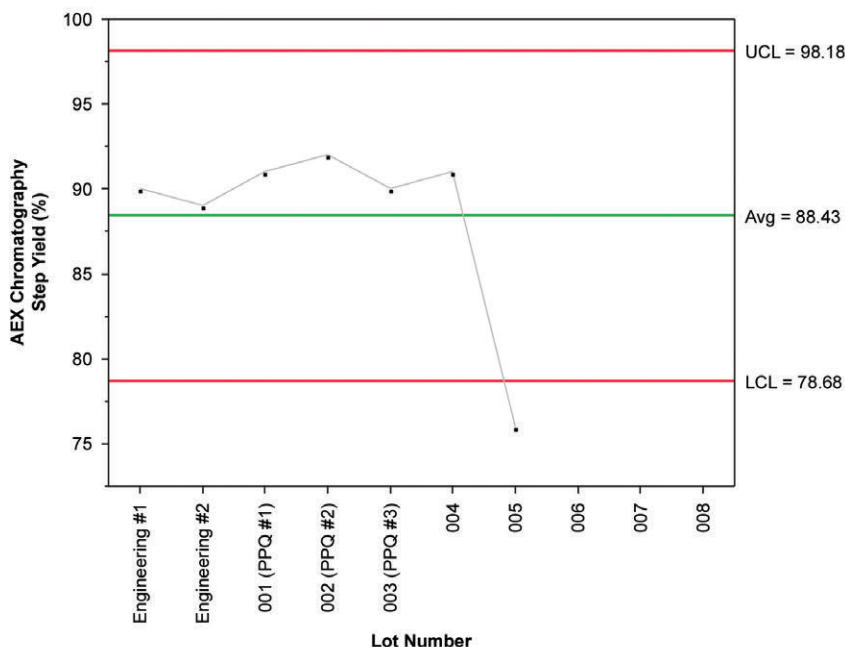
While step yield does not impact the defined CQAs for this process, it is considered a key performance indicator and important for the maintenance of the validated state.

As CPV data was collected and control charted, a value was obtained for Lot 005 that prompted an investigation. The control chart showed a clear out-of-control result, although the defined IPAC was met (see Table 11.3 and Figure 11.1). This result was investigated to ensure that it was not caused by an unknown source of process variability.

Table 11.3: AEX Step Yield Data (through Lot 005) [35]

Lot Number	Result (%)	Lot Number	Result (%)
Engineering #1	90	004	91
Engineering #2	89	005	76
001 (PPQ #1)	91	--	--
002 (PPQ #2)	92	--	--
003 (PPQ #3)	90	--	--

Figure 11.1: Individual Measurement of AEX Chromatography Step Yield (%) [35]



Lot 005 was investigated to assess the out-of-control limit result. While the step yield met the defined IPAC of $\geq 75\%$, the result of 76% was below the calculated lower control limit. Upon investigation, it was determined that an operator had switched over to the waste fraction prematurely on the back side of the main peak collection (Target: 0.2 AU; Actual: 0.5 AU).

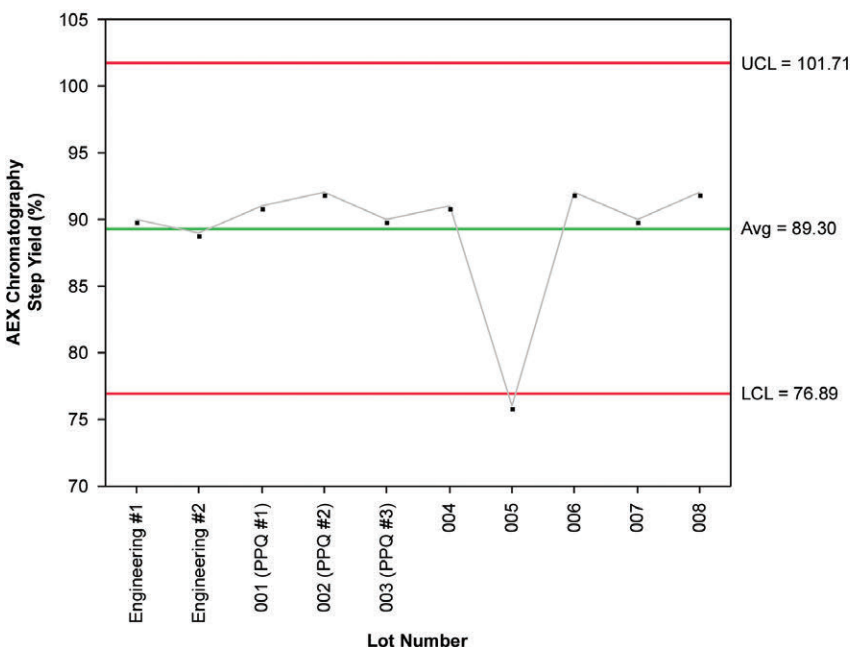
Since this out-of-control value was explained by operator error, the resulting step yield value meets the defined IPAC, and the out-of-control result is not attributable to inherent process variability, there is no impact to the validated state and no further action is required.

Inclusion of the data point artificially inflates the calculated control limits, which would no longer represent the true process variability. Additional data is presented in Table 11.4 and in the revised control chart in Figure 11.2.

Table 11.4: AEX Step Yield Data (Through Lot 008) [35]

Lot Number	Result (%)	Lot Number	Result (%)
Engineering #1	90	004	91
Engineering #2	89	005	76
001 (PPQ #1)	91	006	92
002 (PPQ #2)	92	007	90
003 (PPQ #3)	90	008	92

Figure 11.2: Individual Measurement (Revised) of AEX Chromatography Step Yield (%) [35]

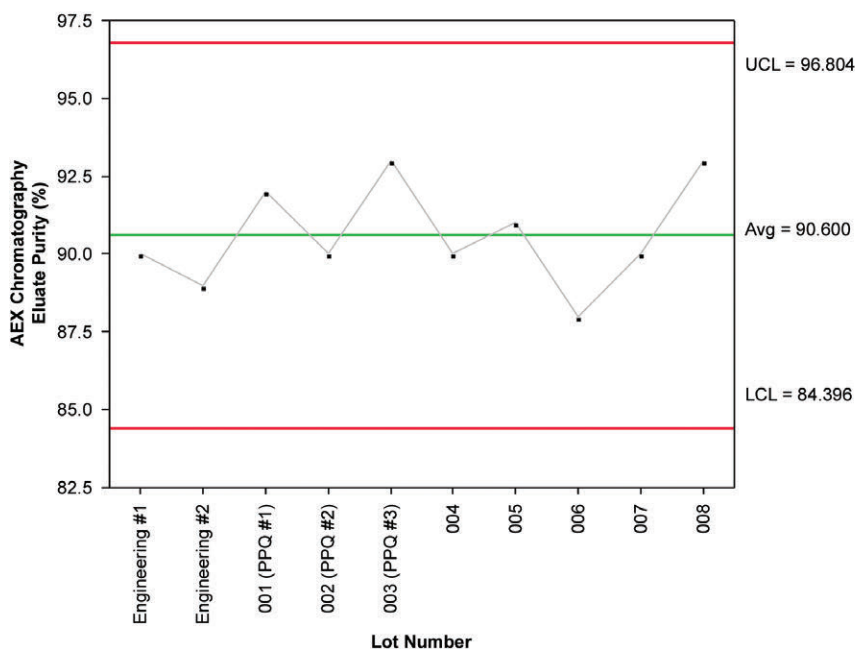


Eluate purity by RP-HPLC has a defined IPAC of $\geq 85\%$. Data was control charted on a per-batch basis. Data for 10 batches is provided in Table 11.5 and Figure 11.3, Final Control Chart.

Table 11.5: AEX RP-HPLC Purity Data [35]

Lot Number	Result (%)	Lot Number	Result (%)
Engineering #1	90	004	90
Engineering #2	89	005	91
001 (PPQ #1)	92	006	88
002 (PPQ #2)	90	007	90
003 (PPQ #3)	93	008	93

Figure 11.3: Individual Measurement of AEX Chromatography Eluate Purity (%) [35]



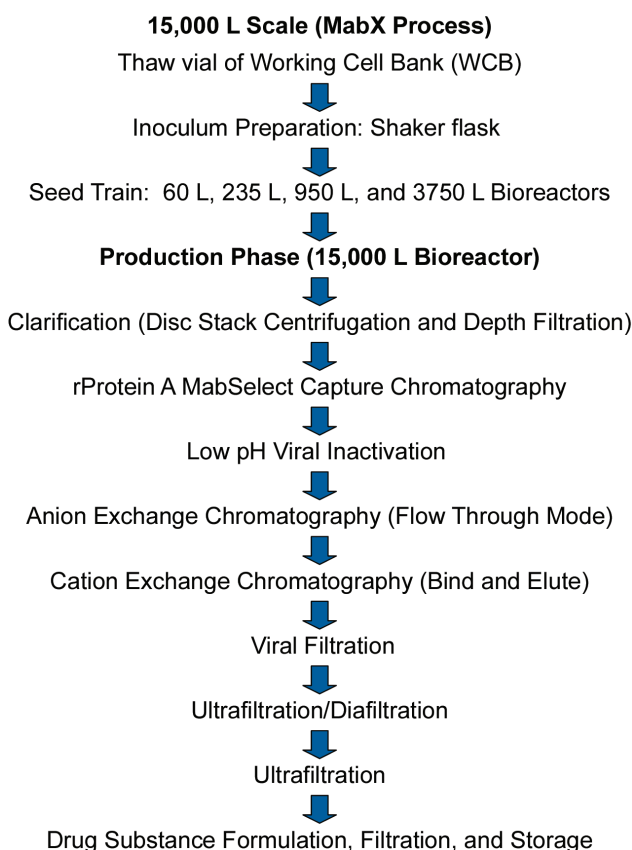
While SPC rules (e.g., Western Electric) cannot yet be applied, the plot is useful for demonstrating tightness of control within the calculated control limits. In addition, the lower control limit (84.396) confirms that the defined acceptance criterion for eluate purity was appropriately established based on the inherent process variability (assumes that the CQAs are being met).

11.2 Case Study 2: Process Validation of a Cell Culture Product

Using a cell culture production bioreactor step as an example, this case study describes the risk assessment and process characterization studies performed to define the control strategy, confirm the control strategy during PPQ, and conduct the CPV program. The description of the drug substance “MabX” validation illustrates that the process is in a state of control.

The manufacturing process of MabX is shown in Figure 11.4.

Figure 11.4: MabX Manufacturing Process Flow Diagram



11.2.1 MabX Process Design and Characterization

11.2.1.1 Process Control Strategy Development Overview

The MabX manufacturing process and control strategy was developed based on initial process development studies, clinical manufacturing experience, process characterization (robustness and range finding) studies, and process and product risk assessments.

Product risk assessments were carried out to identify CQAs. In addition, process risk assessments were conducted to identify high and medium risk parameters, and to help select parameters for investigation and modeling process characterization studies.

Process characterization studies included multiple variables using a statistical DoE approach. The CQAs were monitored as appropriate during these studies, and individual parameters within unit operations were identified that impact CQAs, titer, and yield.

The results were used to classify the process parameters and define the process control strategy. Process parameters, including ranges tested in development and the control ranges for GMP manufacturing, were documented in Process Parameter Reports (PPRs) for both the cell culture (upstream) and the purification (downstream) processes. The PPRs were approved prior to initiation of the PPQ campaign.

After the PPQ campaign, additional structure-activity-relationship and process characterization studies were completed. The product and process risk assessments were revised to incorporate knowledge gained from these studies and the PPQ studies. The PPRs were updated with revised parameter classifications and control ranges.

11.2.1.2 Risk Assessment Overview

Risk assessments were carried out throughout the product development lifecycle of MabX in order to increase assurance of patient safety, product efficacy, and manufacturing consistency.

The methodology employed for product risk assessment and determination of MabX CQAs involved ranking the potential impact of each quality attribute on potency, efficacy, and/or safety of the product, and the certainty with which the impact was understood at the time of the risk analysis.

Numerical scoring systems for the "Impact Factor" and "Uncertainty Factor" were developed and used to determine the overall risk score, the RPN. The RPN determined whether an attribute was classified as a CQA or a non-CQA. Following identification of the initial CQAs of MabX, two process risk assessments were conducted on the manufacturing process focusing on those parameters that impact CQAs and process consistency.

In the initial process risk assessment, prior knowledge of the process, including development and manufacturing history, was used to identify high and medium risk parameters and to select parameters for subsequent process characterization studies.

The information acquired from those studies, plus knowledge gained from manufacturing experience and structure-activity-relationship studies, provided the basis for a second assessment to evaluate process risk.

For parameters that had high or medium risk after the second assessment, the process control strategy was adjusted to mitigate their risk, which included adjustment of control ranges or addition of IPCs or tests.

11.2.1.3 Process Characterization

Prior to PPQ, process characterization studies were carried out on each unit operation of the MabX process. These consisted of DoE process modeling studies, column lifetime studies, centrifuge and ultrafiltration robustness studies, column elution fractionation studies, intermediate hold time studies, and solution lot record studies.

An initial process risk assessment was conducted to determine which parameters would be further investigated in process characterization studies for the cell culture process (summarized in Table 11.6).

Some additional parameters identified as medium risk during the initial risk assessment (such as total antifoam addition and batched medium hold time) were studied in a univariate fashion in order to support action limits in the manufacturing process. These parameters are not included in Table 11.6.

For production bioreactor characterization, effects on product quality were assessed by clarifying the cell culture harvest using bench top centrifugation and 0.2 µm filtration, followed by purification using Protein A chromatography.

For the production bioreactor, a 3 L scale-down model (same functions and design as the full-size production bioreactor) was used for the process characterization experiments, which were performed using a DoE strategy. The statistical design and the relationship between the input and output parameters examined during process characterization are provided in Table 11.7.

In the production bioreactor step, three parameters, namely temperature, pH, and dissolved oxygen, were found to impact the product glycoforms (especially Man5, G0F, and G1F), product purity levels, and charge isoforms.

Cell culture duration was identified as a low-risk parameter during the initial process risk assessment; however, subsequent experiments showed an increase in acidic isoforms and oxidation with an increase in culture duration. These parameters were classified as critical parameters and appropriate action limits were set.

The set points and action limits for pH and culture duration varied from the manufacturing set points used in the previous clinical campaign, but the changes were justified by the improved robustness on the PQ attributes.

Table 11.6: MabX Production Bioreactor Step Process Parameters from Initial Process Risk Assessment

Step	Input Parameters Studied in Screening Studies	Parameters Dropped Based on Screening Studies	Input Parameters Studied During Response Surface Modeling Studies
Production Bioreactor	- High Risk - Bioreactor Temperature - Bioreactor pH - Bioreactor Dissolved Oxygen - Day 0 Seed Density - Medium Concentration	Medium Concentration	- High Risk - Bioreactor Temperature - Bioreactor pH - Bioreactor Dissolved Oxygen - Day 0 Seed Density

Table 11.7: Summary of Process Characterization Studies for the MabX Production Bioreactor Steps

Process Step	Statistical Design and Scale	Output Parameters	Input Parameter(s) that Impact Output Parameters
Production Bioreactor	Screening DoE: five factor two level resolution V fractional factorial design – 20 runs at laboratory scale Response Surface Model DoE: face centered four factor central composite design – 11 runs at laboratory scale	Peak viable cell density	- pH - Seed density - Temperature - Dissolved Oxygen
		Cumulative integral of cell growth	- pH - Seed density - Temperature - Dissolved Oxygen
		Culture viability	- pH - Dissolved Oxygen
		Titer	- pH - Seed density - Temperature - Dissolved Oxygen
		Glycoforms	- Temperature - pH - Dissolved Oxygen
		Product purity	- Temperature - pH
		Charge isoforms (acidic isoforms)	- Temperature - pH - Culture Duration
		Oxidized species	Culture Duration

11.2.1.4 Define Process Control Strategy

Based on the risk assessment and results from process characterization studies, the control strategy for the MabX process was determined, including the identification of key controlled parameters and critical controlled parameters, along with IPCs and In-Process Tests (IPTs).

Process parameters for each unit operation were first categorized as input parameters or output parameters. Input parameters were then classified as critical, key, or non-key based on the process characterization data. (**Note:** these are company-specific terms.)

A **critical controlled parameter** is an input process parameter that impacts product quality within a unit operation and may also affect process performance. Critical controlled parameters have operating ranges and action limits. Exceeding the action limit for a critical controlled parameter triggers the filing of a deviation.

A **key controlled parameter** is an input process parameter that may affect process performance (e.g., yield), but is unlikely to affect product quality. Key controlled parameters have operating ranges and action limits. Exceeding the action limit of a key controlled parameter triggers the filing of a deviation.

A **non-key controlled parameter** is an input process parameter that is unlikely to impact either the process performance or product quality. Non-Key controlled parameters have operating ranges.

Output parameters were classified as IPCs*, IPTs**, or In Process Measurements (IPMs). IPCs and IPTs were further classified as critical or not. Each output was monitored during PPQ along with its action limits.

**IPCs and **IPTs are steps and adjustments that occur during the production process to ensure that the process remains in control.*

The process controls for the production bioreactor step are presented in Tables 11.8 to 11.10.

The rationale for the categorization of key controlled parameters and critical controlled parameters for the production bioreactor is summarized in Table 11.8.

The action limits for these key controlled parameters and critical controlled parameters were assigned based on process characterization studies and the resulting statistical models. The action limits for critical controlled parameters were set to achieve the proposed specification for charge heterogeneity and product purity in the MabX drug substance, as well as to maintain adequate control of oxidation and glycosylation.

Table 11.8: Controlled Parameters for the Production Bioreactor

Parameter	Parameter Type	Rationale
Bioreactor Temperature Storage (°C)	Key Controlled Parameter	Impact to cell growth, viability
Bioreactor Temperature Storage (°C) (if inoculating less than 24 hours after batching)	Key Controlled Parameter	Impact to cell growth, viability
Bioreactor Temperature Equilibration (°C)	Key Controlled Parameter	Impact to cell growth, viability Overheating of the medium can inactivate medium components and reduce cell growth
Bioreactor pH Post Equilibration Storage	Key Controlled Parameter	Impact to online pH, cell growth, viability

Table 11.8: Controlled Parameters for the Production Bioreactor (continued)

Parameter	Parameter Type	Rationale
Transfer Time to Inoculate Production Bioreactor (hours)	Pre-process consistency validation campaign: <i>Key Controlled Parameter</i> Post PPQ campaign: <i>Non-Key Controlled Parameter</i>	Originally classified as key based on potential to impact cell growth and Day 0 viable cell density if the temperature and pH control are not maintained. Was downgraded to a non-key parameter post PPQ as the transfer is an automated process occurring between two controlled bioreactors and control is always maintained.
Seed Density (viable cells/mL)	Pre-process consistency validation campaign: <i>Critical Controlled Parameter</i> Post PPQ campaign: <i>Key Controlled Parameter</i>	Originally classified as critical due to impact on cell growth, product concentration, acidic isoforms, glycoforms, and single highest impurity. Post PPQ campaign, reclassified because impact of seed density on acidic isoforms, glycoforms, and single highest impurity is not of practical significance, and its impact on harvest titer, although significant, is expected to satisfy harvest titer action limit criteria. Due to these reasons the parameter was downgraded from a <i>Critical Controlled Parameter</i> to a <i>Key Controlled Parameter</i> .
Online pH: Day 0 – Harvest	Critical Controlled Parameter	Impact to cell growth, product concentration, acidic isoforms, other charge isoforms, glycoforms, single highest impurity. At higher pH, there was an increase in the following glycoforms: %Man5, %sialylation, and %peak3 levels; however, at lower pH the acidic species were higher. pH also impacted terminal galactosylation.
Online Temperature (°C)	Critical Controlled Parameter	Impact to cell growth, product concentration, acidic isoforms, other charge isoforms, glycoforms, single highest impurity. Higher temperature led to higher percent acidic species, while lower temperature led to higher %Man5 and %peak3 glycoform levels
Online Dissolved Oxygen (%): Days 0 – 5	Key Controlled Parameter	Impact to cell growth
Online Dissolved Oxygen (%): Days 5 – Harvest	Critical Controlled Parameter	Impact to cell growth, product concentration, charge isoforms, glycoforms, aggregate. Increase in dissolved oxygen led to increase in %Man5 and also impacted terminal galactosylation levels.
Agitation Days 0 – 10 (rpm)	Key Controlled Parameter	Impact to cell growth
Nutrient Feed Media Daily Amount (L)	Key Controlled Parameter	Impact to cell growth
Maximum Total Antifoam Added (kg)	Key Controlled Parameter	Keep level below validated clearance level
Culture Duration (days)	Key Controlled Parameter/ Critical Controlled Parameter	Culture duration is classified as a <i>Critical Controlled Parameter</i> at the upper end due to its impact on acidic isoforms and oxidation. At the lower end it is a <i>Key Controlled Parameter</i> , due to its impact on cell mass accumulation, cell viability, and titer.

The rationale for the production bioreactor IPCs and IPTs (including Critical In-Process Tests (CIPTs)) is summarized in Tables 11.9 and 11.10, respectively.

Table 11.9: In-Process Controls for Production Bioreactor

Parameter	Parameter Type	Rationale
Culture Viability, Stage L, Day 0 (%)	IPC	Ensures inoculated culture is healthy enough for growth consistent with historical experience.
Culture Viability, Stage L, Day 10 (%)	IPC	Ensures input to clarification and purification process is consistent with historical experience.

Table 11.10: In-Process Tests for Production Bioreactor

Parameter	Parameter Type	Rationale
Stage L Harvest Titer (mg/L)	IPT	Ensures that the cell culture process performs within expectations and that the amount of product produced is within the designed capacity of the purification process.
Stage L Harvest Sample, CNC	CIPT	Ensure the product stream is not subjected to microbial contamination.
Stage L Harvest Sample, <i>In Vitro</i> Adventitious Virus	CIPT	Ensure the product stream is not subjected to viral contamination.
Stage L Harvest Sample, Mycoplasma	CIPT	Ensure the product stream is not subjected to mycoplasma contamination.
Stage L Day 5 Sample, MMV Q-PCR	Pre-process consistency validation campaign: <i>CIPT</i> Post-process consistency validation campaign: <i>IPT</i>	The MMV-QPCR assays on Day 5 and at Harvest are an additional control that limits the potential impact to downstream processing operations. Batch release criteria still require a passing <i>in vitro</i> adventitious agents assay, which will detect MMV if present.
Stage L, Harvest sample, MMV Q-PCR*	Pre-process consistency validation campaign: <i>CIPT</i> Post-process consistency validation campaign: <i>IPT</i>	
*Sample is routinely taken but only tested if Day 5 MMV Q-PCR sample is inconclusive or incomplete. Key: CNC = Confirmation of No Contamination MMV = Mice Minute Virus Q-PCR = Quantitative Polymerase Chain Reaction		

11.2.2 MabX PPQ – Campaign Summary

Manufacturing MabX PPQ was performed in a large-scale facility that consists of three equivalent bioreactor trains and two equivalent purification suites.

Each bioreactor train contains four seed train bioreactors (60 L, 235 L, 950 L, and 3,750 L) and two equivalent 15,000 L production bioreactors. The harvest equipment is located in the cell culture area. The purification suites and rooms have chromatography, viral inactivation, viral filtration, and ultrafiltration equipment.

The MabX PPQ campaign consisted of five batches planned and designated as PPQ batches on equivalent bioreactor Trains 2 and 3, Harvest Area 2, and Purification Suite 1 as shown in Table 11.11.

Three runs were performed in bioreactor Train 3, utilizing production bioreactor T3-BR-1. Two additional runs were produced in bioreactor Train 2, in production bioreactors T2-BR-1 and T2-BR-2, respectively. The five PPQ runs successfully qualified bioreactor Trains 2 and 3, and production bioreactors T3-BR-1, T2-BR-1 and TR-BR-2 for commercial manufacturing of MabX.

Table 11.11: Batch Strategy in MabX Process Performance Qualification Campaign

Batch Number	MabX-001	MabX-002	MabX-003	MabX-004	MabX-005
Bioreactor Train	T3	T2	T3	T2	T3
Production Bioreactor	T3-BR-1	T2-BR-1	T3-BR-1	T2-BR-2	T3-BR-1
Harvest Suite	2	2	2	2	2
Purification Suite	P1	P1	P1	P1	P1

Process consistency validation was completed for each step in the manufacturing process. An approved protocol defined the scope of each process consistency validation exercise and the acceptance criteria, which were based on the ability to maintain controlled parameters within allowable ranges and to produce outputs that reflected the appropriate performance of the unit operations.

The acceptance criteria for MabX process consistency validation protocols are as follows:

- All critical controlled parameters, CIPTs, and Critical IPCs (CIPCs) that fail to meet the action limits and/or ranges must be assessed and determined to not impact the consistent performance of the unit operation and the validity of the study.
- Key controlled parameters, IPTs, and IPCs that fail to meet the action limits and/or ranges must be assessed and determined to not impact the consistent performance of the unit operation and the validity of the study.
- As specified in the Process VMP, consecutive batches are required to demonstrate consistency and/or reproducibility. Non-consecutive batches separated by failed batches whose failure can be attributed to a non process-related cause (e.g., operator error) are acceptable.
- Critical, major, and minor manufacturing and testing deviations that occur during the execution of this unit operation must be listed in the final report and determined to have no impact the validity of the study.
- Any validation protocol exceptions must be described in the final report and determined to have no impact on the validity of the study.

- Any failure of the drug substance to meet product quality release testing requirements specified in the Certificate of Analysis (CoA) or release requirements specified in the certificate of conformance must be shown to be unrelated to the unit operation being validated.

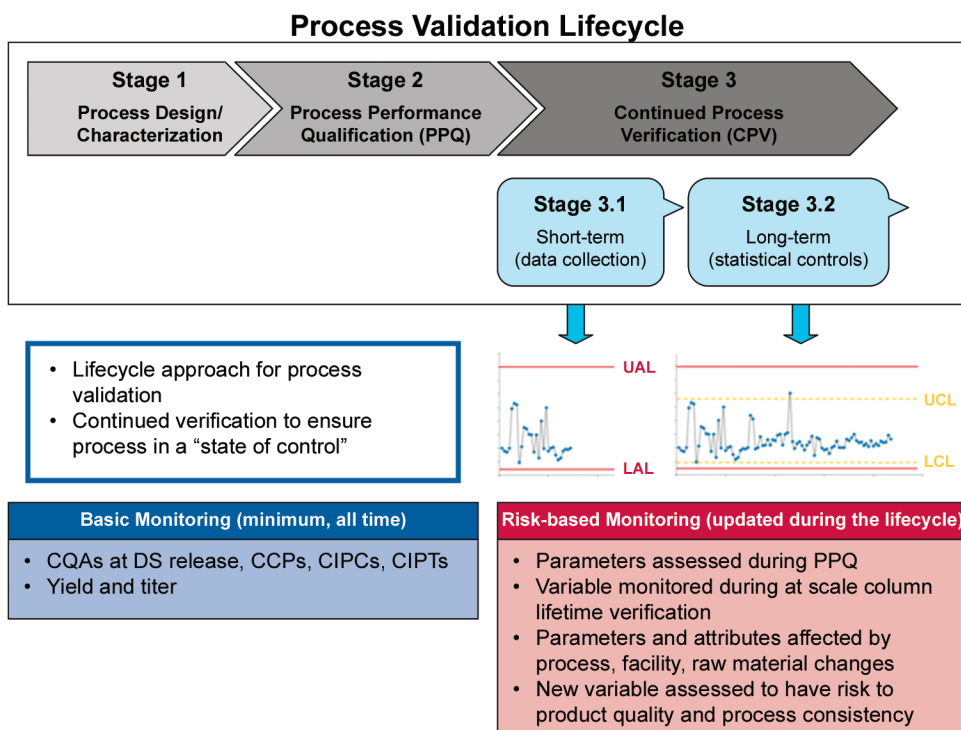
The key controlled parameters, critical controlled parameters, CIPTs, IPTs, CIPCs, and IPCs were monitored for the production bioreactor steps from all of the process consistency validation campaign batches. All five batches were successfully completed and met all product quality specifications.

Based on the acceptance criteria outlined in the validation protocol, the production bioreactor step was validated on bioreactor Trains 2 and 3 and production bioreactors T2-BR-1, T2-BR-3, and T3-BR-1. All controlled parameters, IPCs, and IPTs were maintained within the action limits. Upon investigation, any manufacturing or testing deviations and exceptions to the protocol did not impact the validity of the study.

11.2.3 MabX CPV

After successful PPQ and prior to the commercial manufacturing campaign, the CPV plan is established, which defines control parameters, IPTs, and IPCs, and drug substance to be monitored and trended.

Figure 11.5: Continued Process Verification Strategy



Variables monitored in the CPV plan consist of the minimum variables, including:

- All release assays for drug substance, CIPCs, and CIPTs
- Critical controlled parameters and CMAs (if defined)
- Overall and step yields and cell culture titers

In addition, the risk-based variables are generated from the risk assessment and monitored for a defined period. The CPV plan can be updated for the addition or removal of these variables with appropriate justifications documented. Risk-based variables include:

- Variables monitored during PPQ (excluding minimum variables)
- Variables monitored for the at-scale verification of the resin lifetime of chromatography steps
- Parameters and attributes affected by the changes of sites, process, assay, critical raw material, and equipment

Trending methods and rules for detecting signals are defined for the variables in the CPV plan. Run charts with specifications and action limits will be used in CPV Stage 3.1, during which limited batches (typically < 30) have been manufactured. Statistical Control Limits (SCL) will be established at the end of Stage 3.1 or after the required sample size is achieved.

Control charts will be used in the CPV Stage 3.2 for variables with SCL. Run charts can be continued for variables without SCL in the CPV Stage 3.2.

If a signal (within specification or action limits) is detected from CPV monitoring, it will be assessed for risk to the product or process. An investigation may be initiated to identify the root causes, and corrective and preventive actions assigned, if necessary, to implement process changes or process improvements.

Implementation of the CPV plan ensures that MabX manufacturing is in a state of control during commercial production.

12 Appendix 4 – Contract Manufacturing Product Case Studies

The following case studies are examples of real products that have been manufactured and/or developed at a CDMPO. Some details have been changed to maintain confidentiality. These examples are meant to highlight some scenarios that may occur when the best practices described in Chapter 7 are followed.

12.1 Case Study 1: Insufficient Information Transfer in Design

Product A is a generic product purchased by a virtual company who contracts out manufacture and packaging. This product is a non-sterile solution that is sold over the counter. The company has previously executed batch records and a copy of the original new drug application filing, but no other information. There was no CDO or CPO involved in this process.

The CMO did not have a standard minimum amount of data required to continue with manufacturing but did have a requirement to generate a risk assessment if parameter criticality had not been defined. The client wanted to proceed directly into PPQ without engineering or clinical runs. The original filing did not list critical parameters but included a copy of an unexecuted batch record. The original equipment used for manufacturing was not known.

The CMO generated a batch record using their template with the parameters defined in the batch record provided by the client. The CMO performed a risk assessment (using an FMEA approach) to identify potential risks in the process using the equipment owned by the CMO. It was determined that the mixer used by the CMO was not capable of mixing the product at the speed previously utilized, but all other parameters could be met. The mixer was not capable of reaching the highest speed parameters.

The CMO generated a scaled-down control strategy that outlined the CQAs and CPPs defined in the risk assessment and evaluated all materials. During this process, it was determined that one raw material was not pharmaceutical grade. The CMO recommended that a higher-grade raw material be purchased and that a mixing study be performed using the onsite equipment. Both recommendations were accepted and the mixing study involved mixing the product at a lower speed, but identified that significant foaming occurred.

Due to the potential impact of dose accuracy with foaming product, the CMO recommended that an engineering batch be performed prior to starting PPQ. The client accepted the recommendation and the engineering batch confirmed that the product was able to be dosed accurately using the process that included the mixing study parameters.

While there was not a significant amount of manufacturing data available, the process was very simple and only had three critical parameters defined that were well controlled; therefore, three PPQ batches were manufactured. All three batches met expectations and a CPV plan was generated by the CMO.

During administration of the CPV program, a trend was identified (via Nelson rule 2, nine or more points in a row on the same side as the mean) and investigated. It was determined that the trend was due to variability in an excipient that did not impact the ability of the product to meet all acceptance criteria. No additional actions were required; however, the raw material vendor was notified and able to tighten controls on their process, which eliminated the trend.

The completion of the PPQ report took three months longer than expected to initially qualify due to the addition of the engineering batch and mixing study, but resulted in a consistent manufacturing process, acceptable PPQ study, and an easily managed CPV plan.

12.2 Case Study 2: Allowing Flexibility

Product B is a new parenteral monoclonal antibody that is manufactured, filled, and packaged into a syringe with a safety device at one client location. The development of this product was performed at the client's site. The addition of a CMPO site was a risk mitigation strategy as the existing site did not have sufficient capacity. The company provided drug substance and fill/finish batch records from their internal site as well as a QTPP but did not share the development reports. There was no CDO involved in this process.

The CMO generated a site-specific control strategy and risk assessment to define site-specific parameter criticality. The client agreed to manufacturing engineering batches for both the drug substance and final product at the CMO. There were differences in the equipment used at each site and some differences in manufacturing parameters as a result.

The CMO generated a batch record using their template with the parameters defined in the batch record provided by the client. The language in several of the steps was modified to match the client's documentation and the order of some steps were changed. The engineering batches did not produce the expected results as the operators made several errors. The root cause was determined to be confusion related to the changes in the batch record. The batch record was revised to ensure the process was the same as the transfer site but aligned the flow and language to the routine process and format used by the CMO. An additional engineering batch was manufactured and met all expectations.

A PPQ protocol was developed using the sampling strategy defined by the client. After the engineering runs were performed, a new sampling tool was introduced. Due to the concern that the sampling mechanism was new, hands on training was developed and delivered jointly by the CMO and client SMEs. An engineering run using a surrogate was manufactured challenging the ability to sample effectively. It was determined that one set of samples could not be taken in the time frames specified and the protocol was adjusted.

There was a significant amount of process data available from the alternate manufacturing site and the changes made during transfer were not considered significant; therefore, three PPQ batches were manufactured. All three batches met expectations and a CPV plan was generated by the CMO. This CPV plan contained a formal mechanism to compare data from both sites.

During administration of the CPV program, the performance from the two sites was found to be slightly, but statistically, different with respect to yield. It was determined that this was due to variability in a processing time that did not impact the ability of the product to meet all acceptance criteria. The maximum time in the bioreactor was the same for both sites, but one of the sites worked on all shifts, and therefore was able to transfer earlier than the other site, which only had a single shift. The site with the single shift changed their process to allow earlier transfer when endpoint was reached and improved their yield.

The PPQ report was completed one month earlier than planned. A formal RACI and stage gate process was in place, which provided opportunities for effective information flow between the two teams. Due to the expectation that site differences could result in performance of multiple engineering batches, a contingency plan for four engineering batches was originally designed into the schedule to ensure that the filing date would not be impacted if unexpected data was received.

13 Appendix 5 – Additional Information on Determining the Number of Process Performance Qualification Batches

13.1 Further Explanation of Risk Assessment in Preparation for Determining the Number of PPQ Batches [34]

Ranking Characteristics to Assess Risk – An ASTM E2475 Based Approach [42]

The knowledge and decisions from PV Stage 1 are compared to ranking characteristics to determine the relative risk ranking for product, process, and control strategy. Tables 13.1 to 13.2 below provide examples of characteristics used to guide the ranking assignment for these three elements, respectively.

13.1.1 Evaluation of Product Knowledge

The evaluation of product knowledge focuses on severity of harm to the patient and probability that variability has an impact on the safety, efficacy, and quality of the product.

The risk ranking level is assigned based on an evaluation of methodology applied to identify CQAs and an evaluation of how well the impact of variability is understood.

Table 13.1: Product Knowledge Risk Ranking [34]

Product Knowledge Factor	Relative Risk Ranking Characteristics of Ranking Assignments		
	Low Risk	Medium Risk	High Risk
Identification of CQA and impact of CQA variation on patient	- Physiochemical/ biological, pharmacokinetic knowledge, and QbD approach used to design the formulation of drug product - Impact of variation on bioavailability explored and understood	- Critical Quality Attributes identified and justified - Physiochemical/biological and pharmacokinetic properties identified - Some exploration of impact of variation	- Product specifications established from development trial and error - Impact of variation known only from evaluation of incidents
Product characterization	- Analytical method has direct measurable linkage to clinical performance - Complete product physiochemical/biological characterization	- Analytical method development based on mechanism of action for the therapeutic agent, but linkage to clinical performance is hypothetical. - Product physiochemical/biological characterization identifies categories of structural variants of a heterogeneous product	- Product characterization measures quality against established empirical limits - Heterogeneous product not well defined by physiochemical/biological characterization

13.1.2 Evaluation of Process Understanding

13.1.2.1 Development Phase

For new products, establishing process understanding should include exploration of the relationship between variability of process parameters, material characteristics, and other sources of variability and the effect on CQAs. For new drug products developed under QbD principles, predictive models of these relationships may be available.

Development and clinical batches provide preliminary estimates of process variability and capability. Criticality levels for process parameters are derived from development, characterization, and manufacturing experience (pilot, demonstration, and clinical batches).

For legacy products, full-scale manufacturing data may be useful in establishing the effects of input variations on product attributes.

13.1.2.2 Prior Knowledge

In many cases as new products are developed and commercialized, the manufacturing platform chosen for the commercial process is familiar to the firm. The process technology is likely to have been used to manufacture other products and considerable knowledge has been realized. This knowledge base can be drawn on to make estimates of the expected performance of similar processes being developed and validated.

Inherent process variability can be estimated from this prior knowledge, including experiments and knowledge of similar products and processes. This, along with consideration for variability the process will experience due to process operators and shifts, process interruptions, hold times, multiple equipment sets, and multiple material suppliers, can also help define the number of validation batches that should be planned. If the variability from any of the sources is high, or knowledge about the impact or range of the variability is low, then the risk of demonstrating process reproducibility is increased.

The risk ranking level is assigned from an evaluation of the degree of process understanding, process predictability, and understanding of effect of scale as well as effect of variability on process output.

Table 13.2: Process Understanding Risk Ranking [34]

Process Understanding Factor	Relative Risk Ranking Characteristics of Ranking Assignments		
	Low Risk	Medium Risk	High Risk
Degree of process understanding/unit operation	First principles understanding: based on an understanding of prevailing mechanisms and rationale	Causal knowledge: based on what causes interrelationships between variables	Descriptive knowledge: derived only from observation, reflecting basic facts
Process predictability and modeling	- Models based on first principles. extension of empirical and mechanistic models - Highly predictable process and scale up	- Use of models derived from basic physical, chemical, biological or microbial mechanisms of observed phenomena - Sufficient knowledge to employ PAT methods, if applicable and desired	- Primitive models reflecting only basic understanding of process and scale effects - Process predictability is questionable

Table 13.2: Process Understanding Risk Ranking [34] (continued)

Process Understanding Factor	Relative Risk Ranking Characteristics of Ranking Assignments		
	Low Risk	Medium Risk	High Risk
Process response to input variability	- Design space identified using multivariate data and statistical methods - Impact of material attributes on product quality explored extensively in development - Material-specific CQAs identified and well understood or no material-specific CQAs	- Well-defined criticality for process based on multivariate experiments - Impact of material attributes on product quality explored to some degree - Material-specific CQAs identified – full range of variability not explored in development	- Partially defined, primarily through univariate experimentation - Impact of material attributes to product quality are minimally explored - Material-specific CQAs not identified
Effects of scale changes	Highly predictable – data across different scales is essentially interchangeable	Predictable – data across scales can be projected, but scale effects are anticipated	Unpredictable – scale dependency expected, but not thoroughly explored

Rankings are aligned with definitions and characterizations provided in ASTM E2475, Standard Guide for Process Understanding Related to Pharmaceutical Manufacture and Control [42]. For the purpose of this PV Guide, the characterizations in the ASTM publication have been condensed from five to three risk rankings and some aspects have been included in the control strategy (Section 13.1.3) evaluation rather than here.

13.1.3 Evaluation of Control Strategy Effectiveness

The control strategy should be designed based on product and process understanding to ensure that a product of required quality can be produced consistently. The evaluations of control strategy effectiveness therefore focus on the suitability of the defined control strategies to manage variability.

The risk ranking level is assigned from an evaluation of methodology applied for setting material specifications and process controls as well as an evaluation of equipment capability versus process requirements.

Table 13.3 provides an example of characteristics used to guide the ranking assignment. This table is not meant to be a comprehensive listing of all the factors of the control strategy for a manufacturing process. Rather it attempts to identify those factors most likely to contribute to differences in variability between processes. The overall residual risk levels are shown in Table 13.4.

Table 13.3: Control Strategy Risk Ranking [34]

Control Strategy Factor	Source of Potential Variability and/or Uncertainty	Relative Risk Ranking Characteristics of Ranking Assignments		
		Low Risk	Medium Risk	High Risk
Raw Material specifications	• Different suppliers; different manufacturing processes • Material attributes test method • Different batches • Basis for material specification • Specification wider than experience	Specifications of material attributes impacting product quality justified based on development data	Limited justification of specifications of material attributes	• Specifications are not justified. • Compensial or supplier limits accepted without further investigation
Equipment Capability versus. Process Requirements	Capability of equipment to control operating parameters within acceptable ranges	Comparison of parameter control ranges from equipment qualification with process requirements indicates all parameters are well within equipment control capabilities and supported by qualification data	Comparison of control ranges from equipment qualification with process requirements indicates marginal capability to meet requirements for a limited number of process parameters	Comparison of parameter control ranges from equipment qualification with process requirements indicates a significant number of parameters are similar to equipment control capabilities
Experiences with process performance to date	• Variation observed • Scaling effects • Consistency of past performance	• Underlying cause(s) for variation is understood and addressed (or variation not observed during manufacture) • Impact of scale is well understood • Process has consistently performed as expected	• Variation is managed empirically, but underlying causes are not well understood • Some understanding of scaling issues • Minor departures from expected results that were investigated and satisfactorily explained	• Variation has been observed, but has not been successfully managed • Impact of scale changes has not been explored • Unexplained failure has been experienced
Monitoring capability and detectability	Ability of monitoring tools and methods to detect variation	Attributes measured in real time at a sensitivity where performance variability is likely to be observed	Attributes measured off-line (after batch completion) at a sensitivity where performance variability is likely to be observed	Attribute measurement sensitivity and/or accuracy is inadequate to use for controlling performance

Table 13.4: Overall Residual Risk Levels [34]

Residual Risk Level	Description
Severe (5)	Multiple factors have high risk ratings
High (4)	Few factors have high risk ratings or all have medium risk rating
Moderate (3)	Medium risk level for multiple factors or high risk level for one factor
Low (2)	Medium risk level for a few factors; the others are low risk
Minimal (1)	Low risk level for all factors

13.2 Determining the Number of PPQ Batches Based on a Risk-based Approach Utilizing the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8] [34]

To demonstrate the risk-based approach for justifying and determining the appropriate number of Stage 2 PPQ batches, a case study based on the *ISPE PQLI® Guide Series: Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example* [8] is presented here. The Illustrative Example describes a thorough development approach that results in a low-risk process. For detailed information about designed experiments, design spaces, risk assessments done during development including identification of CPPs and material attributes, and relevant elements of the proposed control strategy, refer to the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

The example illustrates the development of a tablet formulation, 30 mg (small molecule), called PaQLInol, using the enhanced, QbD approach. PaQLInol is a BCS Class 2 compound (low solubility and high permeability). The drug product manufacturing process includes the following steps: dispense, blend, lubricate, compress, and coat.

Although the *ISPE PQLI® Guide Part 2 – Illustrative Example* discusses quality attributes systematically, it focuses on the highest risk CQAs, which are dissolution and UDU [8]. This PV Guide concentrates on the dissolution example since the risk assessment (Table 13.5) identifies it as the highest risk quality attribute. Table 13.5 shows the cause and effect risk assessment matrix for PaQLInol Tablets 30 mg after formulation development and before process development.

Table 13.5: Cause and Effect Matrix for PaQLInol Tablets before Process Development Studies [34]

	Drug Product					
CQA/Unit Operations	Dispense	Blend	Lubricate	Compress	Coat	Package
Appearance	L	L	L	L	M	L
Identity	M	L	L	L	L	M
Assay	M	M	L	M	L	L
Impurities	L	L	L	L	L	L
Uniformity of Dosage Units	L	H	M	M	L	L
Dissolution	L	L	H	H	L	L
Microbiology	L	L	L	L	L	L
Key:	L = Little or no impact		M = Indirect impact/Medium Risk		H = Direct impact	

The *ISPE PQLI® Guide Part 2 – Illustrative Example* describes extensive formulation development that leads to an immediate release formulation with dissolution acceptance criteria of Q = 80% at 20 minutes, and the identification and use of an algorithm as an important element of the dissolution control strategy. The discussion here is based on information found in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

13.2.1 Evaluation of Product and Process Understanding

Using the risk assessment matrix given in Section 13.1, Tables 13.6 and 13.7 are developed using information given in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8], further explanation being given below the tables.

Table 13.6: Evaluation of Product Knowledge for PaQLInol Tablets [34]

Product Knowledge Factor	Relative Risk Ranking Characteristics of Ranking Assignments		
	Low Risk	Medium Risk	High Risk
Identification of CQA and impact of CQA variation on patient	- Physiochemical/ biological, pharmacokinetic knowledge, and QbD approach used to design the formulation of drug product - Impact of variation on bioavailability explored and understood PaQLInol Tablets	- Critical Quality Attributes identified and justified - Physiochemical/biological and pharmacokinetic properties identified - Some exploration of impact of variation	- Product specifications established from development trial and error - Impact of variation known only from evaluation of incidents
Product characterization	- Analytical method has direct measurable linkage to clinical performance - Complete product physiochemical/biological characterization PaQLInol Tablets	- Analytical method development based on mechanism of action for the therapeutic agent, but linkage to clinical performance is hypothetical. - Product physio-chemical/biological characterization identifies categories of structural variants of a heterogeneous product	- Product characterization measures quality against established empirical limits - Heterogeneous product not well defined by physio-chemical/biological characterization

From an evaluation of the impact of CQA variation on the patient, the product understanding risk factors are all assigned as **Low** risk, based on the following arguments:

- Physiochemical, biological, and pharmacokinetic information is used as input to process development using the enhanced, QbD approach.
- The role of excipients in providing an acceptably formulated product is well understood based on designed experiments, and the formulation is optimized based on this information.

- The impact of variation in dissolution profiles on bioavailability was assessed in an *in vivo* study. Acceptance criterion for the *in vitro* dissolution CQA is established as Q = 80% in 20 minutes from this study. The *in vitro* dissolution method is able to differentiate between tablet variants (*in vitro-in vivo* relationship variants) with acceptable and unacceptable *in vitro* release rates and has a relationship to *in vivo* behavior.

All product understanding factors are considered to be at a low risk level; therefore, the relative risk ranking for product understanding is **Low**.

A similar evaluation is performed to assign a risk ranking for process understanding.

Table 13.7: Evaluation of Process Understanding for PaQLInol Tablets [34]

Process Understanding Factor	Relative Risk Ranking Characteristics of Ranking Assignments		
	Low Risk	Medium Risk	High Risk
Degree of process understanding/unit operation	First principles understanding: based on an understanding of prevailing mechanisms and rationale	Causal knowledge: based on what causes interrelationships between variables PaQLInol Tablets	Descriptive knowledge: derived only from observation, reflecting basic facts
Process predictability and modeling	- Models based on first principles. extension of empirical and mechanistic models - Highly predictable process and scale up	- Use of models derived from basic physical, chemical, biological or microbial mechanisms of observed phenomena - Sufficient knowledge to employ PAT methods, if applicable and desired PaQLInol Tablets	- Primitive models reflecting only basic understanding of process and scale effects - Process predictability is questionable
Process response to input variability	- Design space identified using multivariate data and statistical methods - Impact of material attributes on product quality explored extensively in development - Material-specific CQAs identified and well understood or no material-specific CQAs PaQLInol Tablets	- Well-defined criticality for process based on multivariate experiments - Impact of material attributes on product quality explored to some degree - Material-specific CQAs identified – full range of variability not explored in development	- Partially defined, primarily through univariate experimentation - Impact of material attributes to product quality are minimally explored - Material-specific CQAs not identified
Effects of scale changes	Highly predictable – data across different scales is essentially interchangeable	Predictable – data across scales can be projected, but scale effects are anticipated PaQLInol Tablets	Unpredictable – scale dependency expected, but not thoroughly explored

The process understanding factors are assigned as **Medium** to **Low** risk, based on the following arguments explained in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8]:

- Causes of interrelationships between variables are identified and explored sufficiently by DoEs to be expressed in a design space algorithm for dissolution. The algorithm contains factors for:
 - Drug substance particle size
 - Magnesium stearate specific surface area
 - Lubrication time
 - Crushing force of tablets

The ranges assessed in the DoE for these four factors are included in the proposed design space for dissolution as acceptable ranges. The largest contribution to the prediction of dissolution values using this algorithm comes from drug substance particle size.

- A design space is proposed.
- PAT tools are applied during process development (Stage 1) but are not relevant for controlling dissolution. Dissolution is highly dependent on three material attributes – drug substance particle size, magnesium stearate surface area, and tablet crushing force, all of which are process- and scale-independent. Lubrication time is easily determined and controlled.
- Material-specific CQAs are identified.
- Effect of scale changes is predictable.

Three process understanding factors are considered to be **Medium** risk level, one factor is considered **Low**; therefore, the relative risk ranking for process understanding is assigned as **Medium**.

13.2.2 Evaluation of Control Strategy

Several control strategy options are considered in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8] and four are discussed.

One option, a feed forward mechanism, is preferred. In this option, the API Particle Size Distribution (PSD) value is obtained from its CoA, the MgSt SSA (Magnesium Stearate Specific Surface Area) value is determined on receipt, and assuming a target crushing force of 85 N (Newtons), the lubrication time is calculated based on the algorithm to target 90% dissolution.

The dissolution value for release is calculated from the equation using actual lubrication time and crushing force, instead of being measured using a QC method. Tables 13.8 and 13.9 summarize this control strategy. A detailed risk assessment regarding CPPs is available in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8].

Table 13.8: Dissolution Control Strategy for the PaQLInol Tablet Process [34]

CQA	Acceptance Criteria	Control Strategy Element	Control Strategy Acceptance Criteria	Control Type
Dissolution	Q = 80% in 20 minutes	API particle size (D0.9)	5 – 30 µm	CoA value
		MgSt SSA	3000 – 12000 cm ² /g	Test on receipt
		Lubrication Time	1 – 8 minutes	Calculated to target 90% dissolution
		Crushing Force	60 – 110 N	Target 85N

Table 13.9: Evaluation of Control Strategy Effectiveness for PaQLInol Tablets [34]

Control Strategy Element	Source of Potential Variability and/or Uncertainty	Relative Risk Ranking Characteristics of Ranking Assignments		
		Low Risk	Medium Risk	High Risk
Raw Material specifications	- Different suppliers; different manufacturing processes - Material attributes test method - Different batches - Basis for material specification - Specification wider than experience	Specifications of material attributes impacting product quality justified based on development data PaQLInol Tablets	- Limited justification of specifications of material attributes - Compendial or supplier limits accepted without further investigation	Specifications are not justified.
Equipment Capability versus Process Requirements	Capability of equipment to control operating parameters within acceptable ranges	Comparison of parameter control ranges from equipment qualification with process requirements indicates all parameters are well within equipment control capabilities and supported by qualification data PaQLInol Tablets	Equipment control capability marginally meets the requirements for a limited number of process parameters	Comparison of parameter control ranges from equipment qualification with process requirements indicates a significant number of parameters are similar to equipment control capabilities

Table 13.9: Evaluation of Control Strategy Effectiveness for PaQLInol Tablets [34] (continued)

Control Strategy Element	Source of Potential Variability and/or Uncertainty	Relative Risk Ranking Characteristics of Ranking Assignments		
		Low Risk	Medium Risk	High Risk
Experiences with process performance to date	- Variation observed - Scaling effects - Consistency of past performance	- Underlying cause(s) for variation is understood and addressed (or variation not observed during manufacture) - Impact of scale is well understood - Process has consistently performed as expected No issues with PaQLInol Tablets to date but limited before Stage 2	- Variation is managed empirically, but underlying causes are not well understood - Some understanding of scaling issues - Minor departures from expected results that were investigated and satisfactorily explained	- Variation has been observed, but has not been successfully managed - Impact of scale changes has not been explored - Unexplained failure has been experienced
Monitoring capability and detectability	Ability of monitoring tools and methods to detect variation	Attributes measured in real time at a sensitivity where performance variability is likely to be observed PaQLInol Tablets	Attributes measured off-line (after batch completion) at a sensitivity where performance variability is likely to be observed	Attribute measurement sensitivity and/or accuracy is inadequate to use for controlling performance

Risk ranking for all control strategy factors is assigned as **Low** risk from the following arguments:

- Raw materials: critical raw material attributes have been identified as PaQLInol PSD, and magnesium stearate surface area, and the impact of these critical attributes on dissolution has been explored extensively in development. This factor is **Low** risk.
- Equipment capability versus process requirements: equipment capability is not fully described in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8]. However, process understanding indicates that there is Low risk of impact of the process on dissolution CQA when a diffusion mixer, and a gravity and power-assisted press are used. Different equipment of these designs may influence the algorithm, which requires verification for any new piece of equipment. For the purpose of this example, equipment capability is assumed to meet the requirements of process parameter control, the major process parameter being lubrication time, which can be set automatically or be controlled manually, both facile equipment capabilities to achieve. This factor is **Low** to **Medium** risk.
- Experience with process performance to date: although not extensively discussed in the *ISPE PQLI® Guide Part 2 – Illustrative Example* [8], the formula and process are used to manufacture batches for Phase III clinical studies. It is unlikely that the final proposed control strategy will be fully applied for clinical manufacture and the scale may not be that proposed for commercialization; however, it is assumed that all batches are manufactured satisfactorily and product complies with CQA acceptance criteria. Scale impact is well understood. This factor is **Low** risk.

One factor in this risk assessment of the control strategy is considered **Low** to **Medium** risk level and the others are **Low** risk. The relative risk ranking for control strategy is therefore assigned as **Low** risk.

13.2.3 Determine Residual Risk Level for PaQLInol Illustrative Example [8] and Recommendation for Number of Validation Batches

From the above risk ranking assessments, the residual risk level is assigned as Low. Although there is a Medium risk level for a few factors, the majority of factors are Low risk. The number of validation batches required for dissolution is defined accordingly in Table 13.10.

Table 13.10: Risk Level of Three Factors and Overall Residual Risk

Risk Factors	Assigned Risk Level
Product understanding	Low
Process understanding	Medium
Control strategy risk	Low
Overall residual risk level (see Table 13.4)	Low

With the overall process and product risk ending at Low, the recommended number of validation batches can now be determined using, for instance, one of the approaches described in the ISPE discussion papers [34, 33, 35]. (See also Table 13.11).

Table 13.11: Number of Process Performance Qualification Batches Derived Using Four Alternative Methods

Approach	Number of Batches
1. Based on rationales and experiences	3 batches
2. Tolerance Interval based approach	5 total batches
3. Probability of Success	10 total batches
4. Consistency of Means	6 total batches

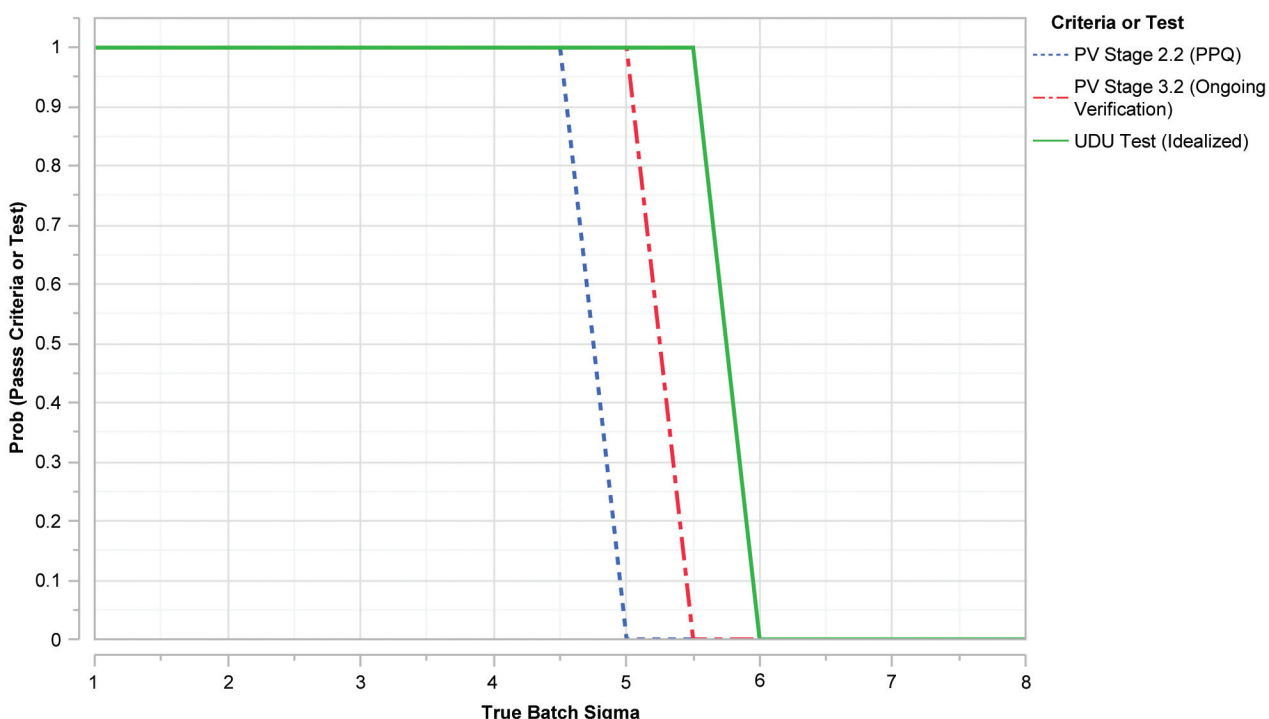
It is assumed that the facility, utilities, and equipment are qualified.

14 Appendix 6 – Statistical Detail

14.1 Operating Characteristic Curves of Sampling Plans and Acceptance Criteria

When selecting sampling plans and acceptance criteria for CPV or blend uniformity and CU, one approach is to evaluate the OC curves for Stage 2, Stage 3.2, and the regulatory UDU test requirement [46]. An idealistic depiction of this relationship is shown in Figure 14.1.

Figure 14.1: Idealistic Relationships of Operating Characteristic Curves



In Figure 14.1, it is observed that the PPQ OC curve is the most conservative/restrictive, the UDU_{Idealized} test is the most liberal, and the OC curve for CPV is in between. Except where the probability of passing is 1 or 0, there is no overlap of the OC curves. This is ideal for the following reasons. When PPQ or CPV criteria are met, the batch has a 100% probability of passing the UDU_{Idealized} test. Further, for CPV, it is desired that any batch meeting PPQ criteria would also meet the CPV criteria. Stated another way, it would be undesirable to pass PPQ only to later fail batches of the same quality/variability during Stage 3.

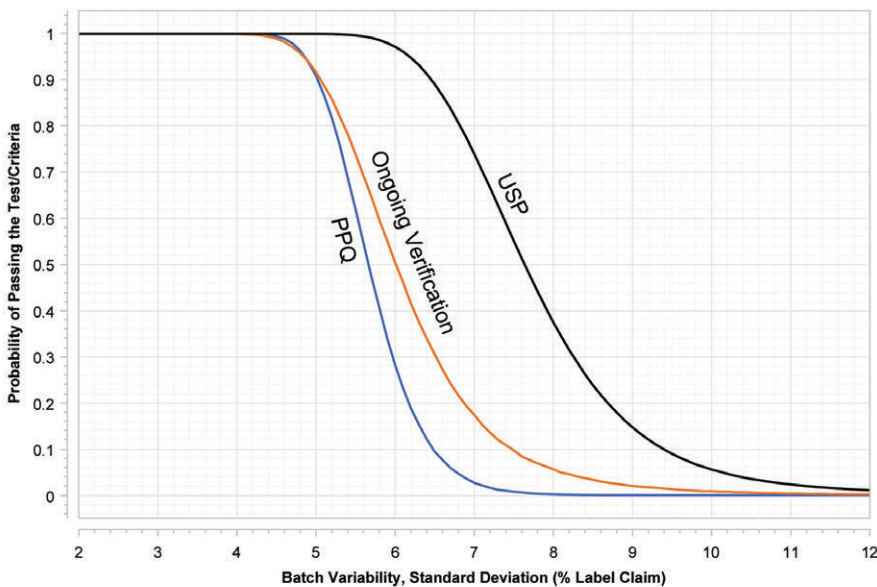
While Figure 14.1 shows the ideal situation, reality is less neat. The manufacturer will need to make trade-offs on how conservative the PPQ and CPV OC curves are relative to the UDU test [46] and how conservative PPQ is relative to CPV.

If the PPQ criteria are too tight, it will be difficult to meet the criteria while having negligible, if any, practical impact to the patient as demonstrated by having no practical impact on the probability of passing the UDU test [46].

For example, if the PPQ OC curve in Figure 6.6 was moved to the left to start coming down at a batch sigma of 2.5% label claim, then standard deviations between 2.5% and 5.0% LC, all of which have a 100% probability of passing the UDU test [46], would fail PPQ. This would be an unnecessary tightening of the PPQ criteria.

Additionally, to the degree there is overlap of the curves there is risk in both false accept and false rejection of batches. Figure 14.2 depicts one set of OC curves that represent a reasonable risk trade-off.

Figure 14.2: Relationship of Process Performance Qualification, Ongoing Verification, and USP Operating Characteristic Curves

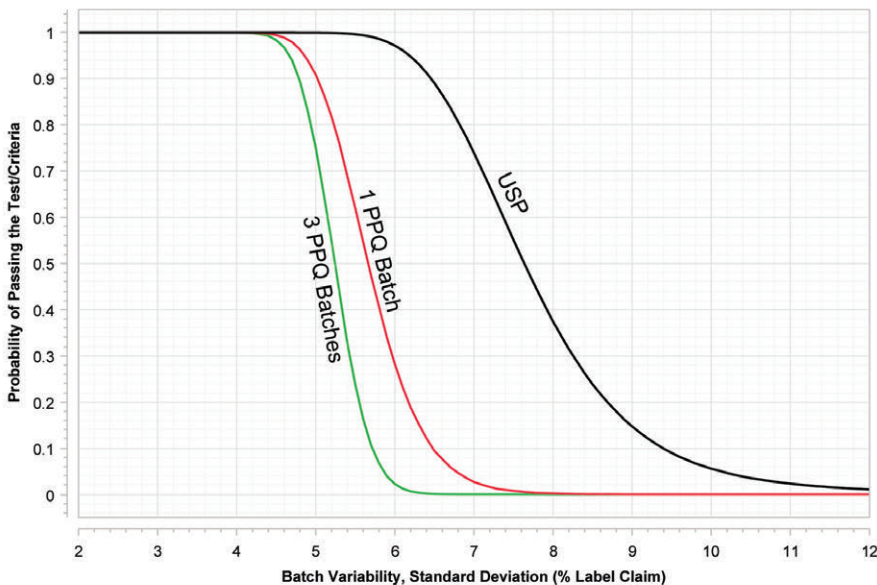


In Figure 14.2, both the PPQ and CPV OC curves are very conservative relative to the USP OC curve. In fact, when there is still a 90% probability of passing the USP test [46], there is only a 10% probability of passing the PPQ criteria and a 31% probability of passing the CPV criteria.

There is some crossover of the PPQ and CPV curves. However, the crossover covers a relatively small interval of batch standard deviations, between 4.3% and 5.0% LC, while having a high probability of passing both criteria, that is, > 90%.

Additionally, the risk of failing CPV batches after a successful PPQ of at least three batches is small. This low risk is further confirmed in Figure 14.3, which shows the OC curve for passing three consecutive PPQ batches in relation to the OC curve for a single PPQ batch and the USP test [46].

Figure 14.3: Operating Characteristic Curves for Passing Three Consecutive PPQ Batches, a Single Process Performance Qualification Batch, and the USP Test [46]



The OC curve for three PPQ batches is shifted left and is steeper than for one PPQ batch; therefore, the amount of within batch variability that will pass PPQ is reduced. It also reduces the risk of failing CPV batches after a successful PPQ.

14.2 k Value Approximation for Two-Sided Tolerance Interval

calculate the k value for Two-Sided Tolerance Intervals (i.e., R, JMP, or Minitab). A very accurate approximation of k given by Howe [69] is:

$$k = \sqrt{((n-1) \times (1+1/n) \times Z_{(1-p/2)}^2 / X_{\alpha, n-1}^2)}$$

Where:

n = sample size

Z = standard normal quantile

p = coverage

α = 1- confidence level

$X_{\alpha, n-1}^2$ = chi-square quantile

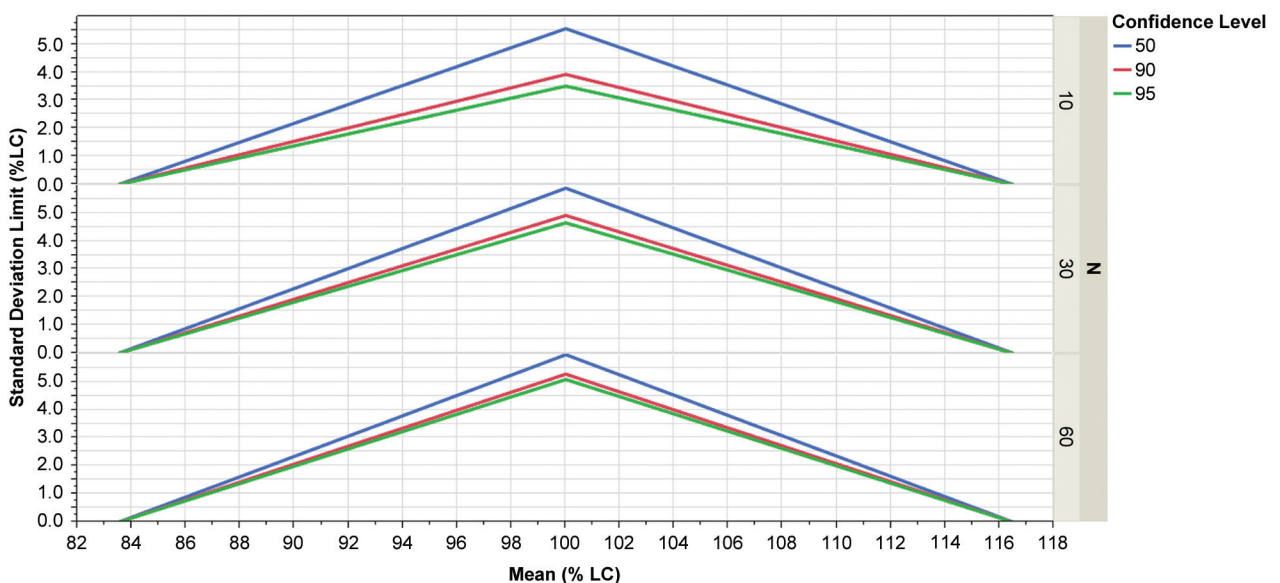
14.3 Generation of Acceptance Limit Table for Two-Sided Tolerance Interval Approach

Due to symmetry about 100% LC, this means that the distance from $100 + k \times s$ must be less than or equal to 16.5. The maximum s for a given k and sample mean can be found by solving the $|100 - \bar{X}| \pm k \times s = 16.5$ for s given below:

$$\text{Maximum } s = (16.5 - |100 - \bar{X}|)/k$$

Using this relationship, an acceptance limit table can be generated for various sample means. A plot of the acceptance table for $n = 10, 30$, and 60 is shown in Figure 14.4 for confidence levels of 50%, 90%, and 95% to pass the USP <905> UDU test [46] with at least 95% probability.

Figure 14.4: Two-Sided Tolerance Interval Acceptance Limits for $n = 10, 30$, and 60

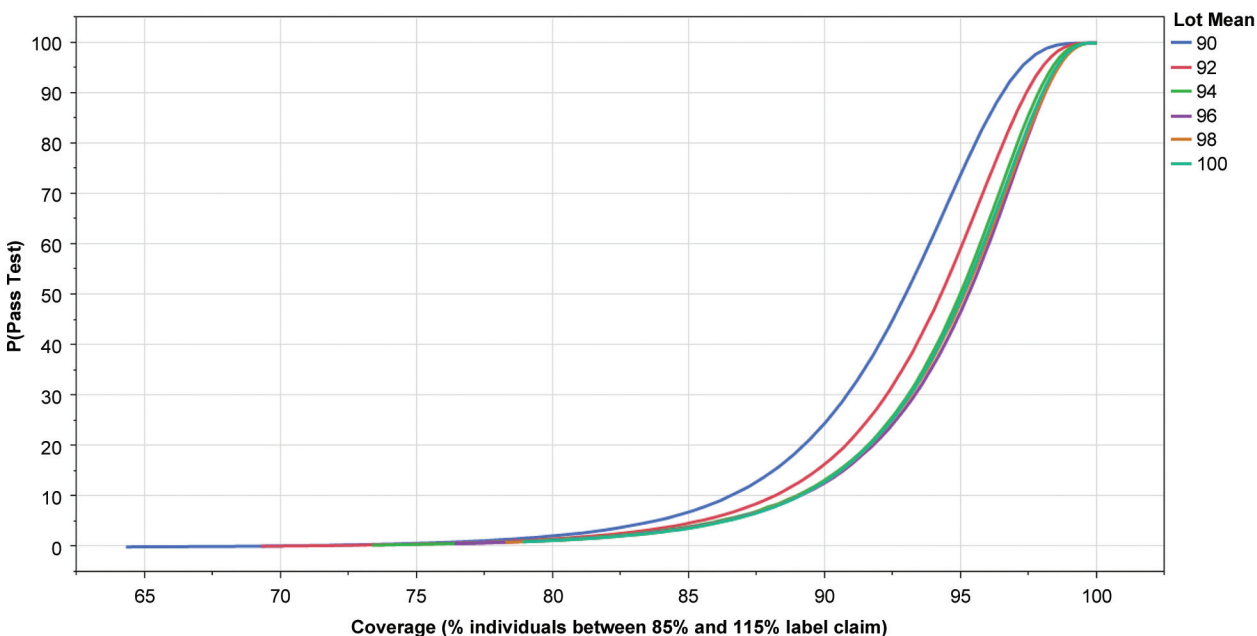


Using a 90% confidence level, the overall maximum s (mean = 100) is 3.941, 4.937, and 5.295 for $n = 10, 30$, and 60 respectively.

14.4 OC Curves for USP UDU <905> Test [46] Based on 85% – 115% Coverage

Figure 14.5 shows the OC curve for passing the USP UDU test [46] based on simulation. The vertical axis is the probability of passing the USP UDU test and the horizontal axis is the coverage which is the probability that a single result will fall between 85% – 115% LC. A separate curve is shown for “true” lot means from 90% to 100% LC. The OC curves for 104% and 102% are the same as 96% and 98%, respectively (i.e., the OC curves are the same for lot means the same distance from 100% LC) [70].

Figure 14.5: Operating Characteristic Curves for Passing USP Uniformity of Dosage Units [46] versus % Individuals Between 85.0% and 115% Label Claim for Lot Means between 90% and 110% Label Claim

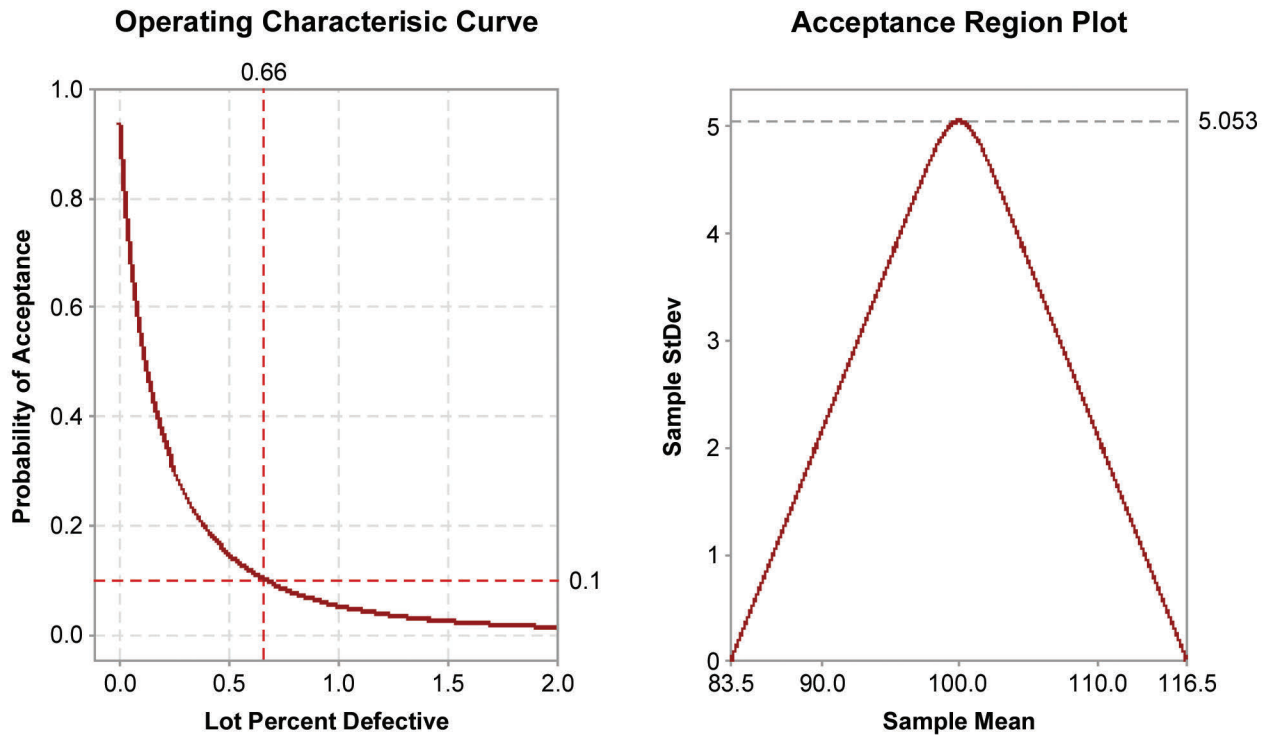


The probability of passing USP UDU [46] has a dependency on the “true” lot mean giving the impression that the probability of passing the USP UDU test increases as the lot means get further away from 100% LC.

14.5 “Exact” Method – Statistical Details

The “Exact” method is similar to a sampling plan by variable with $RQL = (1 - 0.9934) = 0.66\%$ at $\beta = 10\%$ (1-confidence level) acceptance. This is illustrated in Figure 14.6.

Figure 14.6: Operating Characteristic Curve and Acceptance Region Corresponding to 99.34% Coverage between 83.5% and 116.5% with 90% Confidence for 30 Samples



Sample Size = 30, Critical Distance = 3.064

Wallis [64] provided the following four step algorithm to generate an acceptance region (i.e., the set of means and maximum standards such that the total percent of results outside 83.5% to 116.5% is 0.66%).

Step 1: Compute k from non-central t-distribution

$$k = \frac{t^{-1}(1-\alpha, n-1, \Phi)}{\sqrt{n}}$$

Where:

$1-\alpha$ = confidence level

n = sample size

$\Phi = \sqrt{n} \times Z_p$ (p = coverage (0.9934))

This is the k value used to construct a one-sided tolerance interval at a $100 \times (1-\alpha)$ % confidence level and a $100 \times p$ coverage level. k values for various n at confidence levels of 50%, 90%, and 95% are given in Table 6.3 (Section 6.3.2).

Several approximate methods for calculating k exist in the literature. One of the most used approximate for k factor for one-sided tolerance intervals [71] uses the following set of formulae:

$$k = \frac{Z_p + \sqrt{Z_p^2 - ab}}{a}$$

$$a = 1 - \frac{Z_{1-\alpha}^2}{2(n-1)}$$

$$b = \frac{Z_p^2 - Z_{1-\alpha}^2}{n}$$

The approximation and non-central t-distribution method lead to very similar results when $n > 10$.

Step 2: Find p_o , such that $z_{(1-p_o)} = k$

Table 14.1 shows the k values and their associated p_o values with 99.34% coverage for sample sizes of 10, 30, and 60 using 50%, 90%, and 95% confidence levels as well as the Maximum Standard Deviation (MSD).

Table 14.1: Selected k and p_o Values

n	Confidence Level	k	p_o	MSD
10	50	2.574040	0.005025932	5.882
	90	3.756605	0.000086117	4.202
	95	4.231531	0.000011605	3.763
30	50	2.510944	0.006020439	6.007
	90	3.070756	0.001067588	5.043
	95	3.260596	0.000555892	4.779
60	50	2.497033	0.006261866	6.036
	90	2.870070	0.002051907	5.353
	95	2.989559	0.001396902	5.164

Note that the exact k values are less than those using the Two-Sided Tolerance Interval method.

Step 3: Divide p_o into two parts p_o' and p_o'' such that $p_o = p_o' + p_o''$

p_o' and p_o'' are the selected proportions less than 83.5% and greater than 116.5%, respectively, that add up to p_o . Note each pair results in a different mean and standard deviation, which are computed in Step 4.

Step 4:

Let LSL = Lower Specification Limit (83.5%) and USL = Upper Specification Limit (116.5%),

For a given p_o' , p_o'' , LSL, and USL, $LSL = \bar{X} - z_{(1-p_o')} \times s$ and $USL = \bar{X} + z_{(1-p_o'')} \times s$.

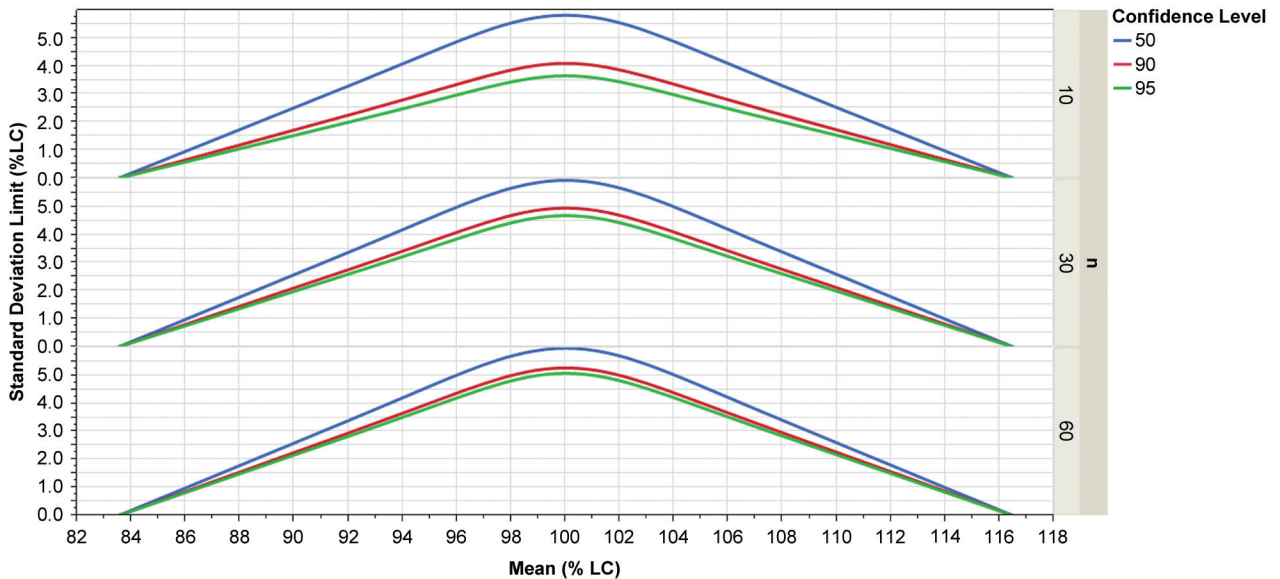
Solving this system of equations for $\bar{X}$ and s gives the following:

$$\bar{X} = \frac{USL \times z_{(1-p_o')} + LSL \times z_{(1-p_o'')}}{z_{(1-p_o')} + z_{(1-p_o'')}} \quad s = \frac{USL - LSL}{z_{(1-p_o')} + z_{(1-p_o'')}}$$

Note that $\bar{X}$ is a weighted average of the interval endpoints (LSL and USL) with normal z scores as weights associated with p_o' and p_o'' , respectively.

Acceptance region boundaries for sample sizes $n = 10, 30$ and 60 for confidence levels of 50% , 90% , and 95% are shown in Figure 14.7.

Figure 14.7: Exact Acceptance Limits for Coverage 0.9934, $n = 10, 30$, and 60 , and Confidence Levels 50% , 90% and 95%



Using a 90% confidence level, the overall maximum s (mean = 100) is 4.210 , 5.052 , and 5.363 for $n = 10, 30$, and 60 respectively compared to 3.211 , 4.479 , and 5.002 using ASTM E2709/E2810 [44].

14.6 R Program to Generate Acceptance Limit Tables for the Exact Method

```
rm(list=ls())
n <- 60                                #nb samples
P <- 0.9934                            #coverage
conf <- 0.50                           #confidence
nc <- qnorm(P)*sqrt(n)                 #non centrality (one sided)
k <- qt(conf, n-1, nc)/sqrt(n)         #this is the k value from non-central t distribution
LSL <- 83.5                           #Lower specification limit
USL <- 116.5                           #Upper specification limit
pp <- 1-pnorm(k)                       #fraction outside the LSL to USL
xx <- c(0.5, 0.48, 0.45, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01, 0.001, 0.0001, 0.00001, 0.000001, 0.0000001, 1e-12, 0)
#log scaled multipliers
p1 <- xx*pp                            #p1 is what is below LSL
p2 <- pp-p1                           #p2 is what is above USL
#p1+p2=coverage

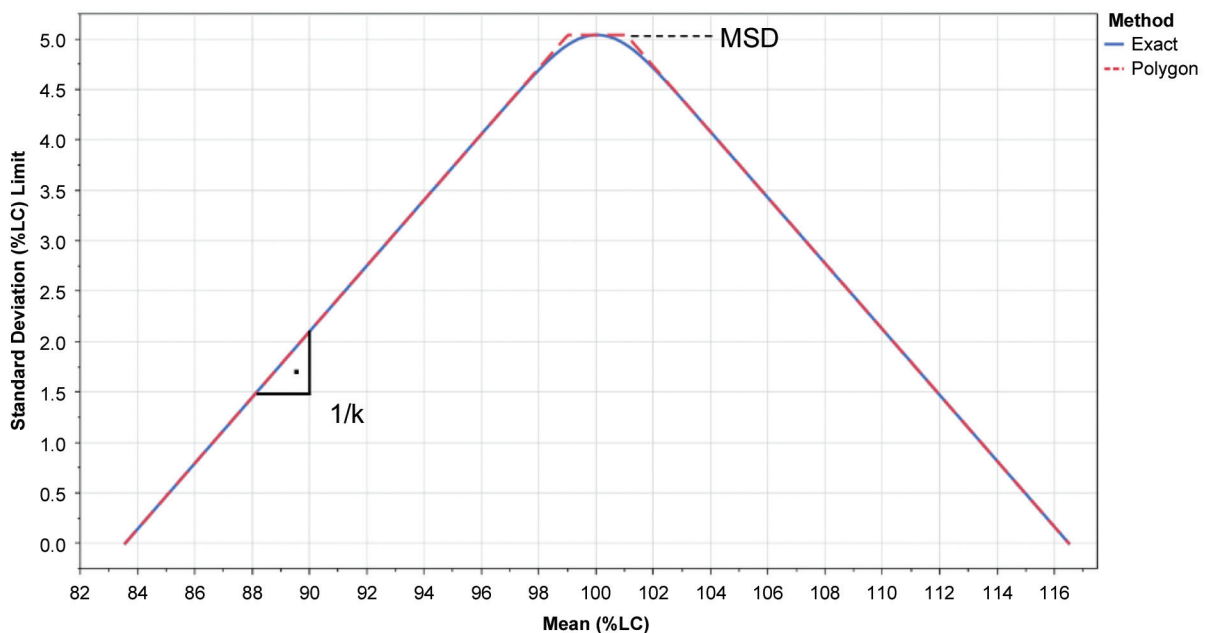
z1 <- -qnorm(p1)
z2 <- -qnorm(p2)
Xbar <- (USL*z1 + LSL*z2)/(z1+z2)
s <- (USL - LSL)/(z1+z2)
Xbar[16] <- USL #cosmetic for last line
s[16] <- 0
Xbar2 <- 200 - Xbar
s2 <- s
p2_1 <- p2
```

```
p2_2<-p1
Xbar<-c(Xbar,Xbar2[2:16])
s<-c(s,s2[2:16])
out<-data.frame(Xbar, s)
out<-out[order(out$Xbar),]
#print(out)
print(k)
ot<-spline(out$Xbar,out$s,331)      #interpolates the acceptance region
out2<-data.frame(ot$x, ot$y)
out2<-signif(out2,4)
#print(out2)                        #final result
#write.csv(out2,file="Exact Stacked N=60 CI50.csv")
plot(out2$ot.x,out2$ot.y)
names(out2) <- c("Mean","SD Limit")
#write.csv(table2,file="Test Stacked.csv")
# *** Print Table in Five Pairs of Columns each with mean and standard deviation ****
table2a<-out2[1:55,]
table2b<-out2[56:110,]
table2c<-out2[111:165,]
table2d<-out2[166:220,]
table2e<-out2[221:275,]
table2f<-out2[276:330,]
newtable<-cbind(table2a,table2b,table2c,table2d,table2e,table2f)
newtable
#write.csv(newtable,file="Exact Table N=60 CI50.csv")
```

14.7 Approximation to Exact Acceptance Limits Using a Polygon

Notice that the exact acceptance regions in Figure 14.7 are quite linear outside the range from 98.5% – 101.5% LC. Schilling [72] suggested using a polygon as an approximation to the exact acceptance region called the k method. Figure 14.8 shows the acceptance region as well as the polygon approximation for a 90% confidence level and sample size of 30.

Figure 14.8: Acceptance Polygon



The polygon acceptance region is defined as follows:

$$\min((16.5 - |100 - \bar{X}|) / k, \text{MSD})$$

where MSD is the value of s on the acceptance region when $\bar{X} = 100$ and k is the value from Table 6.2 (Section 6.3.2).

As can be seen from the plot, the approximation is very close if the means are outside 98% – 102% LC. The maximum difference occurs around 99% and 101% LC.

Using the acceptance polygon, the acceptance criteria simplify to:

$$s < \text{MSD}$$

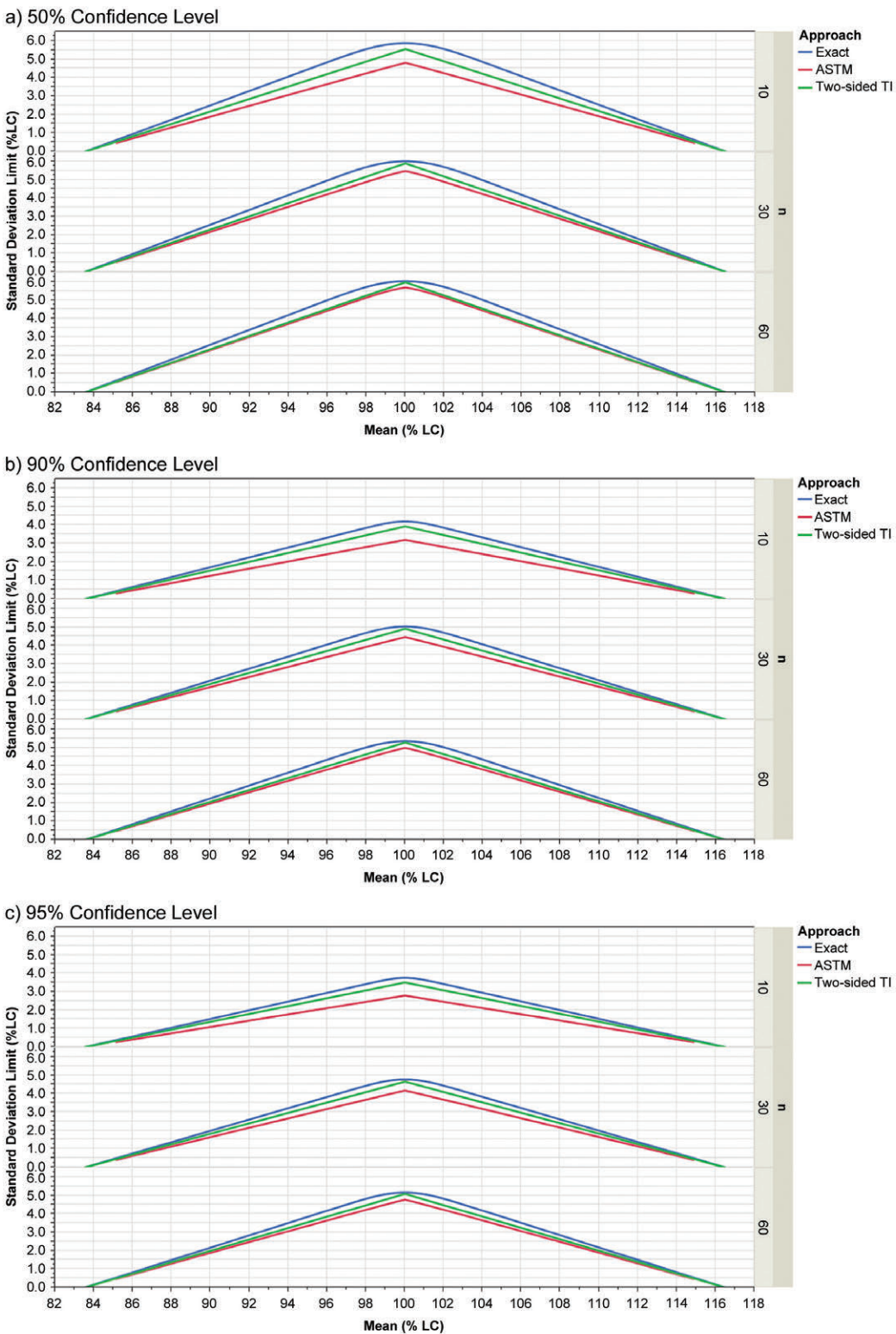
$$\bar{X} + ks < 116.5$$

$$\bar{X} - ks > 83.5$$

14.8 Graphical Comparison of Acceptance Limit Tables

Figure 14.9 (a,b,c) is a graphical version of Table 6.3.

Figure 14.9: Acceptance Limits on s for all Three Methods to Pass USP Uniformity of Dosage Units [46] with 95% Probability



14.9 Operating Characteristic Curves to Help Select Sampling Plan

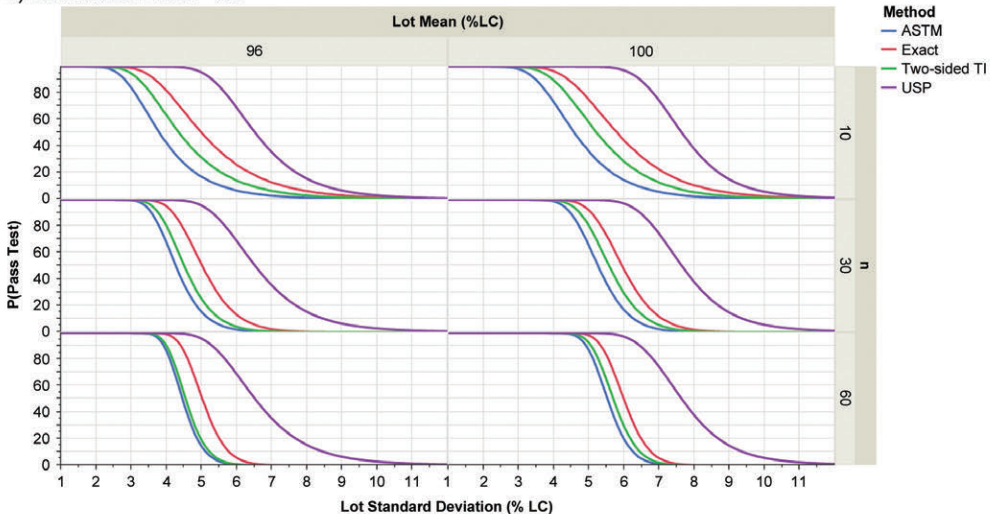
Figure 14.10 (a,b,c) are OC curves for sample sizes $n = 10, 30$, and 60 at confidence levels of $50, 90$, and 95% . The x-axis is the “true” lot standard deviation. The y-axis is the probability of passing the acceptance limit table associated with each plan: ASTM E2709/E2810 [44], Two-Sided Tolerance Interval, and “Exact,” as well as the USP UDU test [46].

Note that all of the plans assure with the specified confidence level that a lot will pass the USP UDU test [46] with 95% probability. A reference line is drawn at the 95% probability of passing.

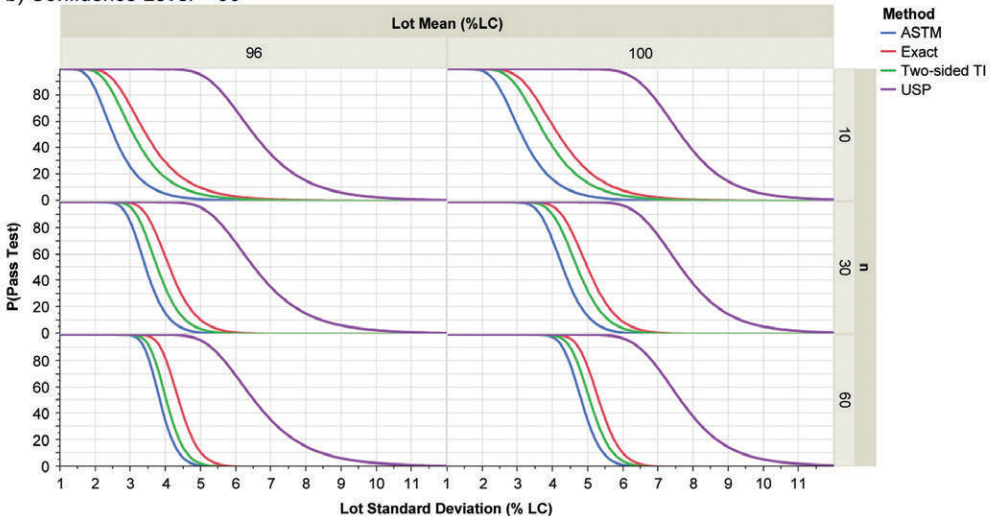
These plots can be used to select a sample size. For example, in Figure 14.9, if the “true” lot mean and standard deviation were 100% LC and 4.0% respectively, then the probability of passing an acceptance limit table based on a sample size of 10 would only be about 73% , 89% , and 96% for ASTM E2709/E2810 [44], Two-Sided Tolerance Interval, and “Exact” approach, respectively. However, passing the acceptance limit tables based on a sample size of 30 would pass all three methods with over 99% probability.

Figure 14.10: Operating Characteristic Curves – P(passing test) versus Lot Standard Deviation at Lot Means of 100% and 96% for USP Uniformity of Dosage Unit [46], ASTM E2709/E2810, Two-Sided Tolerance Interval, and “Exact” Method (n = 10, 30, and 60)

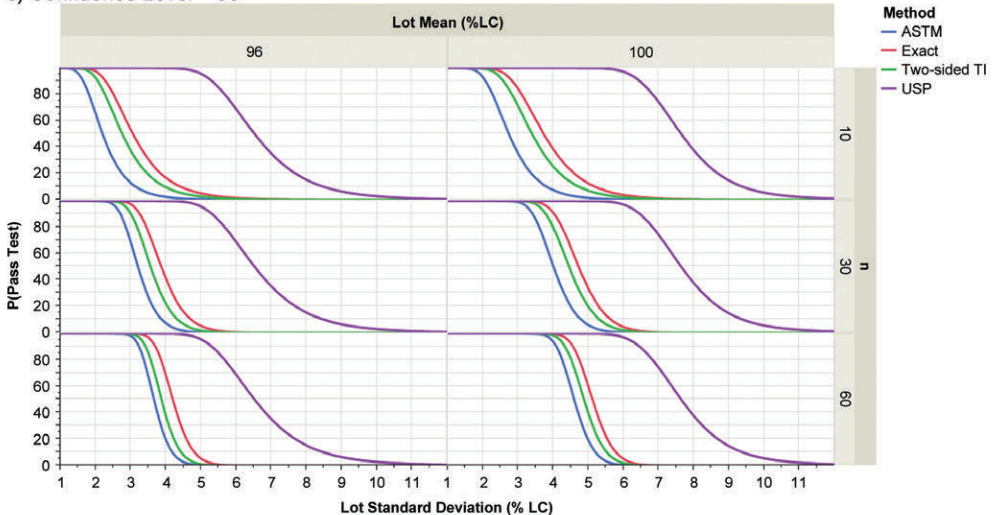
a) Confidence Level = 50



b) Confidence Level = 90



c) Confidence Level = 95



Note that for the same lot standard deviation, the probability of passing the “Exact” method acceptance limit table is higher than the Two-Sided Tolerance Interval method, which is higher than the ASTM E2709/E2810 method [44].

14.10 Formula for Calculating the Tolerance Interval Endpoints [54]

$$\bar{Y} \pm z_{(1+\beta)/2} \sqrt{1 + N_{\epsilon}^{-1}} \sqrt{\hat{\sigma}_Y^2 + \left\{ H_1^2 \left(\frac{1}{J} \right)^2 S_l^2 + H_2^2 \left(\frac{J-1}{J} \right)^2 S_2^2 \right\}^{1/2}}$$

$$\text{Where } N_{\epsilon} = \frac{l(S_l^2 + (J-1)S_2^2)}{S_l^2}, H_1 = \frac{1}{F_{1-\gamma, l, 1, \infty}} - 1, H_2 = \frac{1}{F_{1-\gamma, l, (J-1), \infty}} - 1$$

S_l^2 = Mean Square Between Locations S_2^2 = Mean Square Error

$$\hat{\sigma}_Y^2 = \frac{1}{J} S_l^2 + \left(\frac{J-1}{J} \right) S_2^2$$

Where:

$\bar{Y}$ = overall mean

l = number of locations

J = replicates at l location

β = coverage

γ = confidence level

Z = standard normal quantile

If the tolerance interval endpoints are contained between 83.5% to 116.5% LC, then with $(1-\gamma)$ 100% confidence, there is at least $100\beta\%$ of future samples from the batch will meet UDU criteria.

14.11 Dissolution Acceptance Limit Tables

Table 14.2: Acceptance Limit Tables 90% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53]

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
0.2	0.10	0.16	0.20	0.23	0.26	0.29	0.31	0.35
0.4	0.19	0.32	0.40	0.45	0.53	0.58	0.62	0.69
0.6	0.29	0.48	0.60	0.68	0.79	0.87	0.93	1.04
0.8	0.38	0.64	0.80	0.90	1.06	1.16	1.24	1.38
1.0	0.48	0.80	0.99	1.13	1.32	1.45	1.55	1.73
1.2	0.58	0.96	1.19	1.36	1.36	1.74	1.86	2.07
1.4	0.67	1.12	1.39	1.58	1.85	2.03	2.17	2.42
1.6	0.77	1.28	1.59	1.81	2.11	2.32	2.48	2.76
1.8	0.87	1.44	1.79	2.03	2.38	2.61	2.79	3.11
2.0	0.96	1.60	1.99	2.26	2.64	2.90	3.10	3.45
2.2	1.06	1.76	2.19	2.49	2.90	3.19	3.41	3.80
2.4	1.15	1.92	2.38	2.71	3.17	3.48	3.72	4.14
2.6	1.25	2.08	2.58	2.94	3.43	3.78	4.03	4.49
2.8	1.34	2.24	2.78	3.16	3.70	4.07	4.35	4.83
3.0	1.44	2.41	2.98	3.39	3.96	4.36	4.66	5.18
3.2	1.54	2.57	3.18	3.62	4.22	4.65	4.96	5.52
3.4	1.63	2.73	3.38	3.84	4.49	4.94	5.27	5.85
3.6	1.73	2.89	3.58	4.07	4.75	5.22	5.58	6.17
3.8	1.83	3.05	3.78	4.29	5.01	5.51	5.87	6.47
4.0	1.92	3.21	3.97	4.52	5.27	5.78	6.15	6.74
4.2	2.02	3.37	4.17	4.74	5.52	6.04	6.41	6.99
4.4	2.11	3.53	4.37	4.96	5.76	6.28	6.64	7.21
4.6	2.21	3.69	4.57	5.18	5.99	6.50	6.86	7.40
4.8	2.31	3.85	4.76	5.39	6.20	6.71	7.05	7.58
5.0	2.40	4.01	4.95	5.59	6.40	6.89	7.23	7.74
5.2	2.50	4.17	5.14	5.78	6.58	7.06	7.39	7.89
5.4	2.59	4.32	5.31	5.96	6.74	7.21	7.53	8.02
5.6	2.69	4.48	5.48	6.12	6.89	7.36	7.67	8.15
5.8	2.79	4.63	5.64	6.27	7.03	7.49	7.79	8.27
6.0	2.88	4.77	5.78	6.41	7.16	7.61	7.91	8.38
6.2	2.98	4.91	5.92	6.54	7.28	7.72	8.02	8.48

Table 14.2: Acceptance Limit Tables 90% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53] (continued)

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
6.4	3.07	5.04	6.05	6.66	7.39	7.83	8.12	8.58
6.6	3.17	5.17	6.17	6.78	7.50	7.92	8.22	8.67
6.8	3.26	5.29	6.28	6.88	7.60	8.02	8.31	8.76
7.0	3.35	5.40	6.39	6.98	7.69	8.11	8.39	8.84
7.2	3.44	5.50	6.49	7.08	7.78	8.19	8.48	8.92
7.4	3.53	5.60	6.58	7.17	7.86	8.27	8.56	9.00
7.6	3.62	5.70	6.67	7.25	7.94	8.35	8.64	9.08
7.8	3.70	5.79	6.75	7.33	8.02	8.43	8.71	9.15
8.0	3.78	5.87	6.83	7.41	8.09	8.50	8.78	9.22
8.2	3.86	5.95	6.91	7.48	8.16	8.57	8.85	9.29
8.4	3.94	6.02	6.98	7.55	8.23	8.64	8.92	9.36
8.6	4.01	6.10	7.05	7.62	8.30	8.71	8.99	9.43
8.8	4.08	6.16	7.11	7.68	8.36	8.77	9.06	9.50
9.0	4.14	6.23	7.18	7.75	8.43	8.84	9.12	9.57
9.2	4.20	6.29	7.24	7.81	8.49	8.90	9.19	9.63
9.4	4.26	6.35	7.30	7.87	8.55	8.97	9.25	9.70
9.6	4.32	6.41	7.36	7.93	8.61	9.03	9.31	9.77
9.8	4.37	6.47	7.41	7.99	8.67	9.09	9.38	9.83
10.0	4.43	6.52	7.47	8.04	8.73	9.15	9.44	9.89
10.2	4.48	6.58	7.53	8.10	8.79	9.21	9.50	9.96
10.4	4.53	6.63	7.58	8.16	8.85	9.27	9.56	10.02
10.6	4.57	6.68	7.63	8.21	8.91	9.33	9.62	10.09
10.8	4.62	6.73	7.68	8.26	8.97	9.39	9.69	10.15
11.0	4.66	6.77	7.74	8.32	9.02	9.45	9.75	10.21
11.2	4.70	6.82	7.79	8.37	9.08	9.51	9.81	10.27
11.4	4.74	6.87	7.84	8.42	9.14	9.57	9.87	10.34
11.6	4.78	6.91	7.89	8.48	9.19	9.63	9.93	10.40
11.8	4.82	6.96	7.94	8.53	9.25	9.68	9.99	10.46
12.0	4.86	7.01	7.99	8.58	9.30	9.74	10.05	10.52
12.2	4.90	7.05	8.03	8.63	9.36	9.80	10.10	10.59
12.4	4.93	7.09	8.08	8.69	9.42	9.86	10.16	10.65
12.6	4.97	7.14	8.13	8.74	9.47	9.92	10.22	10.71
12.8	5.00	7.18	8.18	8.79	9.53	9.97	10.28	10.77

Table 14.2: Acceptance Limit Tables 90% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53] (continued)

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
13.0	5.03	7.22	8.23	8.84	9.58	10.03	10.34	10.83
13.2	5.07	7.27	8.28	8.89	9.64	10.09	10.40	10.89
13.4	5.10	7.31	8.32	8.94	9.69	10.14	10.46	10.96
13.6	5.13	7.35	8.37	8.99	9.75	10.20	10.52	11.02
13.8	5.16	7.40	8.42	9.04	9.80	10.26	10.58	11.08
14.0	5.20	7.44	8.47	9.09	9.85	10.32	10.64	11.14
14.2	5.23	7.48	8.51	9.15	9.91	10.37	10.69	11.20
14.4	5.26	7.52	8.56	9.20	9.96	10.43	10.75	11.26
14.6	5.29	7.56	8.61	9.25	10.02	10.49	10.81	11.32
14.8	5.32	7.61	8.66	9.30	10.07	10.54	10.87	11.38
15.0	5.35	7.65	8.70	9.35	10.13	10.60	10.93	11.44

Table 14.3: Acceptance Limit Tables 95% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53]

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
0.2	0.07	0.13	0.17	0.19	0.23	0.26	0.28	0.32
0.4	0.14	0.26	0.34	0.39	0.46	0.52	0.56	0.63
0.6	0.22	0.39	0.50	0.58	0.70	0.78	0.84	0.95
0.8	0.29	0.52	0.67	0.78	0.93	1.03	1.11	1.26
1.0	0.36	0.66	0.84	0.97	1.16	1.29	1.39	1.57
1.2	0.43	0.79	1.01	1.16	1.39	1.55	1.67	1.89
1.4	0.50	0.92	1.17	1.36	1.62	1.81	1.95	2.20
1.6	0.58	1.05	1.34	1.55	1.85	2.07	2.23	2.52
1.8	0.65	1.18	1.51	1.75	2.09	2.33	2.51	2.84
2.0	0.72	1.31	1.68	1.94	2.32	2.58	2.79	3.15
2.2	0.79	1.44	1.84	2.14	2.55	2.84	3.07	3.47
2.4	0.87	1.57	2.01	2.33	2.78	3.10	3.35	3.78
2.6	0.94	1.70	2.18	2.52	3.01	3.36	3.63	4.10
2.8	1.01	1.83	2.35	2.72	3.25	3.62	3.90	4.41
3.0	1.08	1.97	2.51	2.91	3.48	3.88	4.18	4.73
3.2	1.15	2.10	2.68	3.11	3.71	4.14	4.46	5.04
3.4	1.23	2.23	2.85	3.30	3.94	4.39	4.74	5.35

Table 14.3: Acceptance Limit Tables 95% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53] (continued)

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
3.6	1.30	2.36	3.02	3.50	4.17	4.65	5.02	5.66
3.8	1.37	2.49	3.19	3.69	4.41	4.91	5.29	5.95
4.0	1.44	2.62	3.35	3.88	4.64	5.16	5.56	6.23
4.2	1.51	2.75	3.52	4.08	4.87	5.41	5.82	6.49
4.4	1.59	2.88	3.69	4.27	5.09	5.65	6.06	6.73
4.6	1.66	3.01	3.86	4.46	5.31	5.88	6.29	6.94
4.8	1.73	3.15	4.02	4.65	5.53	6.10	6.50	7.13
5.0	1.80	3.28	4.19	4.84	5.73	6.30	6.69	7.31
5.2	1.87	3.41	4.35	5.03	5.92	6.48	6.86	7.46
5.4	1.95	3.54	4.52	5.20	6.09	6.65	7.02	7.61
5.6	2.02	3.67	4.68	5.37	6.26	6.80	7.17	7.74
5.8	2.09	3.80	4.83	5.53	6.41	6.94	7.31	7.87
6.0	2.16	3.93	4.98	5.68	6.55	7.07	7.43	7.98
6.2	2.24	4.05	5.12	5.82	6.68	7.20	7.55	8.09
6.4	2.31	4.18	5.26	5.95	6.80	7.31	7.66	8.19
6.6	2.38	4.30	5.39	6.08	6.91	7.42	7.76	8.29
6.8	2.45	4.41	5.51	6.19	7.02	7.52	7.85	8.38
7.0	2.52	4.53	5.62	6.30	7.12	7.61	7.94	8.47
7.2	2.59	4.64	5.73	6.40	7.21	7.70	8.03	8.55
7.4	2.67	4.74	5.83	6.50	7.30	7.78	8.11	8.63
7.6	2.74	4.84	5.92	6.59	7.39	7.86	8.19	8.71
7.8	2.81	4.93	6.01	6.67	7.47	7.94	8.27	8.78
8.0	2.88	5.02	6.10	6.75	7.54	8.02	8.34	8.86
8.2	2.94	5.11	6.18	6.83	7.62	8.09	8.41	8.93
8.4	3.01	5.19	6.25	6.90	7.69	8.16	8.48	9.00
8.6	3.08	5.26	6.33	6.97	7.75	8.23	8.55	9.06
8.8	3.14	5.33	6.40	7.04	7.82	8.29	8.62	9.13
9.0	3.20	5.40	6.46	7.11	7.88	8.36	8.68	9.20
9.2	3.26	5.47	6.53	7.17	7.95	8.42	8.75	9.26
9.4	3.32	5.53	6.59	7.23	8.01	8.48	8.81	9.33
9.6	3.38	5.59	6.65	7.29	8.07	8.54	8.87	9.39
9.8	3.43	5.65	6.70	7.35	8.13	8.60	8.93	9.45
10.0	3.48	5.71	6.76	7.40	8.18	8.66	8.99	9.52

Table 14.3: Acceptance Limit Tables 95% Confidence Level, 95% Probability to Pass USP Dissolution <711> Test [53] (continued)

Mean – Q	Sample Size							
	6	12	18	24	36	48	60	90
10.2	3.53	5.76	6.81	7.46	8.24	8.72	9.05	9.58
10.4	3.58	5.81	6.87	7.51	8.30	8.78	9.11	9.64
10.6	6.63	5.86	6.92	7.56	8.35	8.84	9.17	9.70
10.8	3.67	5.91	6.97	7.62	8.41	8.89	9.23	9.76
11.0	3.72	5.96	7.02	7.67	8.46	8.95	9.29	9.82
11.2	3.76	6.01	7.07	7.72	8.52	9.01	9.35	9.88
11.4	3.80	6.05	7.11	7.77	8.57	9.06	9.40	9.94
11.6	3.84	6.10	7.16	7.82	8.62	9.12	9.46	10.01
11.8	3.87	6.14	7.21	7.87	8.68	9.17	9.52	10.07
12.0	3.91	6.18	7.26	7.92	8.73	9.23	9.58	10.13
12.2	3.94	6.22	7.30	7.97	8.78	9.28	9.63	10.19
12.4	3.98	6.26	7.35	8.02	8.84	9.34	9.69	10.25
12.6	4.01	6.30	7.39	8.06	8.89	9.39	9.75	10.31
12.8	4.04	6.34	7.44	8.11	8.94	9.45	9.80	10.36
13.0	4.08	6.38	7.48	8.16	8.99	9.50	9.86	10.42
13.2	4.11	6.42	7.53	8.21	9.04	9.56	9.92	10.48
13.4	4.14	6.46	7.57	8.26	9.10	9.61	9.97	10.54
13.6	4.17	6.50	7.61	8.30	9.15	9.67	10.03	10.60
13.8	4.19	6.54	7.66	8.35	9.20	9.72	10.08	10.66
14.0	4.22	6.58	7.70	8.40	9.25	9.78	10.14	10.72
14.2	4.25	6.62	7.75	8.44	9.30	9.83	10.20	10.78
14.4	4.28	6.65	7.79	8.49	9.35	9.88	10.25	10.84
14.6	4.30	6.69	7.83	8.54	9.41	9.94	10.31	10.90
14.8	4.33	6.73	7.88	8.59	9.46	9.99	10.36	10.96
15.0	4.36	6.77	7.92	8.63	9.51	10.04	10.42	11.01

Example

Suppose the specification is $Q = 85$ at 30 minutes. A sample of 12 tablets using Sampling Plan 1 are collected from the lot with $\bar{X} = 92.0$ and standard deviation of 3.70% Released. Then using Table 14.2, the upper limit on the standard deviation is 5.40% Released. Therefore, the sample meets the acceptance criteria since 3.70% is less than 5.4%.

15 Appendix 7 – References

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16 Appendix 8 – Glossary

16.1 Acronyms and Abbreviations

ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
APR	Annual Product Review
AQL	Acceptable Quality Level
ASEAN	Association of Southeast Asian Nations
AV	Acceptance Value
BCS	Biopharmaceutics Classification System
CA	Critical Aspect
CAP	Capability Analysis
CDMO	Contract Development and Manufacturing Organization
CDMPO	Contract Development, Manufacturing, and Packaging Organization
CDO	Contract Development Organization
CFDA	China Food and Drug Administration
CIPC	Critical In-Process Control
CIPT	Critical In-Process Test
CMA	Critical Material Attribute
CMC	Chemistry, Manufacturing and Control
CMO	Contract Manufacturing Organization
CMPO	Contract Manufacturing and Packaging Organization
CNC	Confirmation of No Contamination
CoA	Certificate of Analysis
COD	Critical Operating Data
CPO	Contract Packaging Organization
CPP	Critical Process Parameter
CPV	Continued Process Verification
CQA	Critical Quality Attribute
CS	Control Strategy
CU	Content Uniformity

DoE	Design of Experiment
DQ	Design Qualification
DS	Drug Substance
EMA	European Medicines Agency
EU	Europe
FAT	Factory Acceptance Testing
FMEA	Failure Modes and Effect Analysis
FMECA	Failure Modes Effects and Criticality Analysis
FDA	Food & Drug Administration (US)
FP	Finished Product
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
HMP	Heightened Monitoring Plan
IPAC	In-Process Acceptance Criteria
ICH	International Council for Harmonisation
IPC	In-Process Control
IPM	In Process Measurement
IPT	In-Process Test
IQ	Installation Qualification
ISO	International Organization for Standardization
IT	Information Technology
IVIVC	<i>In Vitro-In Vivo</i> Correlation
JP	Japanese Pharmacopoeia
KFDA	Korea Food & Drug Administration
LC	Label Claim
LCCB	Lower Capability Confidence Bound
LOQ	Limit of Quantitation
LSL	Lower Specification Limit
MA	Material Attribute
MCC	Microcrystalline Cellulose
MFDS	Ministry of Food and Drug Safety (South Korea)

MgSt	Magnesium Stearate
MHLW	Ministry of Health, Labour and Welfare (Japan)
MMV	Mice Minute Virus
MSA	Measurement System Analysis
MSD	Maximum Standard Deviation
n	Sample size
NDA	New Drug Application (US)
NIR	Near Infrared
NMPA	National Medical Products Administration (China)
NOR	Normal Operating Range
OC	Operating Characteristic
OFAT	One-Factor-at-a-Time
OPV	Ongoing Process Verification
OQ	Operational Qualification
PAR	Proven Acceptable Range
PAT	Process Analytical Technology
PD	Process Design
PFMEA	Process Failure Mode and Effect Analysis
Ph. Eur.	European Pharmacopoeia
PI	Process Indicator
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PPQ	Process Performance Qualification
PPR	Process Parameter Report
PQ	Performance Qualification
PQLI	Product Quality Lifecycle Initiative®
PSD	Particle Size Distribution
PV	Process Validation
QA	Quality Assurance
QbD	Quality by Design
QC	Quality Control
Q-PCR	Quantitative Polymerase Chain Reaction

QRM	Quality Risk Management
QTPP	Quality Target Product Profile
RACI	Responsible, Accountable, Consulted, Informed
RP-HPLC	Reverse Phase-High Pressure Liquid Chromatography
RPN	Risk Priority Number
R&R	Repeatability and Reproducibility
RSD	Relative Standard Deviation
RTRT	Real Time Release Testing
s	Standard Deviation
SAT	Site Acceptance Testing
SCL	Statistical Control Limit
SE	Within Location Standard Deviation
SME	Subject Matter Expert
SOP	Standard Operating Procedure
SPC	Statistical Process Control
SSA	Specific Surface Area
StDev	Standard Deviation
SUPAC	Scale-up and Post-Approval Changes
UDU	Uniformity of Dosage Unit
ULS	Upper Confidence Limit on the Standard Deviation
URS	User Requirements Specification
US	United States
USL	Upper Specification Limit
USP	United States Pharmacopeia
VCA	Variance Components Analysis
VMP	Validation Master Plan
WCB	Working Cell Bank
WHO	World Health Organization

16.2 Definitions

Attribute (Data) (ASTM E2587 [73])

Observed values or test results that indicate the presence or absence of specific characteristics or counts of occurrences of events in time or space.

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).

Capability of a Process (ICH Q10 [6])

Ability of a process to realise a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Note: also see Process Capability

Common Cause Variability (Chance Cause) (ASTM E456 [74])

Source of inherent random variation in a process which is predictable within statistical limits. E2587

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.

Confidence Interval (ASTM E456 [74])

An interval estimate $[L, U]$ with the statistics L and U as limits for the parameter θ and with confidence level $1-\alpha$, where $\Pr(L \leq \theta \leq U) \geq 1-\alpha$.

Confidence Level (ASTM E456 [74])

The value, $1-\alpha$, of the probability associated with a confidence interval, often expressed as a percentage.

Continued Process Verification (FDA PV Guidance [3])

Assuring that during routine production the process remains in a state of control.

Continuous Process Verification (ICH Q8(R2) [1])

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Control Chart (ASTM E456 [74])

Chart on which are plotted a statistical measure of a subgroup versus time of sampling along with limits based on the statistical distribution of that measure so as to indicate how much common, or chance, cause variation is inherent in the process or product.

Control Limits (ASTM E456 [74])

Limits on a control chart that are used as criteria for signaling the need for action or judging whether a set of data does or does not indicate a state of statistical control based on a prescribed degree of risk.

Control Strategy (ICH Q10 [6])

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.

Critical Aspects (ASTM E2500 [36])

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.

Critical Material Attribute (CMA)

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.

Critical Process Parameter (CPP) (ICH Q8(R2) [1])

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.

Critical Quality Attribute (CQA) (ICH Q8(R2) [1])

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.

Design Space (ICH Q8(R2) [1])

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.

Legacy Product (ISPE [33])

A product initially validated and commercialized prior to the formal introduction of the current lifecycle architecture.

Measurement Uncertainty

A parameter associated with the result of a **measurement**, that characterizes the dispersion of the values that could reasonably be attributed to the measurement.

Ongoing Process Verification (*also known as Continued Process Verification*) (EU Annex 15 [11])

Documented evidence that the process remains in a state of control during commercial manufacture.

Operating Characteristic Curve (ISO 3534-2:2006 [29])

Curve showing the relationship between probability of acceptance of product and the incoming quality level for a given acceptance sampling plan.

Process Capability (ASTM E456 [74])

Statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control.

Note: also see Capability of a Process.

Process Capability Index (ASTM E456 [74])

An index describing process capability in relation to specified tolerance.

Process Performance (ASTM E456 [74])

Statistical measure of the outcome of a characteristic from a process that may not have been demonstrated to be in a state of statistical control.

Process Performance Index (ASTM E456 [74])

Index describing process performance in relation to specified tolerance.

Process Performance Qualification (PPQ) (FDA PV Guidance [3])

The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Process Robustness (ICH Q8(R2) [1])

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Process Validation (PV) (EU Annex 15 [11])

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Process Validation (PV) (FDA PV Guidance [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 products.

Quality by Design (QbD) (ICH Q8(R2) [1])

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quality Risk Management (QRM) (ICH Q9 [2])

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality Target Product Profile (QTPP) (ICH Q8(R2) [1])

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.

Revalidation (ISPE Glossary [75])

Validation of a previously validated system that has been changed or modified. Revalidation can be performed as the result of a change to the system, or a time-based assessment.

Risk (ICH Q9 [2])

The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Management (ICH Q9 [2])

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Ranking (ICH Q9 [2])

Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks.

Robust Process

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

Simple Random Sample (ASTM E456 [74])

- (without replacement) probability sample of n sampling units from a population of N units selected in such a way that each of the $\frac{N!}{n!(N-n)!}$ subsets of n units is equally probable.
- (with replacement) a probability sample of n sampling units from a population of N units selected in such a way that, in order of selection, each of the N^n ordered sequences of units from the population is equally probable.

Stable Process (ISO 3534-2 [29])

A process in a state of statistical control (constant mean and variance) subject only to random causes. **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.

Stage 1 Process Validation – Pharmaceutical Development (ICH Q8(R2) [1])

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.

Stage 1 Process Validation – Process Design (FDA PV Guidance [3])

The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 Process Validation – Process Qualification (FDA PV Guidance [3])

During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ).

Stage 2 Process Validation – Process Validation (EMA [12])

Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process.

Stage 3 Process Validation – Continued Process Verification (FDA PV Guide [3])

Ongoing assurance is gained during routine production that the process remains in a state of control. We recommend 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. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level.

Stage 3 Process Validation – Ongoing Process Verification (EU Annex 15 [11])

Documented evidence that the process remains in a state of control during commercial manufacture.

State of Control (ICH Q10 [6])

A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

Statistical Distribution

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

Technology Transfer (ICH Q10 [6])

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

Tolerance Interval

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 ($1-\alpha$).

Trend (ICH Q9 [2])

A statistical term referring to the direction or rate of change of a variable(s).

Uncertainty (ASTM E456 [74])

An indication of the magnitude of error associated with a value that takes into account both systematic errors and random errors associated with the measurement or test process. E2655

Validation Master Plan (VMP) (EU Annex 15 [11])

The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP).

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.

Variables, Data (ASTM E456 [74])

Observations or test results defined on a continuous scale.

Verification (ASTM E2500 [36])

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



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