Connecting a World of Pharmaceutical Knowledge

Topic 2 – Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products

This discussion paper proposes ideas for answering the questions "How is Stage 3 monitoring and testing following PPQ determined, as part of the lifecycle approach to PV?" "What is the impact of the lifecycle approach to monitoring and testing of existing/legacy products?" The purpose of this paper is to stimulate further discussion and suggest potential practical application. Approaches to providing answers, are proposed, but more experience in implementation of the lifecycle approach to PV is needed to finalize a consensus a position. Considerable input has already been received, considered, and/or incorporated. The author team is interested in hearing about other approaches that could be used, and lessons from use of the proposed approaches described in the discussion paper. The paper may be modified or expanded sometime in the future to reflect additional input.

Additional input in the following areas is sought:

- Examples of how the approaches described in this paper have been used or modified, especially for:
    - Other types of drug product processes
    - API processes
    - Biopharma processes
    - Revalidation of existing/legacy processes
- Other ideas about scope of CPV plan
- Other approaches to identifying parameters and critical quality attributes to be monitored at a heightened level in CPV
- Considerations for when enhanced monitoring is required/triggered
- Is maintenance of models for RTRt applications part of CPV?
- Application of statistically based release sampling and testing for existing (legacy) products
- Application of basic and advanced Statistical Process Control (SPC) and predictive modeling

Please direct all feedback to pvstage3@ispe.org. The authors would prefer that all input be focused primarily on the themes identified above.

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ISPE Discussion Paper

Topic 2 – Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products

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1 Introduction

In January 2011, the FDA issued a Guidance for Industry on "Process Validation: General Principles and Practices" [1]. EMA has also issued a draft revision to the Guideline on Process Validation [2], which is circulated for public comment for completion by 31 October 2012. This document is intended to clarify how organizations can take advantage of opportunities arising from ICH Q8 [3], ICH Q9 [4], and ICH Q10 [5] and the possibility to use continuous process verification (which is differentiated from continued process verification used in the PV Guidance from the FDA [1]) in addition to, or instead of, traditional process verification. The PV Guidance from the FDA [1], which is the main focus of this document, describes a lifecycle approach to Process Validation that links product and process development, *qualification of the commercial manufacturing process*, and maintenance of the process ***in a state of control*** during routine commercial production.

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*** thereby also assuring reliability of supply***.***

The revised PV Guidance from the FDA [1] and the draft revision to the EMA PV Guidance [2] both emphasize that process validation should not be viewed as a one-off event. A lifecycle approach should be applied 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. The goals and typical activities of each Stage are summarized in the Table 1:

Table 1: Goals and Typical Activities of the Stages of Process Validation

Stage of Process Validation	Definition	Goals	Typical Activities
Stage 1	Process Design	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	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. 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 (CPV)	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.

While process performance analysis may have been adopted by some organizations to support continuous improvement, bringing this activity under the umbrella of process validation is a significant change for the pharmaceutical industry. Different interpretations and approaches may be taken by pharmaceutical organizations to satisfy the requirements and apply the recommendations of the PV Guidance from the FDA [1]. The intent of this discussion paper is to provide some practical approaches for applying Continued Process Verification (CPV) (PV Stage 3) including some considerations for the selection of appropriate attributes and parameters for a Stage 3 sampling plan, and discussion of when heightened sampling may be appropriate. The discussion paper also presents some specific examples developed by industry on how to establish and apply Stage 3 monitoring. This topic was chosen as it represents one of the most significant changes in process validation expectations.

2 Scope

The PV Guidance from the FDA [1] defines Stage 3, Continued Process Verification (CPV) as "assuring that during routine production the process remains in a state of control." It refers to the cGMPs, section 211.180(e) [6], which require collection and evaluation of information and data about the performance of the process and this information should be collected to verify that the quality attributes are being appropriately controlled throughout the process, to provide statistical confidence of quality including evaluation of process stability and capability, and to identify variability and/or potential process improvements. CPV could be considered as an on-going program and applies to the following cases:

1. **New products** that have been developed through FDA Process Validation Stages 1 and 2 and are entering routine commercial manufacturing (Stage 3).

   This discussion paper focuses on how to establish a monitoring plan for new products immediately following a successful Process Performance Qualification (PPQ – Stage 2). The revised PV Guidance from the FDA [1] recommends "…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." This discussion paper discusses considerations to determine whether enhanced monitoring and/or sampling may be appropriate both immediately following successful completion of PPQ, but also throughout the commercial phase of the lifecycle.

   Example #1 (ISPE PQLI Guide: Illustrative Example (PQLI IE) [7]) and Example #2 (Large Molecule) demonstrate a stepwise approach to establishing a monitoring post Stage 2 (see Appendix).

2. **Existing (or legacy) products** (existing validated products in commercial manufacturing). A monitoring plan should be established or enhanced for existing products. The scope of CPV (i.e., the attributes and parameters to be included) should be defined and an initial evaluation of process performance conducted based on historical manufacturing data/routine monitoring data for the identified attributes and parameters. As for a new process, this evaluation should then determine the appropriate level of monitoring and sampling and/or a potential return to some of the activities described in Stages 1 and 2.

   This document also discusses and offers an example approach (Example #3 in Appendix) of establishing monitoring for an existing, validated product.

Once a process has been commercialized, a well-defined system for process and product performance monitoring should be applied to assure that the process remains in a state of control and is capable of consistently meeting the registered specifications during routine production. Based on routine performance data, the same principles can be applied as when defining the initial monitoring plan following PPQ to determine any need for enhanced monitoring throughout the commercial phase of the lifecycle.

A systematic approach to maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control, including periodic review of the equipment and facility qualification status. These elements of the quality system may be included in or referenced by the CPV monitoring plan.

The routine monitoring plan also should help to identify improvement areas (e.g., adjustments to the control strategy, including specifications), support evaluation of proposed post approval changes, facilitate investigations, support technical transfers, and confirm that changes or process improvements have had the desired impact.

The concepts and approaches presented in this document apply to all product categories, including:

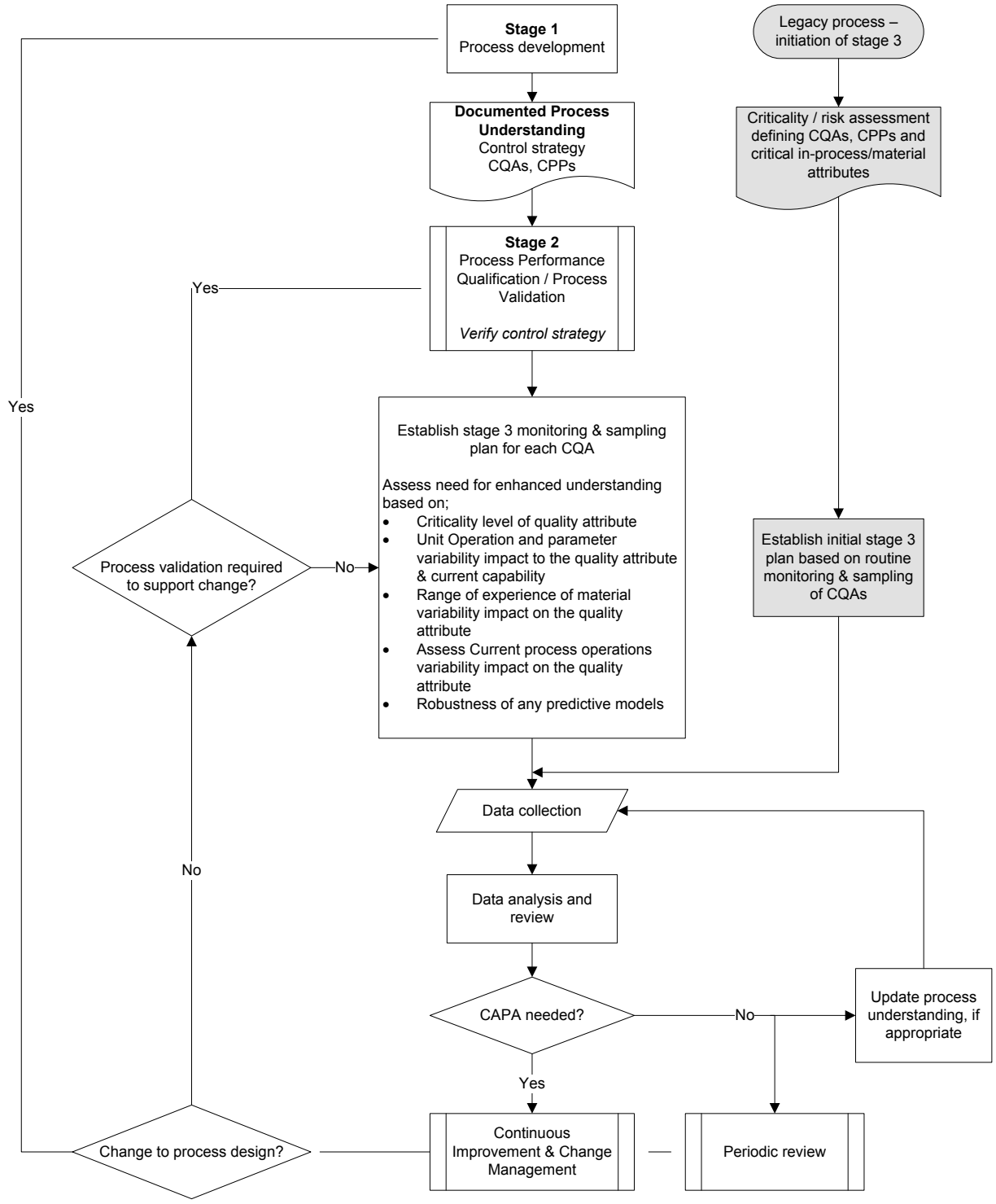
- Small and large molecules
- Sterile and non-sterile products
- Finished products
- Active Pharmaceutical Ingredients (APIs or biological drug substance)
- Combination products (drug and administrative device)

3 Establishing a Continued Process Verification Monitoring Plan

A successful PPQ (Stage 2) confirms 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. However, a period of enhanced monitoring after completion of PPQ may be required for certain identified attributes or parameters to further increase the level of confidence in the process. Following a successful Stage 2, the main purpose of the CPV (Stage 3) monitoring plan is to provide assurance throughout the commercial phase of the lifecycle that the process remains in a state of control. A CPV monitoring plan should be established to evaluate process capability and to evaluate 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 statistical process control acceptance criteria and to adjust levels and frequency of routine sampling and monitoring, as appropriate. Any statistically Out-Of-Control (OOC) or Out-Of- Trends (OOT) and input-output relationships identified from continued process monitoring may then trigger opportunities for changes in the control strategy, elimination/addition of monitoring parameters or process improvements.

A potential approach to selecting parameters/attributes for the CPV plan and the overall process is summarized in Figure 1.

Figure 1: Flow chart for establishing a Stage 3 Monitoring Plan for new products.



It is recommended that for all new products that a monitoring plan is established immediately following Stage 2 if full PPQ level sampling and testing will not be continued. The approach to analyzing product and process performance data should be documented. This may be in the format of a procedure or

protocol. The plan should be developed by subject matter experts (technical personnel, statisticians, etc.) 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 along with the methodology that will be used to evaluate the data (e.g., statistical methods), and at what frequency these data will be evaluated. The plan could be product–specific, covering all unit operations, raw materials, equipment settings, etc., or products may be grouped (e.g., platform technology approach). The plan also may include elements such as 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 existing data collection and evaluation processes, including the annual/periodic review process. It is recommended that the plan by which potential impact to commercial product quality and release is evaluated is approved by the Quality Unit at the manufacturing site.

3.1 Selection of Parameters and Attributes to be Monitored

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 to understanding based on manufacturing experience.

During Stage 3, significant estimates of 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 attribute or parameter criticality level (typically, 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 on-going monitoring. However, some CQAs (e.g., viral clearance for a biological product) may be confirmed through separate validation studies and not as part of release of each batch and therefore, 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 and specific residual risks are reduced or new risks are identified. The decision to discontinue testing should be driven by the confidence achieved in the manufacturing process during Stage 1, Stage 2, and throughout Stage 3, based on the robustness of the control strategy and its ability to manage sources of variation. The rationale for the change or discontinuance of the monitoring should be documented.

3.1.1 New/QbD Products

For products developed according to QbD principles, the control strategy identified during development (Stage 1, process design) is based on process understanding and quality risk management and provides the foundation for Stage 3 monitoring. The parameters and attributes included in the enhanced

sampling and testing in Stage 2 should be considered initially for continued monitoring in Stage 3. Both intra- and inter-batch variability should be considered when establishing the monitoring plan. Intra-batch variability is typically assessed during PPQ and if it has already been demonstrated that a smaller number of samples/values/data points represents the batch, i.e., intra-batch variability data demonstrates that worst case locations and time points are not significantly different than other points/locations, then testing can be reduced to routine levels. However, this routine level should be scientifically and statistically justified. It may be prudent to continue enhanced sampling, but the number of samples may be decreased (see Example #1). Where it is not reasonable or practical to assess variability of input ranges of material quality attributes which may impact intra-batch or inter-batch variability during Stage 2, or if product quality attributes values are approaching edge of an acceptance limit, then it may be prudent to continue to perform Stage 2 levels of sampling and testing during Stage 3. With the appropriate risk-based analysis and documented justification, certain Stage 2 parameters may be eliminated or the level of sampling testing could be reduced in the Stage 3 plan. An example of such a decision process is presented in Example #2.

One of the goals of initial Stage 3 monitoring for a new product is to finish establishing the capability of the process, which 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, or the control or alert limits for those inputs also could be considered. That is, if the input variability evaluated to date is limited compared to the input specification limits, more data should be complied 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. A batch may yield one or more data points: process capability analysis can be performed with groups of samples (e.g., 6 samples for each batch), taking into account the intra-batch variability. It also should be noted that process capability may be calculated using batches from all three stages of process validation.

A criticality/risk assessment should determine the level of impact each process variable or material attribute has on the Critical Quality Attributes (CQAs); that is, where each variable falls in the continuum of criticality. This criticality assessment will typically have been 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 assessed, one of the objectives of the CPV plan will be to evaluate potential sources of variability and their impact on the CQAs or process performance, and confirm or establish the inputs versus CQAs correlations.

3.1.2 Existing/Legacy Products

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; that is, the critical attributes and parameters. 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) and product performance on stability. An example of such an evaluation is presented in Example #3 (Small Molecule Example- Legacy product).

Stage 3 for existing/legacy products should begin based on existing routine monitoring of the defined critical attributes and parameters. The initial evaluation may be based on retrospective review of existing process performance data (i.e., from batches made before the decision to formally initiate Stage 3). Similarly to new products, as data is collected and analyzed, additional aspects that require evaluation may be identified. One potential action may be to implement monitoring of additional parameters across batches or 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 any cause and effect relationships, and help to identify which inputs need to be better controlled to reduce output variability.

3.2 Review of the Stage 3 Plan

Throughout the commercial phase of the lifecycle, the monitoring plan should be reviewed periodically, after defined intervals (typically stated as a number of batches) to assess whether it remains appropriate based on the increasing understanding of process and process variability. The plan also should be reviewed following a change to the process that potentially impacts product quality or process performance, taking into account any Stage 2 activity that may be associated with the change.

The data sources included in the Stage 3 monitoring plan focus on process or materials data. However, it is acknowledged that data from other quality systems also may be useful when reviewing process performance. For example, information on the performance of facilities, utilities, and equipment would be assessed during investigation of special cause event, or if unacceptable intra or inter batch variability is detected. Other systems may provide further information on product quality, such as product performance on stability, periodic review, complaints, deviations, or other atypical events.

4 Data Analysis and Review

4.1 Process Analysis Tools

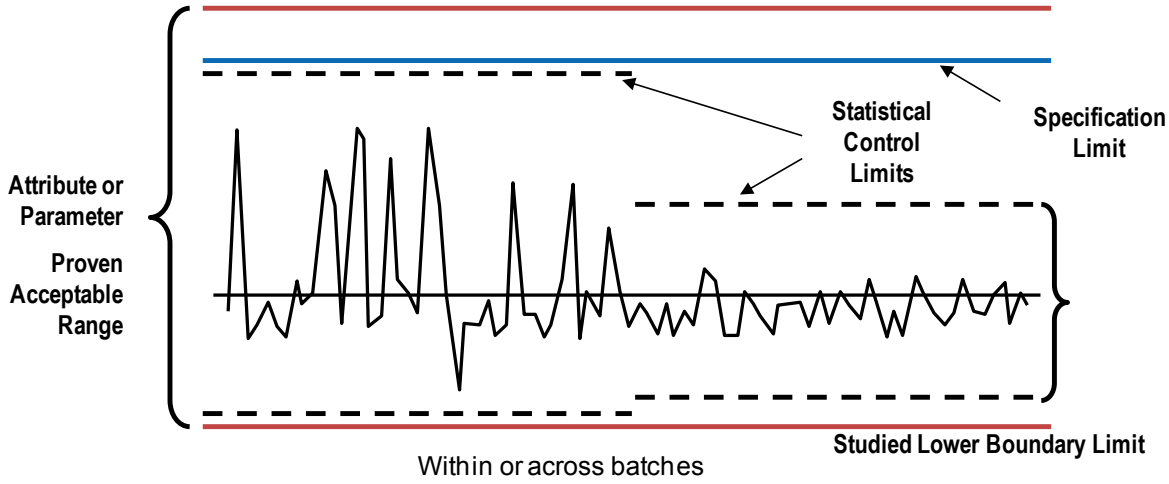
It is recommended that manufacturers develop a process for collecting, analyzing, reporting, and storing data obtained as part of the Stage 3 monitoring plan. Multiple sources of data and their analysis may need to be integrated and organized by appropriate technology tools. Statistical tools of varying complexity can be used to analyze the data on an ongoing basis to continually verify that the process (inputs and outputs) remains in control and is capable. The most common statistical tools are simple descriptive statistics (e.g., time series plots, histograms, box plots), statistical process control charts (I-MR, X-R, or X-S, simultaneous control charts) and process capability (Cp, Pp, Cpk, Ppk). These tools may be used in real time, or off-line, depending on the requirements of the monitoring plan, and can be very useful in identifying process trends and/or signals and input/output correlations.

The distribution of the data (i.e., normal versus non-normal) should be taken into consideration when choosing the appropriate analysis tool. How the results of any process analysis will be reported should be defined, e.g., process capability may be reported as an index, or as Defects Per Million Opportunities (DPMO). Identified excursions outside approved procedures, formulas, specifications, standards, or parameters should be cross-referenced with the applicable GMP documentation.

4.2 Setting Control/Action Limits

When evaluating the performance of a process, it is often useful to set limits to provide an indication when the variability of a parameter or attribute may be changing, and therefore, needs further attention. These limits represent the "voice of the process" (e.g., common cause variation inherent in the process) and should not be confused with specifications, proven or studied boundaries, or in-process control limits. The Statistical Process Control (SPC) limits should be compared to any release criteria to determine the process capability (Cpk, Ppk). An illustration of the different limits is shown in Figure 2.

Figure 2: Graphical representation of Statistical Process Control limits and other release or control limits



SPC limits are determined in a number of different ways, depending on the process analysis tool being used. When using control charts for monitoring performance, the data range (e.g., lot numbers, manufacturing date range) used for setting control limits should be documented. Control chart limits could be managed by establishing “temporary” control limits until such time as a sufficient amount of data are available to establish “permanent” or “locked” control limits, or time series run charts may be used for parameter/attribute assessments until a statistically significant (typically requiring a minimum of 25 data points) data set is available, or alternatively initial limits can be set based on historical data and other sources of process understanding. As further data is generated, limits may be based on the calculated control limits.

Control limits should be reviewed where intentional changes are introduced to the system (e.g., additional equipment or process trains, process improvements to reduce variation) to ensure the established control limits are appropriate for the new scenario (see Figure 2 for reduced variation and Example #2 for more detail). If as part of an “out-of-control” assessment a special cause is identified (e.g., change in process), control limits may be suspended until more data are collected for establishing new ones. Where special cause events are identified, these values should be removed from calculations for the establishment of control limits and process capability calculations. Control charts should be reviewed at a predetermined frequency in order to identify process excursions (Out of Statistical Control (OOSC) points or data points which fall outside of the “locked” statistical control limits), trends, and/or shifts (Out of Statistical Trend (OOST) events which may be indicative of a statistical shift or trend in the attribute or parameter under analysis) in as “real time” a method as possible. Statistical out-of-control events should be assessed commensurate with the degree of product quality concern raised by the event and documented. What will constitute an OOST event should be clearly defined in the attribute/parameter monitoring plan. The eight Western Electric rules may be reviewed to establish guidelines for identifying OOST events.

4.3 Capability Analysis

Capability analysis is performed to understand how the voice of the process (routine or common cause process variation) ultimately links to the voice of the customer (attribute/parameter acceptance criteria). Capability analysis should be conducted for continuous (variable) data attributes/parameters where the data is normally distributed, once the process is deemed in statistical control. If a desired level of process capability is not being achieved, implementation of process improvements should be considered. Cp and Cpk measure the potential process capability and are typically referred to as short term (within variability based on the control chart sigma value) process variability indicators. Unlike Cp, Cpk accounts for the amount a process is off target. Pp and Ppk are typically referred to as long term capability indicators and rely upon overall process variability (based on sigma for the n-1 points). For data assessment purposes, the smaller of the capability indices is typically used as a conservative measure.

The larger the index, the more capable the process is of meeting specification limits. Usually a value or Cpk or Ppk >1.33 is desirable. If Cpk <1, the variability of the process is greater than the specification limits. Cpk >1.33 which corresponds to 4 sigma and 99.99% of the data will be within specification.

Capability analysis may be performed on existing processes to establish a baseline of current operations, identify and prioritize improvement opportunities, determine whether an improvement had an impact, and to monitor or control a process as in the case of Stage 3 data. Capability analysis also can be applied to a new process as part of the qualification and approval process; reliability engineering metrics can be used as a means of monitoring equipment wear and tear.

4.4 Data Evaluation and Impact to Product Release Decisions

Data analysis procedures may outline the appropriate actions to follow when investigating out of control/alert values or the occurrence of trends. The extent of the investigation of statistical outliers should depend on the proximity of the results to the specifications and the perceived risk of the process shifting and leading to future out of specification results. Higher focus and intensity investigations which include a broader scope would typically be driven by instances where out of control limit values leave a minimal safety margin versus the specifications. As discussed previously, instances where values are within the control limits, but control limits lie outside of the specifications (e.g., low process capability is identified) would typically also drive more thorough investigations to identify root cause and appropriate corrective/preventative actions. For very low variability processes (which may drive very tight statistical control limits) or where outliers lie very close to the control limits with a sufficient safety margin versus the specifications, a lesser degree of investigation would typically be conducted and root cause identification may not always be definitive.

It is noted that these statistical control limits are assumed to be tighter than the acceptance criteria and should not be considered themselves as acceptance criteria. The statistical control limits are used to alert process subject matter experts and management to potentially unacceptable process variability which could lead to future batches not meeting specifications. Therefore an out of statistical control limit value may not impact batch release decisions but optimally impact should be considered prior to the next manufacturing campaign of the product.

4.5 Frequency of Process Analysis

The desired state is that potential issues are identified as soon as data are entered into the process analysis tool, whether this is direct from the process in real-time or is performed after the batch has been completed (ideally before manufacture of the next product campaign, depending on the analysis tool). An automated alert system can be used to inform those responsible for the process of issues as soon as they are detected. Where this evaluation against control/alert limits is manual, an appropriate interval for process analysis should be established (per campaign or “x” batches, etc.) which allows for the capture of process shifts or trends of concern in an appropriate timeframe.

Management review of process performance typically should be conducted for all processes currently running at the site as part of the routine Operational Excellence/Continuous Improvement, or similar cross-functional team meetings.

4.6 Knowledge Management

The ongoing review of process performance continually increases process understanding, both for those attributes and parameters that are demonstrated to be in control and through investigation of special and common cause variation. Knowledge management should therefore ensure that this information is used to update process understanding and the process design (if applicable).

A firm's knowledge management system should ideally support end to end (raw materials to impact on finished drug product) and network wide (e.g., site to site with the same product manufacture) product performance review and knowledge sharing. Knowledge management tools (e.g., documentation, sharing software, global product meetings, or review metrics) can be useful to facilitate such an overview. Periodic product performance reviews, whether conducted at local site level or network-wide, should include key stakeholders, as applicable, such as operations, quality, laboratory, engineering, etc., to leverage increased process understanding for similar products and process platforms.

4.7 Responsibilities for Process Analysis

The responsibilities for executing the Stage 3 monitoring activities should be clearly defined in a document describing the purpose, scope, business process, and procedures established by the organizations. Activities include data collection, evaluation and analysis (including any recommended actions), escalation mechanism, and management reviews at a frequency determined by product and process performance and campaign length. Personnel supporting process and product performance monitoring, including those conducting the management review, should have an appropriate level of awareness and/or training of the statistical tools being used.

5 Defining Corrective and Preventive Actions

Where undesired special cause variation is identified (e.g., OOSC or OOST events), actions should be identified to eliminate or enhance control of the specific special causes. Short-term actions should limit or remedy the impact, should be timely, and should be based on understanding the root cause of the event. Longer term actions also may be needed that will prevent the special cause from recurring. Special cause variation outside approved procedures, formulas, acceptance criteria, standards, or parameters is typically investigated and corrective and preventative actions identified through the site deviation management process. Common cause variation (as may be the case for investigation of low capability processes) requires a more fundamental approach to understand the sources of variation and identify ways of reducing that variation.

When a potential opportunity for improvement is identified, it should be evaluated for impact on product quality, compliance to regulations and prior regulatory submissions, technical feasibility, and process efficiency. Potential quality and compliance issues should be addressed and may require input from regulatory authorities and/or submissions.

Continual improvement opportunities to reduce in-process and/or end product testing also should be considered when evaluating the performance of robust (in-control and capable) processes.

All corrective and preventive actions should be confirmed through the monitoring plan. Once a need for action is confirmed, this should be documented in the CAPA system and through change management, if applicable. Agreed actions may require a change to process design (returning to Stage 1 of the FDA Process Validation Lifecycle), or process validation (Stage 2 of the lifecycle) as part of change management.

5.1 Verification of Root Causes

Where special cause variation (OOSC or OOST events) or low process capability is identified as part of attribute/parameter statistical analysis, root cause investigations may be conducted in an effort to identify key elements contributing to process variability or impacting the process outputs. Various statistical tools such as hypothesis testing, Principle Component Analysis (PCA), linear regression, analysis of variance (ANOVA-univariate, MANOVA-multi-variate), or multiple-regression tools may be useful in conducting these analyses depending on the scenario under analysis. Dependent on the outcome of the root cause investigation, various measures may be taken such as tightening parameters (unit operation parameters, environmental, etc.) or tightening incoming material specifications to optimal values identified from the analysis.

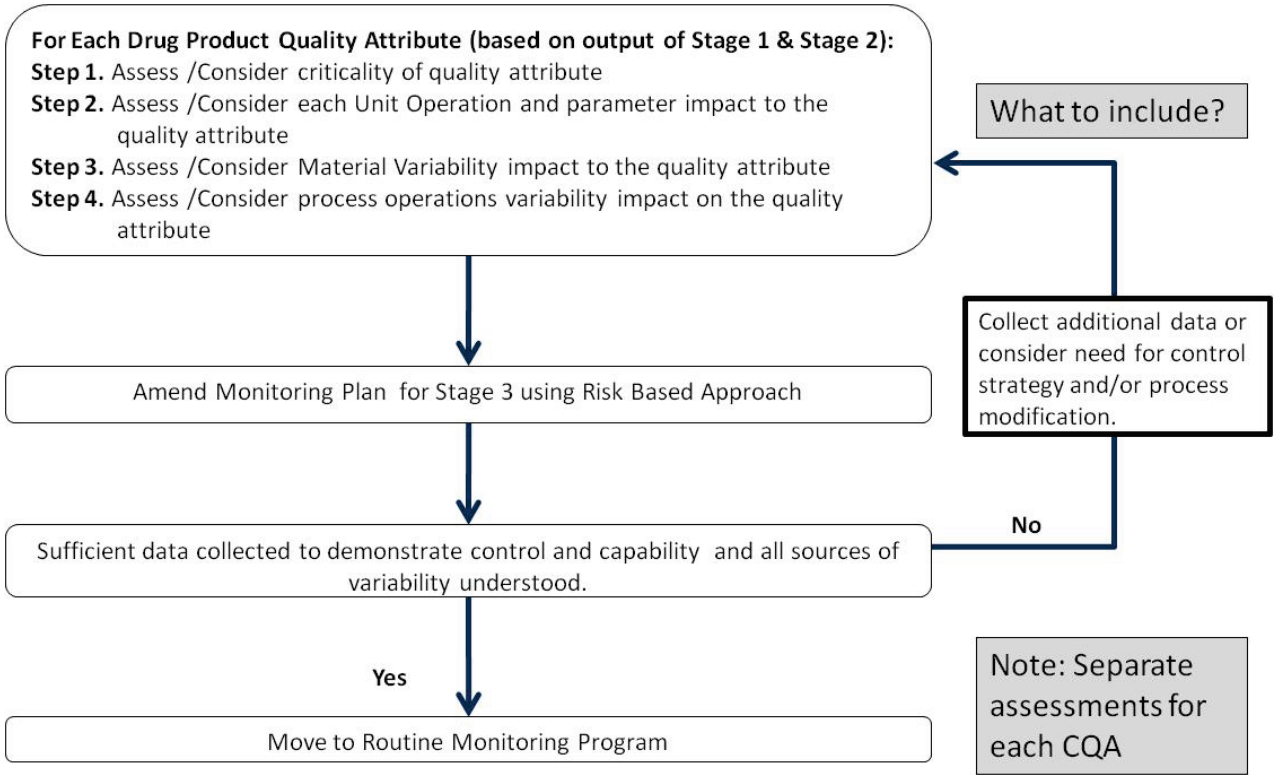
6 Appendix: Examples of Application of Continued Process Verification

It should be noted that the following examples are potential approaches that individual firms have taken on how to apply CPV. Firms need to have a deep understanding of the science, risks and manufacturing experience, before establishing monitoring plans suitable for their specific situations

6.1 Example #1: Selection of CQAs and PPs for Continued Process Verification (CPV) - Applying Risk-Based Approach to CPV Determination to a New Small Molecule Drug Product, Utilizing Data from the ISPE PQLI Illustrative Example [7]

A science- and risk-based approach is used for determining which subset of critical quality attributes and parameters are subject in Stage 3, Continued Process Verification (CPV) to the same or similar levels of monitoring and sampling as Stage 2, process qualification, i.e., heightened monitoring and sampling compared to the eventual routine situation. The flowchart shown in Figure E1.1 outlines the decision-making process.

Figure E1.1: Heightened Monitoring Assessment Decision Process



This assessment is utilized separately for each CQA of the output drug product or drug substance. For the purpose of this example, this process will be applied to the oral solid dosage form CQAs of (content)

Uniformity of Dosage Units (UDU) and dissolution, utilizing data and development knowledge contained in the PQLI IE [7].

For each CQA, questions (Steps 1 to 4 above) are applied taking account of formulation and process development studies, any manufacture using this formula and process, e.g., manufacture of clinical batches or scale-up/technology transfer batches. Data generated during Stage 2, process qualification of process validation, are also reviewed. If sufficient data have 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 have already been justified as part of product submission.

6.1.1 Step 1 – Assessment of Drug Product CQAs to Monitor

Criticality ranking of PaQLInol Tablets CQAs from the PQLI IE [7] is considered, a section from the relevant table is presented in Table E1.1.

Table E1.1: Some Drug Product CQAs with Criticality Ranking

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 PQLI IE [7], the product is PaQLInol Tablets which is dosed orally at 30mg daily. This example focuses on two of the CQAs that are assigned high severity, uniformity of dosage units and dissolution. There is no change in criticality ranking based on Stage 2 process validation data.

6.1.2 Step 2 – Assessment of each Unit Operation and Parameter Impact to the CQAs

The cause and effect matrix for PaQLInol tablet process after formulation development and before process development is given in Table E1.2.

Table E1.2: Cause and Effect Matrix for PaQLInol Tablets before Process Development Studies

	Drug Product					
CQA/Unit Operations	**Dispense**	**Blend**	**Lubricate**	**Compress**	**Coat**	**Package**
Appearance					M	
Identity	M					M
Assay	M	M		M		
Impurities						
Uniformity of Dosage Units		H	M	M		
Dissolution			H	H		
Microbiology						

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 E2). Additionally, development/PV Stage 1 studies to understand and reduce and/or monitor homogeneity of 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 result in:

- Introduction of in-line NIR testing for blend homogeneity and at-line testing of uniformity of dosage units as important elements of the control strategy
- Identification and use of 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 E1.3.

Table E1.3: Cause and Effect Matrix for PaQLInol Tablets after Process Development Studies and Application of the Control Strategy

	Drug Product					
CQA/Unit operations	**Dispense**	**Blend**	**Lubricate**	**Compression**	**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

Note: all risk assignments are now LOW. (See Table 4.4 in PQLI IE [7] 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 Enhance QbD Approaches**

Using 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.

The residual risk assessment, using a different risk assessment tool is more suitable for evaluation of routine manufacturing (e.g., the risk ranking guide given in Appendix 3 Risk Assessment of PaQLInol Tablet Process Using Failure Mode, Effects, and Criticality Analysis (FMECA) of PQLI IE [7]) confirms that PaQLINol tablets have a Low level of residual risk leading to an appropriate number of batches, e.g. 3, being manufactured satisfactorily to support Stage 2, Process Performance Qualification stage of process validation. For further discussion, please see Section 5.7 of PQLI IE [7].

Introduction of Real Time Release Testing (RTRT) as proposed in PQLI IE [7] does require continued monitoring during the initial part of Stage 3, CPV at the same level as during Stage 2 process qualification.

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 predicted green or low level of risk, for each unit operation's impact on each CQA, but variability across a wide range of input material attribute variability in combination with operational conditions, may not have been demonstrated. In regard to robustness, there could be some residual risk. For the purpose of this example, the focus will be on the impact of compression on dissolution and content uniformity. A summary of the control strategy risk assessment for UDU and dissolution after Stage 2 of process validation is seen in Table E1.4 leading to proposed PV Stage 3, part 1 monitoring plan elements.

Table E1.4: Control Strategy Assessment Summary after Stage 2, Process Qualification

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 (Process Analytical Technology (PAT) tool) using stratified sampling
• Each tablet indirectly evaluated for weight (pressure monitoring)
 	
Control strategy established and confirmed
 	
Consideration for Stage 3, part 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 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, process qualification
	• Stratified sampling applied for testing of tablet cores
	
	Control strategy established and confirmed
	
	Consideration for Stage 3, part 1 (based on decision process Step 2 and control strategy)
	
	Continue stratified sampling at same level as above for a pre-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 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.

6.1.3 Step 3 – Assess Material Variability Impact

Table E1.5: Summary Output of Risk Evaluation after Formulation Development and IVIVC Studies Using FMEA

CQA (Severity)/ Failure Mode	App Fri Hard	Impurities	Water	CU	Disso	Micro
Magnesium Stearate Surface Area						
PaQLInol Particle Size						

CU Low level of risk remains for the API particle size

Disso A high level of residual risk remains for Magnesium Stearate specific surface area and PaQLInol particle size

There are two raw materials 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. Due to the particle size of the API; however, tablet strength and testing during development, this has been migrated to a low risk level. 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 and locations which will be tested 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 and material attributes and process parameters impacting dissolution is justified during the first part of CPV to confirm that the model and predictions are acceptable.

6.1.4 Step 4 – Assess Operational Practices Impact

The following operations practices could impact content uniformity 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 indicates that these factors are very low risk. For example, for UDU, there are many control strategy elements which are operator-independent - 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, drug substance particle size, magnesium stearate surface area, and tablet crushing force, and one process parameter, lubrication time. Operators can have impact to the equipment set-up and resulting process parameters and crushing force. Although the powder blend is designed to be free-flowing, variability is estimated during early phases of production with different of batches of excipients and use of operations personnel. Continued monitoring of dissolution and material attributes and process parameters impacting dissolution is justified during the first part of CPV to confirm that the model and predictions are acceptable.

Figure E1.2: Summary of PV Stage 3, Part 1 Evaluation

Risk \ Quality Attribute	Content Uniformity	Dissolution
Patient Risk Level		
Unit Operations Risk		
Material Risk		
Operations Practices Risk		
Residual Overall Risk		

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 period of time until control and capability established.

Figure E1.2 shows a summary of the science- and risk-based evaluation for the four step CPV risk assessment as applied to content uniformity and dissolution for PaQLInol.

6.1.5 PV Stage 3, Part 1, Monitoring Plan Summary and Criteria

Pre-defined criteria could be set, such as a defined confidence interval of process capability (e.g., Cpk >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 which elements of the control strategy could be considered for change. A summary of the monitoring plan for Step 3, continued process verification is given in Table E1.6, with dissolution testing at a heightened level. Note – the table focuses on product (output) CQA testing, but monitoring plan also could include heightened material CQAs testing, process parameter monitoring, etc. and frequent trending, of any and all results.

Table E1.6: Monitoring Summary for CPV – Example

CQA	*HMP	Rationale	Sampling	Acceptance Criteria	Target min Cpk	# of Batches	Rationale
Appearance	No	Routine sampling and inspection uses 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 Cpk	*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 requirem ents	NA	NA

Note 1: acceptance criteria follows ASTM E2709 [8] using 90% confidence interval.

*Abbreviation Key:

AQL – Limiting Quality Level

CS – Control Strategy

MA – Material Attribute

CAP – Capability Analysis

HMP – Heightened Monitoring Plan

6.1.6 Proposed Routine Monitoring Program

When the pre-defined capability measures are achieved as part of Stage 3, CPV, the levels of testing may be adjusted to statistically appropriate routine levels, which in the case of dissolution involves real time release testing. This level of testing is applied as part of the process performance and product quality monitoring system, which is likely to lead to application of statistical evaluation, e.g., capability. If RTRT is implemented, frequent monitoring of some of the direct process measurements, such as blender revolutions, should be considered.

Pre-defined criteria could be set, such as a defined confidence interval of process capability (e.g., Cpk >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. A summary of the monitoring plan for Step 3, continued process verification is given in Table 1.6, with dissolution testing at a heightened level. Note: the table focuses on product (output) CQA testing, but monitoring plan also could include heightened material CQAs testing, process parameter monitoring, etc., and frequent trending, of any and all results.

6.2 Example #2: Large Molecule Example Column Chromatography Step – Parameter Selection for CPV

The greatest challenge for demonstrating continuation of the validated state for a biological product (i.e., Continued Process Verification (CPV)) is often the limited amount of data that a manufacturer has at the commercial scale prior to the commencement of both Process Performance Qualification (PPQ), and subsequently, 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. Since FDA suggests "…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 ramping down 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 they would not be subject to Statistical Process Control methods because the data are below an analytical method's Limit of Quantitation and/or Limit of Detection, 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, the Table E2.1 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, In-Process Controls, In-Process Acceptance Criteria, and Additional Sampling). From that starting point,

parameters were assessed for whether or not they needed to be included in the formal Continued Process Verification 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 sub-set are subject to statistical assessment and/or trending." Just because something is deemed unnecessary to trend during CPV, does not mean that it is 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 should provide some guidance with regard to the types of discussion that should be happening prior to the initiation of the CPV program.

Table E2.1: Example Bridging Strategy between PPQ and CPV

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 > 10x 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 one can achieve the desired product quality in a consistent manner.

The four parameters that were 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 two representative pre-PPQ engineering batch as well as the three PPQ batches) were collected and assessed on an ongoing basis, but summarized for the purpose of this example, although it assumed that testing/monitoring would be ongoing until a pre-defined number of batches is achieved, at which time the CPV acceptance criteria may be re-assessed.

Eluate Endotoxin is a routine In-Process Acceptance Criterion (IPAC) and has an associated Alert Limit of ≥ 5 EU/mL and an Action Limit of ≥ 10 EU/mL. Eluate Bioburden is a routine In-Process Acceptance Criterion (IPAC) and has an associated Alert Limit of ≥ 10 CFU/10 mL and an Action Limit of ≥ 50 CFU/10 mL. As stated in Table E2.1, 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 (i.e., deviation investigation), such an investigation may not include an assessment for data trending upward toward the Alert or Action Limit. In such a 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 each of the data sets in Table E2.1, the conclusion could be drawn after each lot that there are no observable trends; therefore, process in a state of control with regard to AEX eluate endotoxin and bioburden.

Table E2.1: Eluate Data Sets

AEX Eluate Endotoxin Data

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

AEX Eluate Bioburden Data

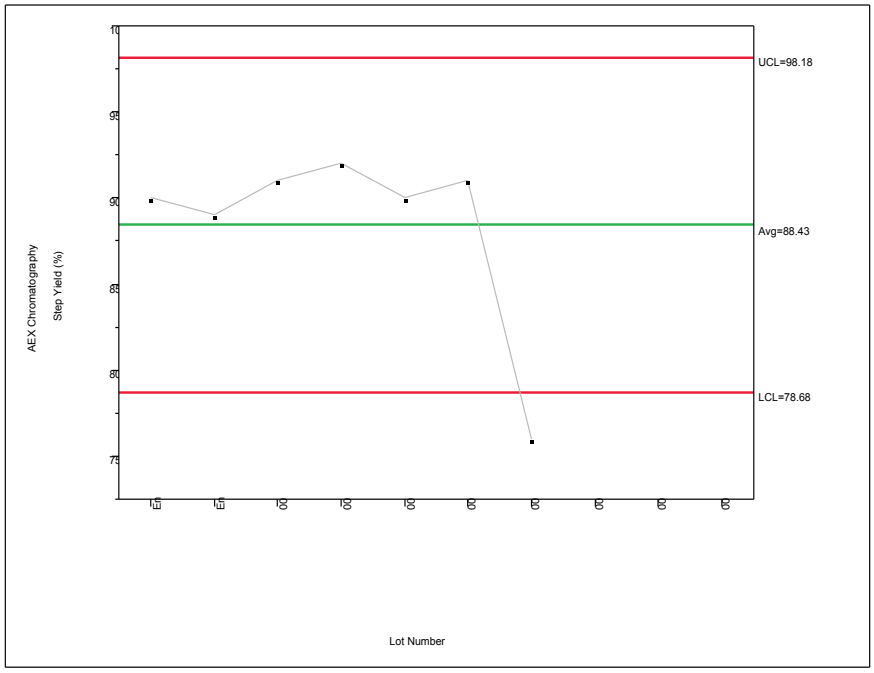
Lot Number	Result (CFU/10mL)	Lot Number	Result (CFU/10mL)
Engineering #1	4	004	0
Engineering #2	0	005	1
001 (PPQ #1)	1	006	2
002 (PPQ #2)	0	007	1
003 (PPQ #3)	0	008	0

While step yield does not impact the defined CQAs for this process, it is considered a key performance indicator and important for maintenance of the validated state. As CPV data were 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 in-process acceptance criterion was met (see Table E2.2 and Figure E2.1, Control Chart). This result was investigated to ensure that it wasn't caused by an unknown source of process variability.

Table E2.2: AEX Step Yield Data (Through Lot 005)

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 E2.1: Individual Measurement of AEX Chromatography Step Yield (%)

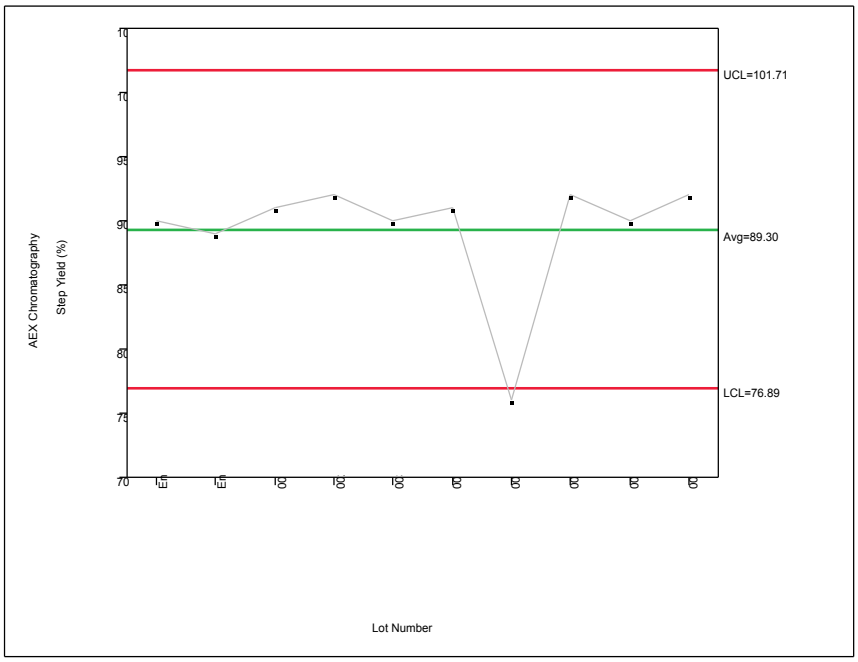


Lot 005 was investigated to assess the out-of-control limit result. While the step yield met the pre-defined in-process acceptance criterion of ≥ 75%, the result of 76% was below the calculated lower control limit. Upon investigation, it was determined that an operator had switched over to the waste 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 met the defined in-process acceptance criterion, 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 would artificially inflate the calculated control limits, which would no longer represent the true process variability. Additional data are presented in the following table and revised control chart.

Table E2.3: AEX Step Yield Data

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 E2.2: Individual Measurement of AEX Chromatography Step Yield (%)

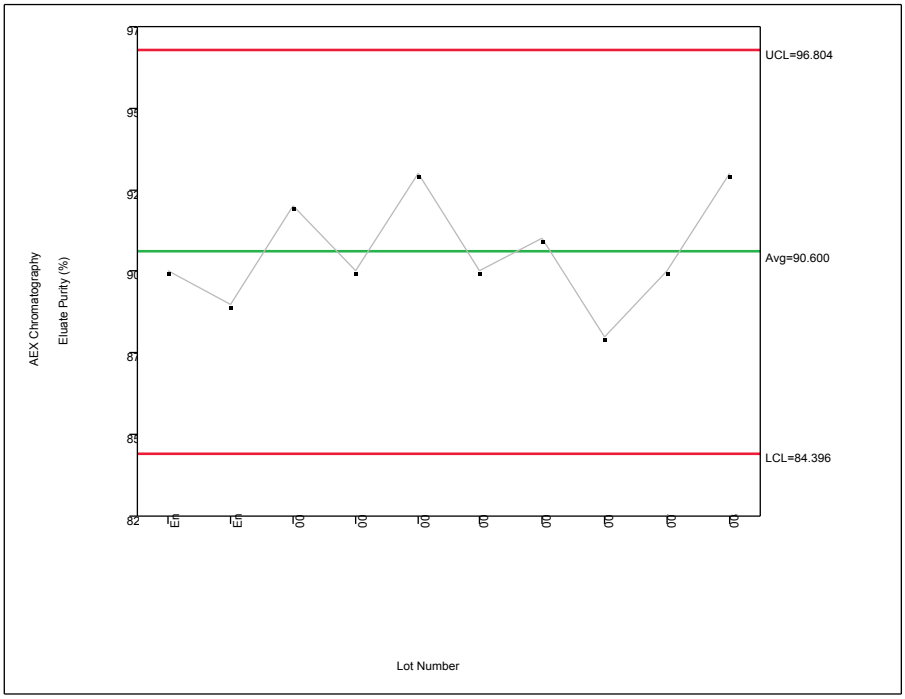


Eluate Purity by RP-HPLC has a defined In-Process Acceptance Criterion of ≥ 85%. Data were control charted on a per-batch basis. Data for 10 batches are provided in the Table E2.4 and Figure E2.3, Final Control Chart.

Table E2.4: AEX RP-HPLC Purity Data

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 E2.3: Individual Measurement of AEX Chromatography Eluate Purity (%)

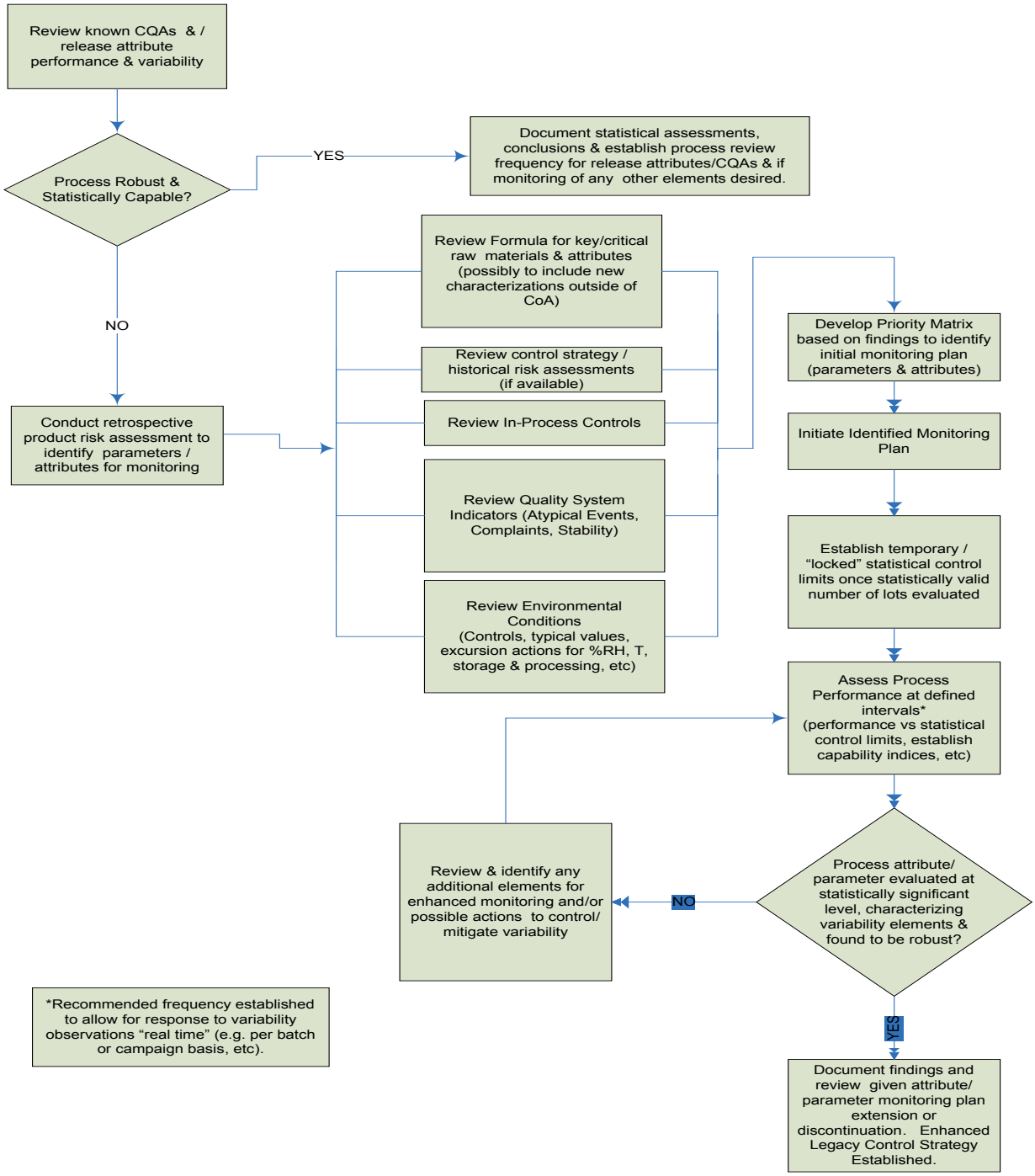


While SPC rules (e.g., Western Electric) cannot yet be applied, the plot is useful for demonstrating tightness of control within the calculated control limits. In addition, the lower control limit (84.396) confirms that the defined acceptance criterion for eluate purity was appropriately established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

6.3 Example #3: Developing a Stage 3 Monitoring Plan for Legacy Products

In this example, the process under review is a legacy product for which the process design phase did not include evaluations of the full range of excipient attributes and their possible contribution to variability nor was a detailed control strategy developed for the process. The historical performance review of this product (an oral dissolving tablet) has indicated potential excipient variability with impact to assay and stability. To assess the process capability and sources of variability and demonstrate that the process remains in its validated state; a Stage 3 monitoring plan was developed and applied to the commercial manufacturing of this product. The process outlined in Figure E3.1 was followed to derive the monitoring plan.

Figure E3.1: Outline Process for a Legacy Product



As part of the development of the initial Stage 3 monitoring plan for this legacy product, an expanded assessment was conducted of the product and process inputs to identify potential process parameters and/or process and material attributes for monitoring and/or enhanced testing. Conventional risk assessment tools were used to streamline the broader list of parameters/attributes to those identified as most likely to impact process variability and performance. Technical, quality, development, and

manufacturing personnel from the manufacturing site were engaged in the risk prioritization development and endorsement of the plan.

The agreed plan was applied to upcoming manufacturing campaigns. Once a statistically valid set of data which included typical process variability conditions (e.g., process shifts, raw material, and environmental variability) are compiled (over the next 20 to 30 batches), an assessment of the initial parameters/attributes and level and frequency of testing will be conducted to determine if parameters will be maintained, may be removed (not found to be impacted by variability, high capability index, characterization only element not found to link to output variability, etc.) or should be added to the plan (high variability seen and additional characterization elements identified, lower capability index, etc.).

As a first step in the assessment process, a review of data from release attributes and known CQAs over a given period was conducted to determine the current level of variability in the attributes and if inputs for the attributes may benefit from enhanced monitoring.

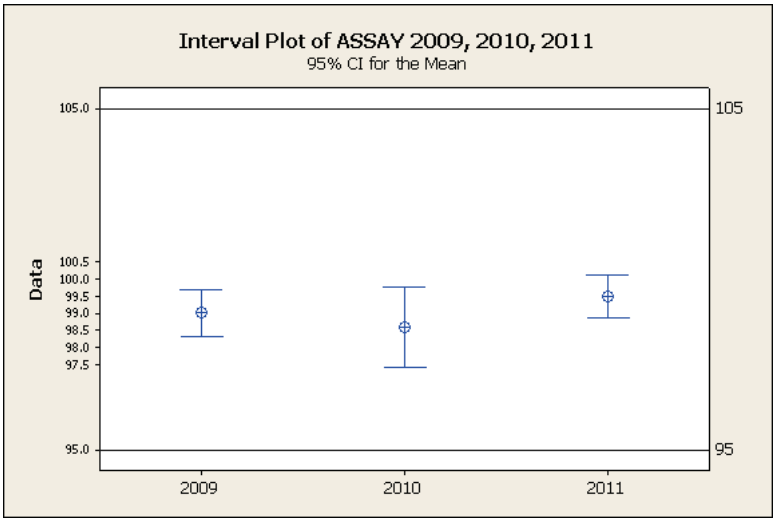
6.3.1 CQAs

For this example, a solid dose tablet, assay, disintegration, dissolution, impurities, and content uniformity were identified as product CQAs. A statistical assessment of CQA variability and control was conducted to assess current process variability.

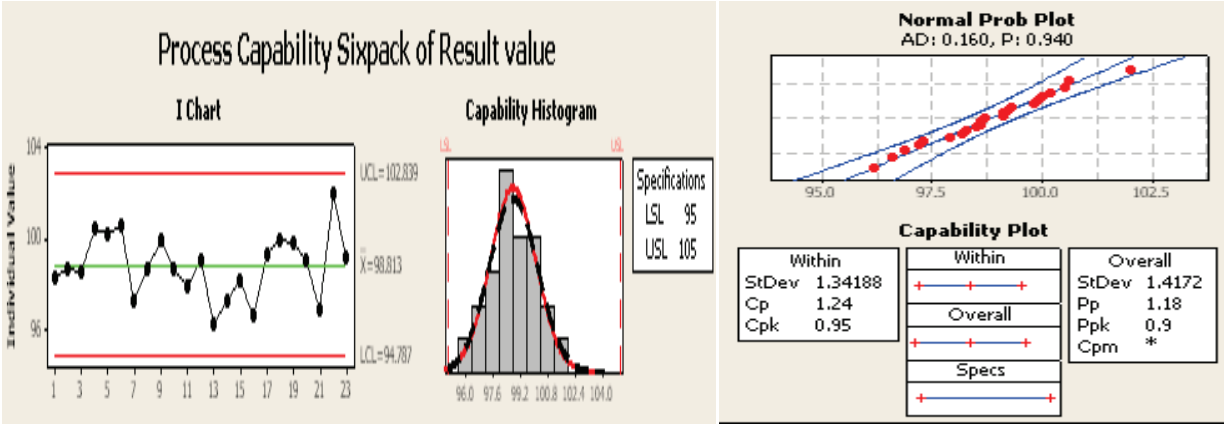
CQA Ppks are summarized in Figure E3.2.

Figure E3.2: Summary of CQA Ppks

Assay	**0.9**	**Disintegration**	**2.16**	**Impurities**	**5.09**
CU	**2.66**	**Dissolution**	**2.34**		



Assay Ppk 0.9



Thresholds for statistical assessment tools were identified (e.g., Ppk < "X" or exceeding statistically derived control limits) which may trigger enhanced monitoring of additional inputs (e.g., raw materials, storage conditions) which may impact the attribute/parameter. In this example, assay data has a lower Ppk and the process has a statistical control limit (+/-3 sigma) which lies slightly below the product specification. The lower Ppk index value indicates lower longer term capability based on an overall estimate of standard deviation (all variation estimates) and suggests a need to reduce variability and center the process. This analysis allowed us to justify parameters like tablet weight (and weight controls), excipient A attributes, and the API particle size and others, identified from the priority matrix, to be included in the monitoring plan to better understand their potential contributions to assay variability.

A priority matrix (cause and effect) was then developed, as this information was not currently available in a detailed format to select optimal parameters/attributes to enhance the general understanding of the process, impact of input parameters and focus on higher risk elements. Inputs (process variables, raw material attributes, etc.) were ranked for impact to potential process outputs (CQAs, release criteria, etc.). In this example, a score of 1=low, 3 = marginal, and 5=high impact was used. CQAs and release criteria were ranked for priority (in this example, 1= low, 3=marginal, and 5= high priority or patient impact). More detailed definitions for low, marginal, and high were provided as a basis for team use in matrix development. Criteria (scores) beyond which monitoring would be required for the parameter/attribute were established prior to the development of the priority matrix. The priority matrix included all attributes/parameters which may impact the product/process or contribute variability. A discussion of these elements is included in the priority matrix. A small section, for a raw material and blending operation, of this overall example priority matrix is provided in Figure E3.3.

Figure E3.3: Section of Overall Example Priority Matrix

Raw Material (Excipient A)

					Product quality driver								
				Parameter priority	Content uniformity (5)	Tablet potency (5)	Dissolution (5)	Disintegration (5)	Impurities (5)	Appearance (1)	Hardness (3)	Thickness (1)	Taste/Mouth Feel (1)
Unit Op	Attribute or Parameter	Type of Attribute or Parameter	Impact Assessment CQA	Value (1,3,5)	Parameter Priority * Patient Impact								
Raw Materials	pH	N/A											
	Water Content	N/A											
	Particle Size	thru #200 thru #400	disso/dis	5			25	25					
	Bulk Density	N/A	disso/dis	5			25	25					
	Loss on Drying	N/A											
	ROI	N/A											
	Heavy Metals	N/A											
	Peroxides	N/A	impurity	5					25				

					Product quality driver								
Unit Op		Attribute or Parameter	Attribute Impact Assessment	Parameter Priority	Content uniformity (5)	Tablet potency (5)	Dissolution (5)	Disintegration (5)	Impurities (5)	Appearance (1)	Hardness (3)	Thickness (1)	Taste/Mouth Feel (1)
Final Blend	Mixer	# of Revolutions	CU										
		Speed	CU										
		Particle Size Distribution/Bulk	CU	3	15								
		yield											
		Magnesium Stearate											
	Bin	Size											
		Fill Fraction											

Similar priority risk assessments were performed for all process steps and unit operations (with raw material inputs considered as a "unit operation.") Product quality drivers (e.g., CQAs, release parameters), impact to the patient (complaints, mouth feel such as grittiness due to oral disintegrating nature of tablet, appearance, etc.), and process performance parameters (yield, packaging impact) were scored in the priority matrix. In this particular example, the particle size, bulk density, and peroxide content of excipient A were selected to be monitored as these attributes correlated with product dissolution/disintegration and impurity levels at release and on stability, respectively.

As part of the formation, review and scoring of the priority matrix the following elements were assessed.

6.3.2 Raw Materials

An assessment of raw material attributes, identified from the process risk assessment to potentially impact process outputs (e.g., CQAs), variability was conducted to identify sources of variability and/or

enhanced process control opportunities. In this example, Excipient A particle size, bulk density, and peroxide levels were identified as a potential monitoring elements due to potential links to product attributes (dissolution, disintegration, and impurity levels). Additionally, a review of specifications for this excipient identified that "use" values for a test attribute (peroxide content) were consistently significantly below the current internal specification and the internal specification was currently above the CoA specification. Concerns were raised around incoming lots actually testing within specification but, well outside of typical experience with the product and potential impacts to assay/stability. Monitoring plan actions were developed to review supplier capability through monitoring and establish a revised internal specification for the excipient attribute.

6.3.3 In-Process Controls

In-process controls were reviewed with tablet hardness as one attribute identified for enhanced monitoring across campaign batches. This parameter also was linked to the review of quality system elements (customer complaints) due to complaints of tablet breakage. Hardness data will be reviewed retrospectively with intent to tighten the current control on the low end of the specification to reduce tablet breakage while maintaining dissolution/disintegration attributes to be met robustly.

6.3.4 Quality Systems Elements

Quality systems elements (stability, warehousing/storage/sampling, customer complaints, equipment preventative maintenance/calibration, deviations) also were reviewed with the in-process control for tablet hardness, as discussed earlier, identified as an element for Stage 3 monitoring and control strategy updates due to customer complaints for tablet breakage.

6.3.5 Process Performance Assessments

A summary of the initial monitoring plan for this process is included in the Table E3.1.

Items identified for enhanced monitoring will be evaluated via statistical control charts on a campaign basis. Decision trees will be used to identify actions to be followed where established control chart values are exceeded where statistically valid process capability limits have been established. At milestones throughout the monitoring process, reviews will be conducted to identify additional actions recommended and/or where monitoring elements may be removed from the plan based on the demonstration of robust process inputs and outputs.

Table E3.1: Summary of Initial Monitoring Plan

Unit Operation	Subpart	Key Material Attribute	Impact to CQA	New Test	Notes
Raw Materials	Excipient A	Particle Size	Assay, CU, Flow Disintegration Oral Performance	No	Grittiness in mouth., impact to CQA's . Typically trend toward lower end of specs.
		Crystallanity	Appearance, Disintegration	No	Capping of tablet and disintegration. Values trend on lower side of specs.
		True density	Appearance, Disintegration	No	Values trend on higher side of spec.
		Cao/Sio2 Ratio	Appearance	No	Values trend on higher side of spec.
	Excipient B	LOD	Disintegration	No	Assess lowering specs based on typical incoming level. Higher LOD may impact flow , blending, assay and CU.
		Particle size	Disintegration Dissolution	No	Need more data (N=3 current database).
		Bulk density	Disintegration and dissolution	Yes	
	Excipient C	LOD	Hardness , Flow, Assay, Cu	No	All current values are ≤ 0.1%. Higher values require alert.
	Excipient D	Peroxides	Impurity	No	Monitor & align internal spec w/ CoA.
		Particle size	Disintegration	No	For 400 mesh values trend on lower side of specs.
		Bulk Density	Disintegration	Yes	Disintegration , Need baseline information
	Excipient E	LOD	Disintegration	No	Values trend on higher side of spec.
Blending	Mixing	Blend homogeneity	Assay, CU & Oral Performance	Yes	Monitor by NIR
Granulation	Roller Compaction	Hydraulic Pressure	CU, Assay	No	Key parameter Impacts CU , Assay
		Roll speed	CU	No	Key Parameter Impact CU
		Screw speed	CU	No	Key Parameter Impacts CU
		Roll Gap Value	CU	No	Impact to CU/Assay/Hardness
		Fines post sieve	CU	No	Impact to flow- CU/Assay
		Yield	Loss of material can impact any CQA	No	Can impact other CQA's
		PSD and BD	Assay and CU	Yes	Hardness,CU, Assay Need baseline data.
		Induced die feeder speed	Hardness, Assay, Disintegration, Disolution	No	Variation may identify root cause for CU, assay and hardness
Blending	Mixing	Blend homogeneity	Assay, CU and mouth feel	Yes	Monitor by NIR
Tabletting		Hardness	Disintegration, Dissolution	No	Key in process parameter Need to identify lower limit
		Tablet weight	CU, Assay	No	Key in process parameter
		# of weight adjustments	CU, Assay	Yes	
		# Machine stops	CU, Assay	Yes	May point to material or equipment issue

7 References

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