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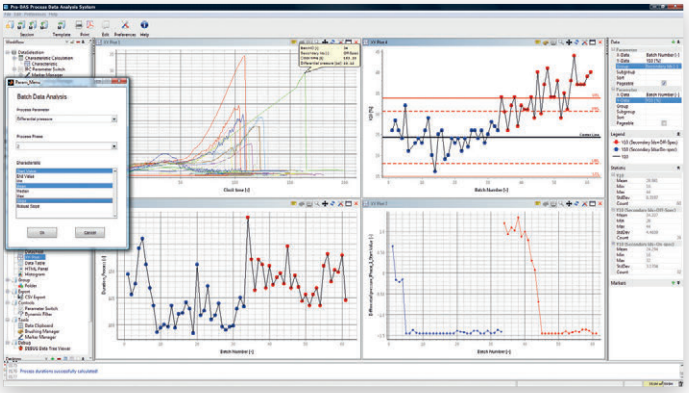
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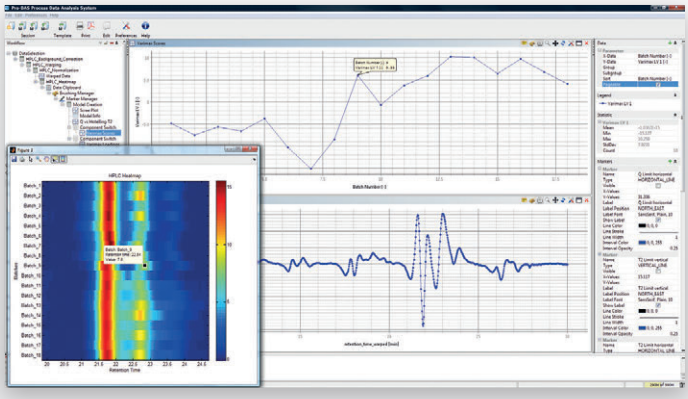


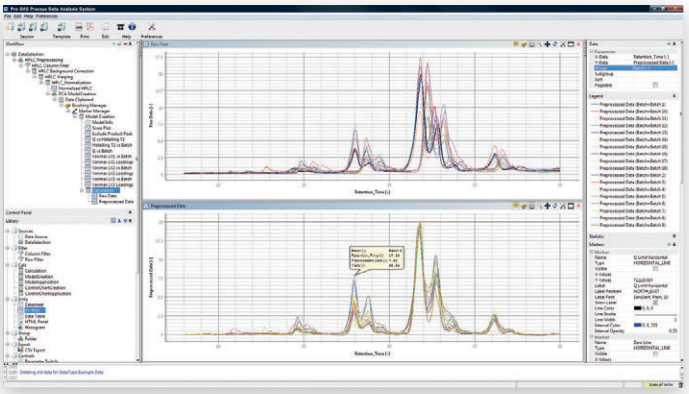
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from Concept to Continual Improvement

Part 4 – Process Performance and Product Quality Monitoring System

Disclaimer:
This Guide aims to provide "how to" guidance for establishing and implementing a Process Performance and Product Quality Monitoring System (PP&PQMS) in line with the expectations of the ICH Q10 guideline. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The ISPE Product Quality Lifecycle Implementation (PQLI) Good Practice Guide (GPG): Process Performance and Product Quality Monitoring System (PP&PQMS) is Part 4 of the ISPE Guide Series: PQLI from Concept to Continual Improvement, which is a product of the ISPE PQLI program.

The modern pharmaceutical quality system described in ICH Q10 is a holistic approach which helps to facilitate the consistent development and production of high quality pharmaceutical products. The ISPE PQLI GPG: Process Performance and Product Quality Monitoring System considers process performance and product quality monitoring systems established to support products and processes developed using the enhanced, Quality by Design approach. This Guide is intended to be compatible with the process validation guidance issued by the FDA and the draft guideline on process validation issued by the EMA.

This Guide is relevant to the development and manufacture of drug substance and drug product for both small and large molecules. It is also applicable to new and existing products.

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Winston R. Brown	Alcon Research, Ltd. – A Novartis Division	USA
Chunsheng Cai, PhD	Vertex Pharmaceuticals, Inc.	USA
Joseph Famulare (Co-Chair)	Genentech Inc.	USA
Jennifer Gehle-Novak	Fresenius Kabi USA, LLC	USA
Jaspreet Gill	Baxter Healthcare Corp	USA
Rob Hughes	Rob Hughes Associates	United Kingdom
Claudia Q. Lin, PhD	Bayer Healthcare	USA
Bryan Liptzin	Amgen Inc.	USA
Steven J. Martino	Johnson & Johnson	USA
George P. Millili, PhD (Co-Chair)	Merck & Co., Inc.	USA
Jason J. Orloff	PharmStat	USA
Christopher Potter, PhD	ISPE PQLI Technical Project Manager	United Kingdom
Ronald C. Stellon	AstraZeneca	USA
Dr. Thirunellai G. Venkateshwaran, PhD	Genentech Inc.	USA

FDA Reviewers

We would like to thank the following FDA representatives for providing comments on this Guide:

Brian J. Hasselbalch, CDER/FDA, USA

Steven J. Lynn, FDA, USA

Grace E. McNally, CDER/FDA, USA

Dr. Tahseen Mirza, FDA, USA

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ISPE Headquarters
600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office
73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office
Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

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1 Introduction

1.1 Objectives

The ICH Q10 guideline, Pharmaceutical Quality System [1], states that a process performance and product quality monitoring system (PP&PQMS) should be planned and executed to ensure that process performance and product quality are maintained in a state of control. The objective of this Guide is to provide "how to" guidance for establishing and implementing a PP&PQMS in line with the expectations of the ICH Q10 guideline. Examples of technical and scientific methodology and supporting management processes are provided.

Part 4 of the ISPE PQLI Guide Series, PP&PQMS, considers process performance and product quality monitoring systems established to support products and processes developed using the enhanced, Quality by Design (QbD) approach as discussed in ICH guidelines:

- ICH Q8(R2), Pharmaceutical Development [2]
- ICH Q9, Quality Risk Management [3]
- ICH Q11, Development and Manufacture of Drug Substances [4]

These systems are exemplified in other parts of the ISPE PQLI Guides Series including, Part 1, Product Realization using Quality by Design, Concepts, and Principles [5] and Part 2, Product Realization using Quality by Design (QbD), Illustrative Example [6].

This Guide is intended to be compatible with the process validation guidance issued by the FDA [7] and the draft guideline on process validation issued by the EMA [8].

This Guide should be read in conjunction with Part 3 of the ISPE PQLI Guide series, Change Management System [9]. These two Guides are PQS parts of the PQLI Guide series and support implementation of two of the Pharmaceutical Quality System (PQS) elements recognized in ICH Q10 [1] as enhancements of regional Good Manufacturing Practice (GMP) regulations.

1.2 Scope

This Guide (as is the case with ICH Q10 [1]) is relevant to the development and manufacture of drug substance and drug product for both small and large molecules. It is also applicable to new and existing products.

A PP&PQMS should apply to an entire organization or a site or division within an organization. The PP&PQMS should apply to all products within the assigned part of an organization. Each product should have its own control strategy and associated process performance and product quality monitoring program.

This Guide applies across all phases of the product lifecycle from development to product discontinuation. In the pharmaceutical development phase, data and knowledge emerge which support the development of the techniques and methodologies, including appropriate acceptance criteria which are monitored within the PP&PQMS. During the development phase, even in the later stages (e.g., Phase 3 clinical supply manufacture) application of the PP&PQMS is likely to be limited. However, in the technology transfer phase, there is potential to experiment with these techniques and methodologies. Full implementation will usually occur throughout the commercial manufacturing phase and will be gradually discontinued during the product discontinuation phase.[1]

[1] Stability testing may still need to be performed.

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The PP&PQMS techniques and methodologies suggested in this Guide are relevant to products developed using both enhanced, QbD approaches (as given in Appendix 1 of ICH Q8(R2) [2]) and to those products developed using the traditional approach.

The scope of these recommendations focuses on process performance and product quality data from manufacture of batches; therefore, this includes all product rejections, non-conformances, and deviations. Evaluation of external product quality data such as recalls, complaints, audits and regulatory inspections and findings as they impact the state of control is addressed briefly in Section 3.6 of this Guide. However, these are covered by other elements of the quality system, e.g., the Corrective Action and Preventative Action (CAPA) system and management review of process performance and product quality.

1.3 Benefits

An important benefit of developing and using the techniques and methodologies suggested in this Guide is that maximum opportunities should arise to gain the benefits listed in Annex 1 of ICH Q10 [1], which is reproduced below as Table 1.1.

Table 1.1: Potential Opportunities to Enhance Science- and Risk-Based Regulatory Approaches

Scenario	Potential Opportunity
Comply with GMPs	Compliance – status quo
Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10)	Opportunity to: • Increase use of risk-based approaches for regulatory inspections
Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9)	Opportunity to: • Facilitate science based pharmaceutical quality assessment • Enable innovative approaches to process validation • Establish real-time release mechanisms
Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9, and ICH Q10)	Opportunity to: • Increase use of risk-based approaches for regulatory inspections • Facilitate science-based pharmaceutical quality assessment • Optimize science- and risk- based post-approval change processes to maximize benefits from innovation and continual improvement • Enable innovative approaches to process validation • Establish real-time release mechanisms

Using the techniques and methodologies suggested in this Guide should lead to opportunities to gain many of the benefits listed and discussed in Part 1 of this Guide series [5], particularly benefits to:

- Improve manufacturing efficiency (e.g., process robustness)
- Support continual improvement
- Propose regulatory flexibility

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1.4 Key Concepts

The Process Performance and Product Quality Monitoring System (PP&PQMS) should emerge in the later stages of product realization (ICH Q10 [1]). Operation of the PP&PQMS should contribute to providing opportunities for continual improvement and illustrates the utility of pharmaceutical quality management over the product lifecycle. A number of important considerations have gone into this Guide:

- The principles can be applied whether using a minimal or enhanced, QbD approach to development.
- In using enhanced, QbD approaches, this Guide is designed to make the most of the potential opportunities described in ICH Q10 Annex 1 [1].
- This Guide is not intended to provide a regulatory pathway. The focus is on technical underpinnings. Regulators in the various authorities around the world indicate requirements.
- This Guide will through implementation pathways and examples focus on the potential opportunities for continual improvement activities by availing the knowledge obtained over the product lifecycle.
- This Guide also provides for the opportunity and the responsibility of the manufacturer to be proactive in monitoring and detecting trends, and taking the necessary steps to produce products consistently of the intended quality.
- The principles of Quality Risk Management (QRM) and knowledge management will be highlighted as they support this PQS element, but they are not the main focus.
- Explanations are given to allow bridging between use of the term “specification” using ICH terminology and “specification” as it is often used in other guidance documents and engineering literature. This document uses the ICH definition as discussed in Section 1.5.1 of this Guide.

The Process Performance and Product Quality Monitoring System section introduces the role of Quality Steward as an owner of product quality. Responsibilities of the role are discussed and examples given in Section 4 of this Guide.

1.5 Definitions

1.5.1 Specification

Throughout this part of the Guide series, the term “specification” is used and some further explanation is required regarding how this term is used in this document and specifically in relation to a PP&PQMS. A specification (ICH Q6A [10] and ICH Q6B [11]) is defined as:

> *A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. “Conformance to specifications” means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.*

This definition specifically refers to drug substance and drug product. In the context of this document and a PP&PQMS, a specification also could apply to materials which are included in a control strategy and potentially a PP&PQMS, e.g., excipients as discussed in ICH M4Q(R1), Common Technical Document for Excipients (Section 3.2.P.4.1) [12]. ICH M4Q(R1) references ICH Q6A [10] and Q6B [11]when discussing excipient specifications; , therefore, an adaptation of ICH definition for drug substance and drug product specification is applied to a relevant input material used in a control strategy, such as drug substance starting materials, excipients, in process materials,

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primary packaging materials. By analogy with ICH Q6A [10] and Q6B [11] definition, a specification for a material contributing to a control strategy is a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an attribute should conform as part of a control strategy.

Control of parameters in a control strategy is usually expressed as ranges of values.

In the multi-factorial situation a control strategy could include an algebraic formula or model linking values for an attribute to values of other parameters or attributes, which together ensure product quality. In such cases, acceptance criteria for attributes of materials or ranges of parameter values could be established in the control strategy in combination with use of the formula or model.

The definition of specification applied to drug substance and drug product still applies.

1.6 Guidance Structure

This Guide provides suggested techniques, methodologies, and management processes for the practical establishment, implementation, and operation of a PP&PQMS across the product lifecycle.

Section 2 discusses sources of variability in pharmaceutical processes and introduces measurement of variability and a short discussion on distribution of data. There is also a short discussion of sampling. This section is intended to assist readers who are not experts in statistics to understand sources of variability and measurement of variability, and sampling in pharmaceutical processes.

Section 3 Establishment and Application of a PP&PQMS expands on Section 3.2.1 of ICH Q10 [1]. Management processes are discussed throughout this section; however, organizations are developing a new role of Quality Steward and a final section is devoted to discussing this role and provides two examples.

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2 Variability and Sampling

This section aims to explain some sources of variability and measurement of variability in pharmaceutical processes.

2.1 Variability

Variability may be inherent to a pharmaceutical process or may result from extrinsic factors (e.g., personnel or environment). Variability may occur in attributes or parameters and can arise from several different sources. Understanding variability depends on being able to identify contributing factors and to measure the variability of intrinsic factors.

Variability should be studied during pharmaceutical development and further understanding should be gained during technology transfer. The level of understanding of variability is likely to depend on both the level of resource applied to the study and the development approach taken, e.g.:

- Where an enhanced, QbD approach has been used during pharmaceutical development, it is likely that major contributors (i.e., attributes and parameters) to process variability would be identified and studied.

- Where a minimal approach is used during pharmaceutical development, there is a greater likelihood that there are poorly understood variables that could contribute to overall process variability. These variables could be identified by a PP&PQMS, if the variability is likely to lead to a product Critical Quality Attribute (CQA) failing to meet acceptance criteria.

2.1.1 Variability of Analytical Measurement

Variability of analytical measurement is a recognized contributor to overall process variability. Measurement systems and methods for collecting data on parameters and attributes should be suitable for their intended use, and appropriately installed and verified as fit for purpose. These measurement systems should be included in routine maintenance and calibration programs, as appropriate. They may be:

- In-line

- On-line

- At-line

- Off-line

The accuracy and precision of the measurements should be considered during data analysis and setting of acceptance criteria, operational limits, and control limits.

For further information on factors that could contribute to the accuracy and precision an analytical procedure, see Appendix 1. (This appendix also provides information on some of the considerations for process analyzers, process controllers, and data acquisition systems.)

Where trend monitoring is used, it is important to ensure that the analytical procedures are consistent, validated and providing the same capacity where ever used. For further information on analytical procedures which may be used in a PP&PQMS, see Appendix 3.

Where effective process performance evaluation is part of a PP&PQMS, it is dependent on measurement variability and the measurement variability needs to be understood.

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2.1.2 *Overall Process Variability*

Risk assessment can be used to identify the impact of variability as part of an enhanced, QbD approach. Risk management exercises can be performed periodically throughout the product lifecycle, in order to manage continually identified risks.

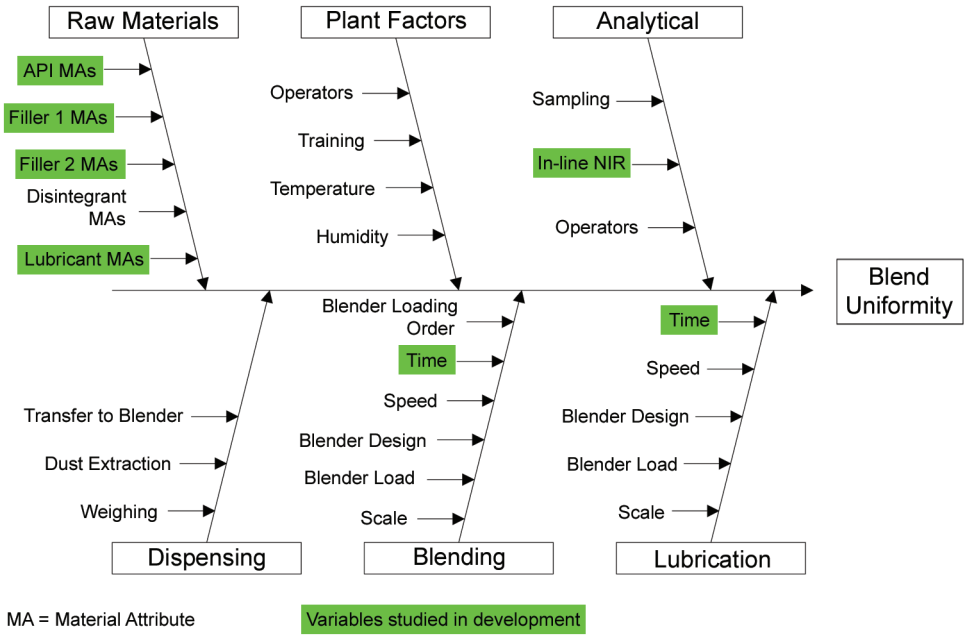
Visualization tools, such as an Ishikawa diagram (see Figure 2.1), may be used to identify potential risks (i.e., variability). Risk priority number charts from a Failure Mode and Effects Analysis (FMEA) and cause and effect matrices, which summarize the output from a risk assessment exercise, also may be used.

Figure 2.1 shows an example Ishikawa diagram for blending and lubrication unit operations for factors which can impact blend uniformity. Blend uniformity is an in-process quality attribute that contributes to the Uniformity of Dosage Units (UDUs) product CQA. The example Ishikawa diagram shows that there are residual lower risk factors which could contribute to overall process variability. A PP&PQMS could be used to confirm (using in-line near infrared (NIR)) that overall process variability remains in a state of control.

The risk management team should review the current level of product and process understanding including:

- Development studies
- Technology transfer activities
- Output from process validation programs

Figure 2.1: Example of an Ishikawa Diagram for Blending and Lubrication Unit Operations



Notes for Figure 2.1:

1. This example Ishikawa diagram is based on Figure 2.15 in Part 2 of this Guide series – Product Realization using Quality by Design: Illustrative Example [6]. (The names of the drug substance and excipients have been made generic.)
2. Factors studied during pharmaceutical development, which were originally considered the highest risk, have been identified by the green shading. Development studies reduced the risk of these factors to acceptable levels by setting appropriate acceptance criteria for inclusion in the control strategy.

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3. The analytical procedure chosen for the unit operation (i.e., in-line NIR) is included.
4. Each branch of the diagram lists the risks, i.e., factors for which the variability may impact a CQA.
5. Each branch lists variables related to a single theme, e.g. analytical, raw materials, etc.

The risk management process usually uses a team of Subject Matter Experts (SMEs) from a variety of relevant disciplines. Risk management exercises should be performed to establish Critical Process Parameters (CPPs) and CQAs forming the basis of process validation programs (e.g., before and after a study to support commercialization of a process) and ongoing evaluation of process performance during the commercial manufacturing phase of the lifecycle,[2] i.e., the PP&PQMS. For further information on process validation, see the FDA Process Validation guidance [7].

Where possible, individuals involved early in the product lifecycle should be involved in risk management exercises later in the product lifecycle, to give continuity and provide knowledge. Risk management exercises also may be used to train new personnel and pass on process knowledge.

For further information on the application of the risk management process to the development of a formulation and associated process, see Section 2.2 of Part 2 of this Guide series – Product Realization using Quality by Design: Illustrative Example [6].

The residual level of risk in complying with drug substance or drug product CQA acceptance criteria should be assessed. (This may be considered as the level of risk of the control strategy failing.)

For further information on understanding and controlling variability in manufacturing processes, see Section 6.3, Continual Improvement Methodology Examples section of Part 2 of this Guide series – Product Realization using Quality by Design: Illustrative Example [6].

2.1.3 Distribution of Data

For the purposes of this Guide, it is assumed that data values follow a normal distribution.[3] This distribution is based upon a measure of the mean value ($\bar{x}$) and the expected variation (standard deviation (s)) around the mean.

The distribution of data can apply to attributes or parameters for which a measured value is obtained. This type of data can be used to establish statistical process control limits for use in a PP&PQMS.

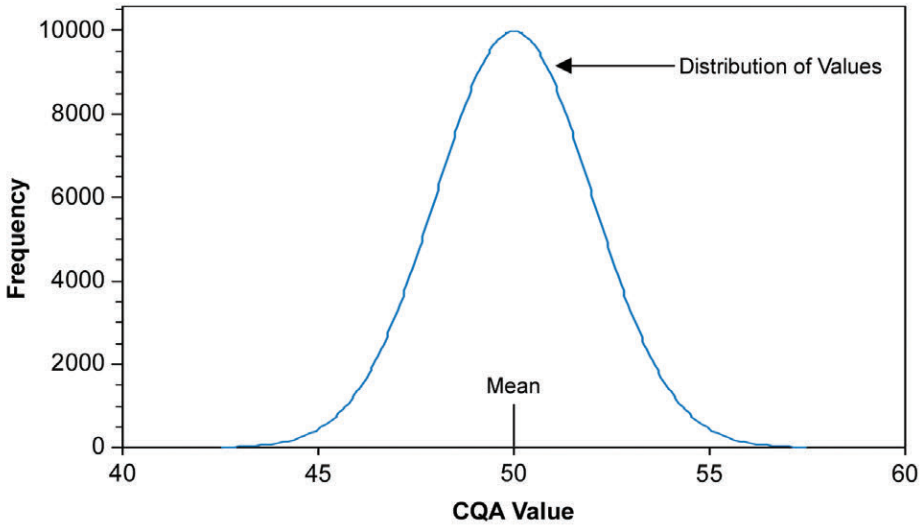
Note: for a non-normal data distribution expert opinion should be obtained.

Figure 2.2 provides an example of normally distributed data values for a single batch containing 500,000 items. The value of a hypothetical CQA is measured for every item within the batch, providing a 100% inspection. The bell curve shown represents the normal distribution of all 500,000 values obtained for the hypothetical CQA.

[2] Stage 2, Part 2, process performance qualification (and FDA Stage 3, continued process verification) of the FDA Process Validation guidance [7]).
[3] For simplicity, the discussion in this Guide is limited to normally distributed processes with the caution that this assumption must hold true for a particular data set.

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Figure 2.2: Distribution of Values of a Hypothetical Critical Quality Attribute



Notes for Figure 2.2:
Mean ($\bar{x}$) = 50 Standard Deviation (s) = 2 Number of values = 500,000

As sample sizes for each batch need to be manageable, only a representative sample is usually taken rather than providing a 100% inspection. This means that a smaller number of values from the batch are sampled and some information is "lost" as a trade-off in order to obtain a manageable sample size.

Where a smaller number of values from a batch are sampled, the mean and standard deviation for that batch can be estimated. These values for mean and standard deviation will probably be different to the values obtained if all values from the batch are measured. However, a range of values for mean and standard deviation for the several samples can be estimated with some confidence that the true mean and standard deviation values will not be statistically different. Larger sample sizes will give a more precise picture of the distribution of values.

A well-controlled process can generate multiple batches and a number of samples from each batch can be tested for a particular CQA; the results for these values for the CQA within each batch and for different batches can be plotted over time. These plots allow the trend in performance of the process to be observed. Figure 2.3 shows distribution curves for different batches over a period of time.

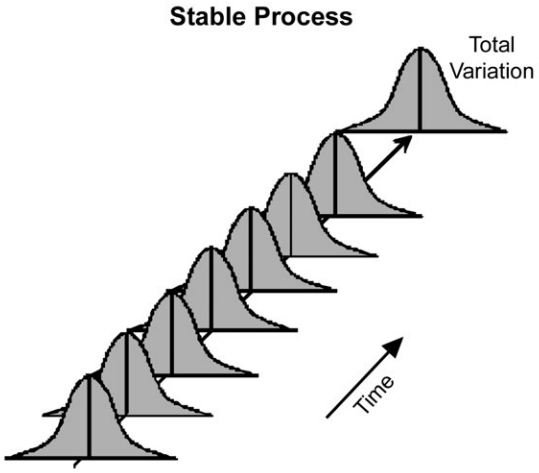
Common Cause Variation

For a stable process, individual samples can be combined to provide a picture of the total variation in the process. When the variation between batches is small, the total variation is similar to the variation within batches. In this case, the variability is often referred to as "common cause variation."

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Figure 2.3: Distribution Curves for Different Lots for a Stable Process



Graph taken from: "Quality Management Systems – Process Validation Guidance," The Global Harmonization Task Force, SG3/ N99-10:2004 (Edition 2) [13]

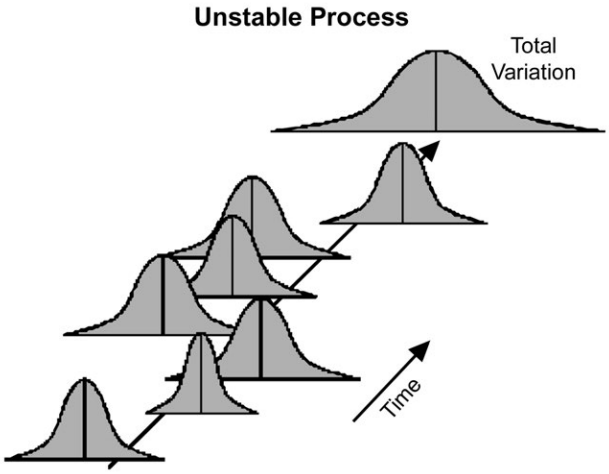
Special Cause Variation

Figure 2.4 shows an unstable process, where the effect of between batch variability on the total variation is much more pronounced. For an unstable process, the variability within one batch can be different to the variability in another batch, i.e.:

- The standard deviation for one batch can be different to the standard deviation for another batch.
- There are systematic differences in mean values between individual batches. The differences in mean values may be statistically significantly.

The total variation (represented by the histogram at the top of the Figure 2.4) in the unstable process can only be seen retrospectively using all data. This type of variation may be referred to as "special cause variation." Common statistical tools such as the "t-test" and "F-test" can be used to help evaluate the type and degree of a special cause variation.

Figure 2.4: Distribution Curves for Different Lots for an Unstable Process



Graph taken from: "Quality Management Systems – Process Validation Guidance," The Global Harmonization Task Force, SG3/ N99-10:2004 (Edition 2) [13]

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2.2 Sampling

A sample should be representative of a batch. Considerations when establishing sampling plans include:

- Clear definition of the objective of the sampling plan
- Definition of the sampling plan relevant to requirement, examples of which may include:
  - Random
  - Stratified
  - Composite
  - Systematic, e.g., beginning, middle and end of a unit operation
  - Targeted (e.g., worst case)
- Taking account of sampling and measurement error
- Determination of the relationship between sample size, statistical power, and statistical precision
- The type of change to the process and the size of change desired to be detected

Sampling plans are usually proposed during the technology transfer part of the lifecycle. Sampling plans are usually established to support a process validation program as part of the introduction of commercial manufacturing, e.g., Stage 2, process performance qualification of FDA Process Validation guidance [7]. A sampling plan may be modified to support Stage 3, continued process verification.

A sampling plan is an output from a risk management exercise for establishing a PP&PQMS. The sampling plan should be reviewed to ensure that it is representative of the batch.

For further information on sampling, see the US Government, Department of Defense standard, MIL-STD-1916 [14].

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3 Establishment and Application of a Process Performance and Product Quality Monitoring System

3.1 Introduction

This section discusses considerations for establishing and applying a PP&PQMS. Topics are listed in the same order as in ICH Q10, section 3.2.1 sub sections (a) to (f) [1].

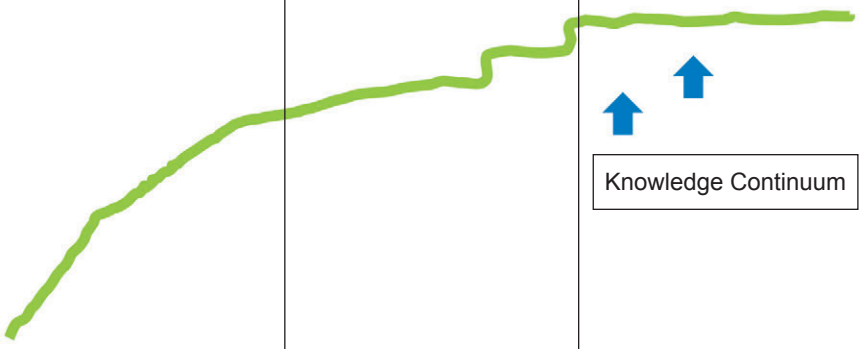
Table 3.1 provides a summary of considerations for establishing and applying a PP&PQMS.

Table 3.1: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

	Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
ICH Q10, Table I	Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing, should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.
Key Objectives of a PP&PQMS	Understand CQAs, parameters and attributes to enable a control strategy to be proposed.	Modify and finalize control strategy. Select CQAs, parameters and attributes to evaluate during process performance qualification. Select CQAs, parameters and attributes for initial process performance and product quality monitoring.	Execute facility/ equipment qualification and process performance qualification. Confirm control strategy as part of process validation program. Evaluate data from initial process performance and product quality monitoring (FDA Process Validation, Stage 3, and continued process verification). Execute in a state of control. Opportunities for continual improvement, including modification of control strategy.	Continue to fulfill process performance and product quality monitoring required by regional regulations.

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Table 3.1: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle (continued)

	Pharmaceutical Development	**Technology Transfer**	**Commercial Manufacturing**	**Product Discontinuation**
Product and Process Knowledge				
Techniques and methodologies for PP&PQMS	Develop Control Strategy: • Measurement Strategy Propose CQAs and CPPs and acceptance criteria. Start to understand variability by experimentation: • Multi-factorial experiments (DoEs) • Trial and error QbD Approach: • Risk management PAT Scale down Process modeling	Establish Control Strategy: • Further understanding of variability • Confirm CQAs and acceptance criteria • Confirm CPPs and ranges • Confirm other material attributes and acceptance criteria Process Model confirmation: • E.g., Monte Carlo simulation Quality risk management	Installation and Operational qualification: • Facilities • Utilities • Equipment • Analytical tools Ongoing evaluation of process performance and identification of opportunities for continual improvement: • Processvariability reduction • Enhancing control strategy based on current knowledge of product and process Multivariate data analysis Process Capability Process Control: • Statistical Process Control	

Notes:
- The top row (ICH Q10, Table I) is reproduced from ICH Q10 [1] and gives example applications of a PP&PQMS in the pharmaceutical lifecycle.
- The second row (Major Activities for a PP&PQMS) summarizes major activities in the relevant part of the lifecycle.

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Table 3.1: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle (continued)

Notes: (continued)
- The third row (Product and Process Knowledge) shows how product and process knowledge may change over the lifecycle. "Step" increases in knowledge could be associated with implementation of continual improvement, the opportunity for which may arise from application of the PP&PQMS.
- The fourth row (Techniques and Methodologies for PP&PQMS) illustrates some of the technologies and methodologies which could be applied during development and application of a PP&PQMS.

Abbreviations:

CQA	Critical Quality Attribute
DoE	Design of Experiments
PAT	Process Analytical Technology

3.2 Establishment and Implementation of a Control Strategy as a Basis for a PP&PQMS

A control strategy serves as the basis for establishing PP&PQMS requirements for a product.

It is helpful to understand the different tools and activity stages that can be utilized throughout the process of implementing a control strategy that will be the foundation of the PP&PQMS for a given product.

A control strategy should be developed during the pharmaceutical development stage, modified and set during the technology transfer phase, and confirmed as part of the process validation program in the early phase of commercial manufacturing, e.g., as part of FDA Stage 2 – process qualification. The on-going effectiveness of the control strategy should be evaluated and continually improved during the commercial manufacturing phase of the lifecycle (see Stage 3, continued process verification of the FDA process validation guidance [7]).

A multi-disciplinary risk management exercise should be performed for each product. This exercise is part of assessing which aspects of the control strategy should be included in the scope of the PP&PQMS.

Establishing and implementing a control strategy is considered an important foundation for the planning and execution of a PP&PQMS. For further information, see Appendix 2.

When real time release testing is included as part of a control strategy, assurance of conformance of a batch with CQA acceptance criteria should be equivalent or better than when finished product testing is applied.

Sampling plans should be re-considered following the early phases of the process validation program as discussed, see Section 2.2 of this Guide.

For further information on feed forward and feedback control, see Juran's Quality Handbook [15] and Process Dynamics, Modeling, and Control [16].

3.3 Provide the Tools for Measurement and Analysis of Parameters and Attributes

Factors potentially contributing to overall process variability are discussed in Section 2.1 of this Guide. Key outputs from the team establishing the PP&PQMS requirements for a product based on an already existing control strategy are:

- Selection of attributes and parameters to be included:

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  - The highest risk drug product CQAs (as determined from the risk analysis of all work performed to that point) will be included. In a real time release testing scheme, where the drug product CQA may not be measured directly on end product, appropriate attributes, parameters, and model predictions which provide assurance that the drug product CQA meets acceptance criteria should be included in the PP&PQMS.

- Confirmation that analytical procedures are in a state of control
- Statistical tools to be used, e.g., control charts, histograms
- Draft of rules for monitoring and trending

Only after sufficient data points (e.g., batches from a stable process) have been obtained is it possible to set meaningful statistical process control limits (typically a minimum of 25 data points or batches). These limits should be revised periodically as more data become available, which should characterize better the variation of the current, typical operation. “Temporary” process control limits, based on historical data, prior experience, and process understanding can be used until a sufficient amount of data is available. For products with relatively low frequency of manufacture (e.g., four or less batches per year), it may not be possible to set statistically meaningful process control limits; therefore, it may be necessary to retain process control limits using empirical methods.

When sufficient data have been generated, the implementation team and management should consider:

- Calculation of baseline performance to provide statistical process control limits and process capability measurements
- Establishment of rules for monitoring and trending
- Defining Out of Trend (OOT) limits and establishment of a process for managing OOT results
- Formalizing investigations and communication required for OOT investigations
- The process for updating baseline calculations based on amount of data generated, process change implementation, etc.

Data should be collected within the Pharmaceutical Quality System (PQS) for trending and monitoring. Appropriate management review of the program and outputs should be performed to ensure that any process performance or product quality issues are dealt with in a timely manner. The purpose of trending is to identify both negative and positive trends.

- Identifying a negative trend before it affects product quality can guard against manufacturing of unacceptable material. Investigations of negative trends and Corrective Actions and Preventative Actions (CAPAs) can facilitate process improvement with the measurable goal of reducing variability.
- Identification of positive trends where variability has been reduced provides a second opportunity to capture and reproduce an improvement, as well as demonstrate the effectiveness of CAPAs or continual process improvements.

The immense volume of data available in modern manufacturing requires strategic planning by people with knowledge of the requirements of pharmaceutical data integrity and storage and the use of information technology where available and appropriate.

Therefore, careful consideration of the strategy and implementation of relevant and practical statistical tools for the monitoring program is of fundamental importance.

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Hence as discussed above, elements to be considered in the implementation of trending programs **before implementation** include:

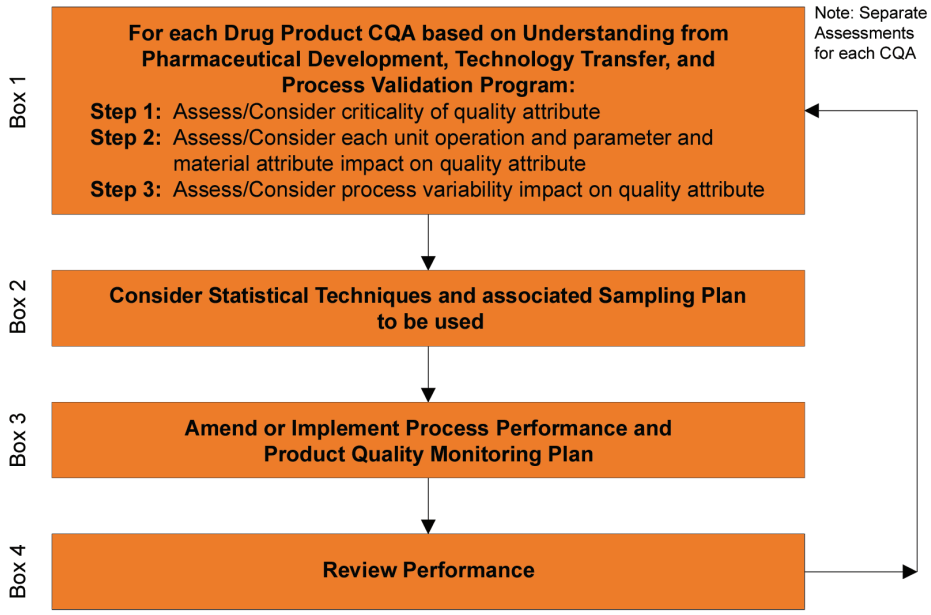
- What is to be trended?
- What are the triggers for action?
- What is the resolution of an actionable event?

The danger is that when misapplied these tools have as much potential to contribute to the confusion as they do to solve it. The approach in ICH guidelines ICH Q8(R2) [2], ICH Q9 [3], ICH Q10 [1], and ICH Q11 [4] begins with assessment of risk to the patient and prioritization of work. ICH Q10 (section 3.2.4) [1] indicates that trending programs should be evaluated by management and appropriate actions should be identified, such as improvements to the process made throughout the product lifecycle.

When implementing a PP&PQMS across the lifecycle it should be recognized that data generated by experimental design are fundamentally different from data collected by the routine monitoring of operations through in-process checks and acceptance sampling. Data from routine monitoring of operations are typically generated by relatively stable processes where variation in the inputs is minimized by the control strategy and varied by chance. Experimentation, on the other hand, deliberately changes inputs to measure the effect on the outputs.

A simple flow chart for implementing a PP&PQMS is given in Figure 3.1.

Figure 3.1: Implementation of a PP&PQMS



For Box 1, much of the information to assess/consider CQAs will have been conducted and finalized as part of pharmaceutical development, technology transfer, and marketing authorization approval. The team implementing the process performance and product quality monitoring plan should, in effect, perform a risk management exercise to determine residual risk (e.g., sources of variability not studied prospectively). The findings from this risk management exercise should be combined with consideration of appropriate statistical tools to be applied. (Appropriate statistical tools may already be in place as part of Stage 3, continued process verification of the FDA process validation guidelines [7]).

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Process performance and product quality data should be evaluated in a timely and effective way based on manufacturing frequency and level of risk to facilitate the communication and escalation process to raise appropriate quality issues to senior levels of management for review. This evaluation may be combined with an annual product review (see Section 3.6 of this Guide). However, a more frequent periodic review may be appropriate to ensure a state of control and detection of near term adverse trends. It also may provide an evaluation of other quality indicator data, e.g., Out of Specification (OOS), complaints, and increased deviations (see Section 3.6.2 of this Guide).

A variety of statistical tools can be employed, e.g.:

- Simple descriptive statistics
- Statistical process control
- Process capability measurements

Note: it is recommended that practitioners consult the literature and arrange for appropriate statistical expertise to be on or available to the team implementing a PP&PQMS.

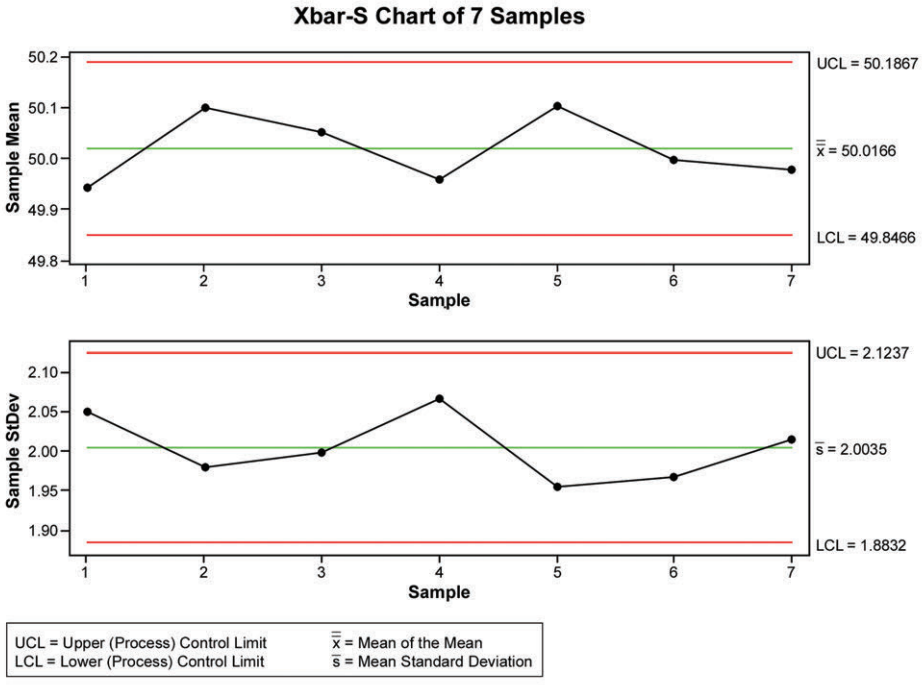
3.3.1 Simple Descriptive Statistics

Data could be presented in several ways, e.g.:

- Time series plots
- Histograms
- Box plots

Figures 3.2, 3.3, and 3.4 are examples. Figure 3.2 provides an example time series plot which includes statistical process control limits.

Figure 3.2: Summary Statistical Values from Samples from Different Lots from a Stable Process



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