IPA

Innovation, Quality and Global Reach

Process Validation Guideline

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1. Preface

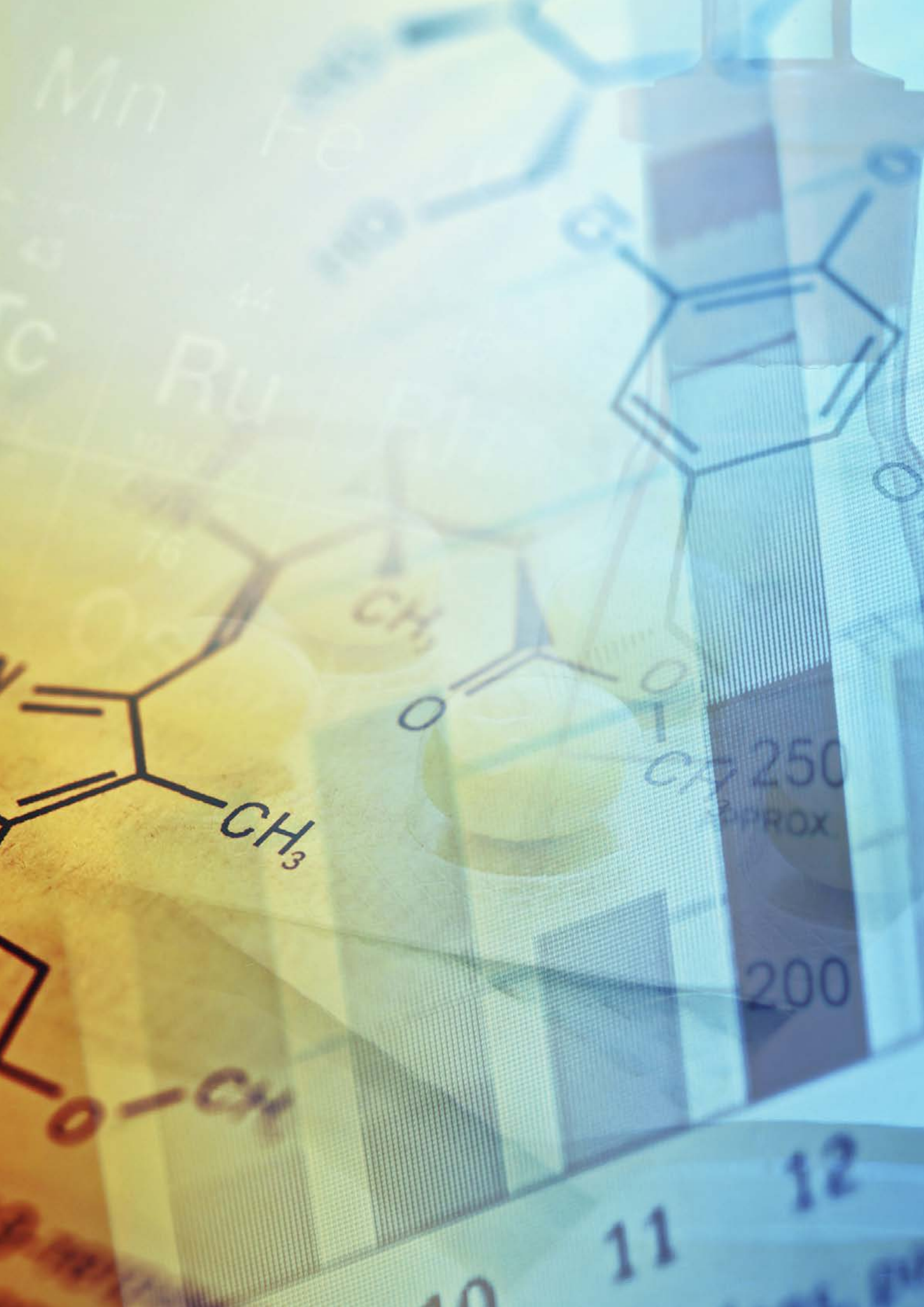
The IPA launched its Quality Forum (QF) in April 2015 to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made a commitment to a multi-year journey to address key issues facing the industry and develop best practices. McKinsey & Company joined this journey as a knowledge partner.

The QF focused on three priority areas in 2015–16, namely, Data Reliability, Best Practices & Metrics, and Culture & Capability. It took upon itself the challenge of establishing robust and seamless data management and documentation systems and processes and released a comprehensive set of *Data Reliability Guidelines* in February 2017. It then took up the task of developing a comprehensive set of *Process Validation Guidelines*. The six participating companies in the QF nominated one senior manager each to study the best practice and frame the Guidelines. They are: Shirish Belapure and Arunava Ghosh (Cadila Healthcare), Gopi Reddy and Rachel Princess (Cipla), Sairam Philkana (Dr Reddy's), Alok Ghosh and Indrajit Bose (Lupin), Jila Breeze and Jigar Marfatia (Sun), and Rakesh Sheth and Sweety Shah (Torrent). They were assisted in this task by Vivek Arora and Jyoti Saini of McKinsey. The IPA wishes to acknowledge their concerted effort over the last 20 months. They shared current practices, benchmarked these with the existing regulatory guidances from the USFDA and other regulatory bodies such as UKMHRA, WHO, etc., developed a robust draft document and got it vetted by a leading subject matter expert and regulatory agencies. The IPA acknowledges their hard work and commitment to quality.

The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's 3rd India Pharmaceutical Forum 2018 in Mumbai, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

Mumbai
16 January 2018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2. Introduction

2.1 Purpose and scope

This Guidance provides useful support for the implementation of a lifecycle approach to pharmaceutical process validation (PV). It contains information that enables manufacturers to implement globally-compliant PV programs consistent with the principles of recent lifecycle-based PV guidance documents and current expectations for Pharmaceutical Quality Systems[1-4].

In pharmaceutical manufacturing, "process validation" is the collection and evaluation of data – from the process design stage through commercial production – that establishes scientific evidence that a process is capable of consistently delivering a quality product[3]. ***It ensures that quality, safety and efficacy by design are built into the product.***

The PV lifecycle concept links product and process development, the qualification of the commercial manufacturing processes, and maintenance of the commercial production process in a coordinated effort[3].

This general Guidance is applicable for the Process Validation activities carried out for new and existing Drug Substance (DS) and Drug Product (DP). This document can be applied as a risk assessment (gap analysis) in those cases – for example, third party manufacturers and packagers who may have policies not aligned with this Guidance – in order to determine mitigation strategies.

2.2 Background

The lifecycle philosophy is fundamental in the ICH guidance documents for Pharmaceutical Development (ICH Q8 (R2), Quality Risk Management (ICH Q9)[7], Pharmaceutical Quality Systems (ICHQ10), and Development and Manufacture of Drug Substances (ICH Q11).

As per the lifecycle philosophy, process validation is not considered as a one-time activity, but rather an activity that spans the product lifecycle, linking process development, validation of the commercial manufacturing process, and its maintenance during routine commercial production.

Key considerations in product and process design include the control strategy and use of modern quality risk management procedures. A successful validation program is one that is initiated early in the product lifecycle and is not completed until the process or product reaches the end of that lifecycle.

This Guidance follows the principles and general recommendations presented in current regulatory process validation guidance documents. In the enhanced approach, manufacturing process performance is continuously monitored and evaluated. It is a scientific and risk-based real-time approach to verify and demonstrate that a process operates within specified parameters and consistently produces material that meets quality and process performance requirements.

The three-stage process validation lifecycle classification (Stage 1 – Process Design, Stage 2 – Process Qualification, and Stage 3 – Continued Process Verification) is used in this Guidance. Application of these stages is discussed in detail in Sections 3–5. These stages are described in Annexure 1 as the Process Validation Lifecycle Flow.

3. Glossary

Terminologies used in a validation program should be clearly defined, documented, and well-understood. Terminology definitions that are widely recognized by the industry should be considered when establishing internal definitions. Hence, the terminologies that are used in this document are defined below.

Active Pharmaceutical Ingredient (API; equivalent to drug substance for large molecules)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that is used in the production of the drug is called an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body[9].

Active Pharmaceutical Ingredient (API) Starting Material

An API Starting Material is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structures[9].

Attribute

An attribute is a physical, chemical, or microbiological property or characteristic of an input or output material[11].

There are different types of attributes, as defined below.

- **Critical Quality Attribute (CQA)**
  A CQA is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality[6].

- **Quality Attribute**
  A Quality Attribute is a molecular or product characteristic that is selected for its ability to indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes[10].

Concurrent approach to PPQ

This is an approach wherein the Process Performance Qualification batches, manufactured using a qualification protocol, are released for distribution based on the fact that the batches meet the lot release criteria established in the Process Performance Qualification protocol, but before complete execution of the Process Performance Qualification study. This approach for PPQ shall be used only under exceptional circumstances.

Control Strategy

A planned set of criteria, derived from current product and process understanding that assures process performance and product quality is known as the Control Strategy. Such controls may include

parameters and attributes related to DS and DP materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. It is recommended to have control strategy as a product/process specific document or series of documents.

Continued Process Verification (CPV)

The CPV is the third stage of Process Validation involving a scientific and risk-based approach, wherein the manufacturing process performance is continuously monitored and evaluated, and documented evidence is established to prove that the process operates within the specified parameters and consistently produces material which meets all its CQAs and control strategy requirements.

Commercial Batch

The manufacturing process resulting in the commercial product (i.e., drug that is marketed, distributed, and sold or intended to be sold) is known as the Commercial Batch. For the purposes of this Guidance, the term commercial manufacturing process does not include clinical trial or treatment IND material.

Critical Process Parameter (CPP)

A CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Material Attribute (CMA)

A CMA is a physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.

Design Space

The design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered a change. Movement out of the design space is considered to be a change, and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval[6].

Drug Product (DP)

The drug product is the dosage form in the final immediate packaging intended for marketing[9].

Drug Substance (DS; equivalent to active pharmaceutical ingredient for small molecules)

The drug substance is the material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product and process related impurities. It may also contain excipients including other components such as buffers[13].

Formal Experimental Design (synonym: design of experiments)

A Formal Experimental Design is a structured, organized method for determining the relationship between factors affecting a process and the output of that process[6].

Good Engineering Practice (GEP)

GEP is a combination of such established engineering methods and standards that are applied throughout the lifecycle to deliver appropriate and cost-effective solutions[14].

Intermediate (or in-process) Material

This is a material produced during the steps of the processing of an API that undergo further molecular change or purification before it becomes an API. Intermediates may or may not be isolated[9].

Lifecycle

Lifecycle includes all phases in the life of a product, from the initial development through marketing until the product's discontinuation[6].

Normal Operating Range (NOR)

The NOR is a defined range, within (or equal to) the Proven Acceptable Range, specified in the manufacturing instructions as the target and range at which a process parameter is controlled, while producing unit operation material or final product meeting release criteria and CQAs[15].

Parameters

- **Key Process Parameter (KPP; synonym: key operational parameter)**
  This is an input process parameter that should be carefully controlled within a narrow range and is essential for process performance. A key process parameter does not affect product quality attributes. If the acceptable range is exceeded, it may affect the process (e.g., yield, duration) but not product quality[8].

- **Non-Key Process Parameter (Non-KPP; synonym: non-key operational parameter)**
  This is an input parameter that has been demonstrated to be easily controlled or has a wide acceptable limit. Non-key operational parameters may have an impact on quality or process performance if acceptable limits are exceeded[8].

- **Process Parameter (synonym: operational parameter)**
  This is an input variable or condition of the manufacturing process that can be directly controlled in the process. Typically, these parameters are physical or chemical (e.g., temperature, process time, column flow rate, column wash volume, reagent concentration, or buffer pH)[8].

Platform Manufacturing

This means the development of a production strategy for a new drug starting from manufacturing processes similar to those used to manufacture other drugs of the same type (the production for which there already exists considerable experience)[4].

Process Analytical Technology (PAT)

A PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality[6].

Process Performance Qualification (PPQ)

This is the second element of Process Qualification. It includes a combination of the actual facility, utilities, equipment, and trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected. Batches prepared are also called 'Conformance batches' or 'PPQ batches'[3].

Process Qualification

This qualification confirms that the manufacturing process, as designed, is capable of reproducible commercial manufacturing[3].

It consists of 2 important elements:

a) Design and Qualification of Facility/Equipment/Utilities

b) Process Performance Qualification

Process Robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality is known as process robustness[6].

Process Validation

- **US FDA**

  Such validation is the collection and evaluation of data from the process design stage to commercial production, which establishes with scientific evidence that a process is capable of consistently delivering quality products[3].

- **EMA**

  Such validation comprises documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes[2].

Prospective approach to PPQ

This indicates an approach wherein the Process Performance Qualification batches, manufactured using a qualification protocol, are released for distribution only after complete execution of the Process Performance Qualification Study [ISPE Guidance].

PPQ re-verification

This indicates the repeating of a part of or a complete PPQ study in the event of changes in the process, equipment, etc. or as a recommendation of the CPV process to verify whether a process continues in a validated state of control and/or to verify that the changes do not adversely impact process characteristics and product quality or the validated state of control of the process [ISPE Guidance].

Product Lifecycle

This comprises all phases in the life of a product from the initial development through marketing until the product's discontinuation.

Process Validation Master Plan (synonym: validation master plan)

This is a document that defines the process validation scope and rationale and that contains the list of process validation studies to be performed[8].

Proven Acceptable Range (PAR)

A PAR is a characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria[6].

Quality

This indicates the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity[16].

Quality by Design (QbD)

This means a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management[6].

Quality Target Product Profile (QTPP)

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product[6].

Verification

Verification is a systematic approach to verify that manufacturing systems, acting alone or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses types of approaches to ensure that the systems are fit for the designed purpose. Other terms used are qualification, commissioning and qualification, system validation, etc.[17].

Worst Case

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure[5].

3.1 Acronyms

- **API**—Active Pharmaceutical Ingredient
- **APR**—Annual Product Review
- **BPR**—Batch Packaging Record
- **CMA**—Critical Material Attribute
- **CPP**—Critical Process Parameter
- **CPV**—Continued Process Verification
- **CQA**—Critical Quality Attribute
- **DoE**—Design of Experiments
- **DP**—Drug Product
- **DS** — Drug Substance
- **FMEA**—Failure Mode Effects Analysis
- **HACCP**—Hazard Analysis and Critical Control Points
- **ICH**—International Conference Harmonization
- **KPP**—Key Process Parameter
- **LB**—Lower bound
- **LCL**—Lower Specification Limit
- **MPD**—Master Packaging Document
- **NOR**—Normal Operating Range
- **OOS**—Out of Specification
- **OOT**—Out of Trend
- **PAR**—Proven Acceptable Range
- **PAT**—Process Analytical Technology
- **PM**—Packaging Material
- **PPQ**—Process Performance Qualification
- **PVMP**—Process Validation Master Plan
- **QbD**—Quality by Design
- **QTPP**—Quality Target Product Profile
- **RM**—Raw Material
- **SPC**—Statistical Process Control
- **TPP**—Target Product Profile
- **TT**—Technology Transfer
- **USL**—Upper Specification Limit

4. Building and capturing process knowledge (Stage 1)

The goal of stage 1 is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets the quality attributes. The process design is the "commercial-scale" design process and the risk assessments and experiments that report it. It is expected that product development and process development at small scale provide important inputs into the Process Design phase (product formulation, manufacturing pathway, analytical method development, QTPP, and quality attributes).

This stage shall cover all activities relating to product research and development, formulation, scale-up/pilot batch studies and final transfer of technology to the manufacturing site.

At the design stage itself, factors that may contribute to the quality of the product e.g., selection of input material, components, product design, process design, etc. shall be carefully considered and this activity shall form the basis for the commercial manufacturing process.

Sources of knowledge available prior to (and that may be used during) Stage 1 of the Process Validation Lifecycle, include:

- Previous experience with similar processes (e.g., platform processes)
- Product and process understanding (from clinical and pre-clinical activities)
- Analytical characterization
- Published literature
- Engineering studies/batches
- Clinical manufacturing
- Process development and characterization studies

The aim of pharmaceutical development is to design a quality product and its manufacturing process in order to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. Information from pharmaceutical development studies can be the basis for quality risk management.

The Pharmaceutical Development section shall describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section shall include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed.

Product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids).

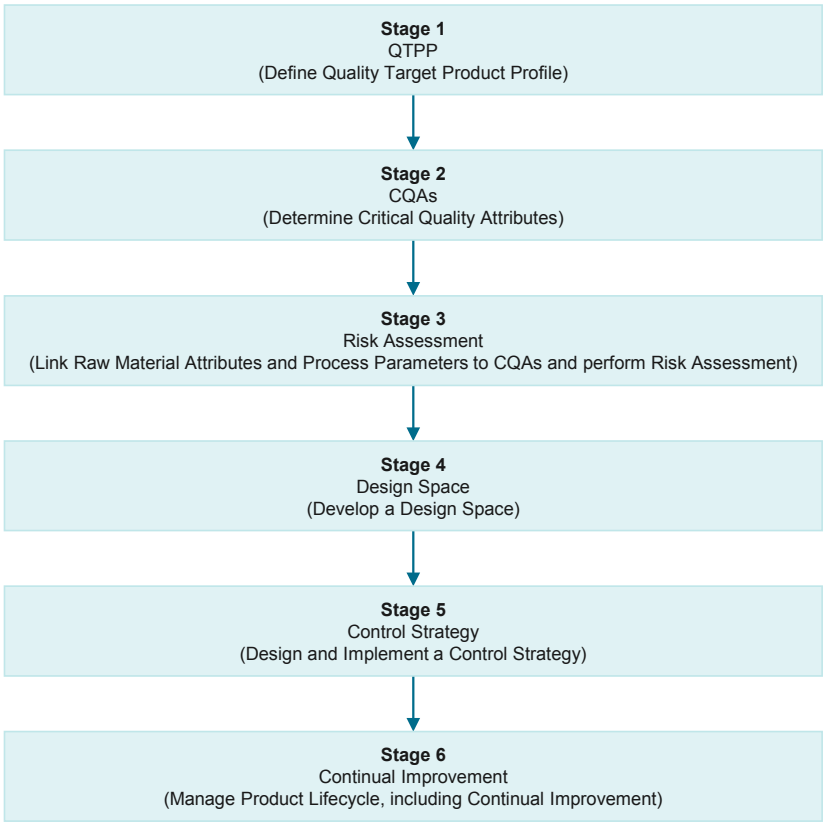
Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual-preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents, etc.) to provide their intended functionality and to perform throughout the intended drug product shelf-life should also be demonstrated.

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration. The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device, etc.), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed.

In this stage, Product shall be developed as per QbD approach (as per Figure 4.0-1) and the commercial manufacturing process shall be defined based on knowledge gained through development and scale-up activities. Process control for each unit operation and overall process shall be established based on process knowledge and understanding. Strategies for process control shall be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output).

QbD approach



For detailed information of individual stages at QbD, refer to ICH –Q8 (R2) – Pharmaceutical Development.

4.1 Deliverables from stage 1 process validation

The list below summarizes the information needed to make the transition from Stage 1 (Process Design) to Stage 2 (Performance Qualification) in the Process Validation Lifecycle. The sub-sections herein discuss these deliverables in more detail and provide references for additional information.

- **Quality Target Product Profile (QTPP)** — this is done at the initiation of Stage 1
- **Critical Quality Attributes (CQAs)** with corresponding Criticality Risk Assessment and desired confidence
- **Manufacturing process design**
  - Process description showing process inputs, outputs, yields, in-process tests and controls, and process parameters (set points and ranges) for each unit operation
  - Process solution formulae, raw materials, and specifications
  - Batch records and production data from laboratory or pilot-scale production.
- **Analytical methods** (for product, intermediates, and raw materials)
- **Quality risk assessment** which provide initial risk-based categorization of parameters prior to process characterization
- **Criticality and risk assessments** for identification of process parameters with corresponding criticality and risk analysis
- **Process characterization**
  - Process Characterization Plan and Protocols
  - Study Data Reports
- **Process control strategy**
  - Release specifications
  - In-process controls and limits
  - Process parameter set points and ranges.
  - Routine monitoring requirements (including in-process sampling and testing).
  - Storage and time limitations for intermediates, process solutions, and process steps.
  - Raw material/component specifications.
  - Design space (if applicable).
- **Process analytical technology applications and algorithms** (if PAT is used).
- **Product characterization testing plan** (i.e., tests not included in the product Release Test Panel).
- **Manufacturing technology**—assessment of production equipment capability and compatibility with process requirements (may be covered in Stage 2a).

- **Scale-up/scale-down approach**—evaluation and/or qualification of laboratory models.
- **Development documentation**—the Process Design Report.
- **Process validation master plan**

4.2 Quality Target Product Profile (QTPP)

The aim of pharmaceutical development is to design a quality product with a manufacturing process that consistently delivers the intended performance of the drug product.

Pharmaceutical development begins with the establishment of pre-defined objectives. These are described in the Quality Target Product Profile (QTPP). The QTPP is defined at the initiation of Stage 1 and is referenced throughout the product lifecycle.

The QTPP captures all relevant quality requirements for the drug product. Consequently, it is periodically updated to incorporate any new data that may be generated during pharmaceutical development.

It addresses relevant characteristics that include:

- Intended use in the clinical setting (e.g., dosage form and strength, route of administration, delivery systems, container and closure system, etc.).
- Drug substance quality attributes appropriate to the drug product dosage form being developed (e.g., physical, chemical, and biological properties).
- Drug product quality attributes appropriate for the intended marketed product (e.g., purity/impurities, stability, sterility, physical, and chemical properties).
- Therapeutic moiety release or delivery, and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance, etc.) appropriate to the drug product.
- Excipient and component quality attributes, drug-excipient compatibility, and drug-container compatibility that affect the process ability, stability, or biological effect of the drug product.

The QTPP summarizes the quality attributes of the product that ensure safety and efficacy. It provides a starting point for assessing the criticality of product quality attributes.

4.3 Critical quality attributes

CQAs can be associated with drug substances, drug products, excipients, intermediates (in-process materials) and with components of containers and closures. At an early stage of process development, the information available on product attributes may be limited. For this reason, the first set of CQAs may come from prior knowledge obtained during early development and/or from similar products rather than from extensive product characterization.

The degree of criticality assigned to quality attributes is derived using risk-based tools and the potential impact of the attributes on safety and efficacy.

Attributes not assigned as CQAs should also be considered in the development of the process.

The identification of potential CQAs is an ongoing activity initiated early in product development. It makes use of general knowledge about the product and its application, as well as available clinical and non-clinical data. CQAs are subject to change in the early stages of product development, and thus require a quality risk management approach that evolves as knowledge about the product and process is generated. CQAs for commercial products should be defined prior to initiation of Stage 2 activities.

4.4 Defining the manufacturing process

A manufacturing process is designed to consistently provide a product that will meet its required quality attributes. As the process is being defined during development, a process description is a tool that is used to assist in execution of risk assessments and in the development of the control strategy.

The manufacturing process is described as a series of constituent unit operations in a process description, block diagram, or process flow diagram that describes each unit operation. Each unit operation in the manufacturing process should be depicted with a similar level of detail.

The following information should be included in the description of each:

- Process requirements, including raw materials, scale, and order of operations.
- Set points and ranges for the process parameters.
- Identification and quantity of all material flows (additions, wastes, product streams).
- Testing, sampling, and in-process controls.
- Hold times and hold conditions for product and additional solutions.
- Estimated step yields and durations.
- Sizing for equipment, including such items as chromatography columns and filtration units.
- Specific identification (manufacturer, part number, etc.) for manufacturing (e.g., filters) and product components (e.g., vials, stoppers).
- Other information necessary to successfully reproduce the process.

The evolution of process knowledge and understanding is reflected in clinical batch records; these are an important source of information for defining the manufacturing process in the process description. Data collected from clinical trial material manufacture may be useful to determine process capabilities, set specifications, design PPQ protocols and acceptance criteria, evaluate laboratory models, and transfer processes.

Process descriptions are documented in reports and may be incorporated into the Technology Transfer (TT) Package for the product.

The process may change during Stage 1 due to increases in material demand (i.e., process and analytical development, clinical needs), improved product understanding that leads to changes to CQAs, or improved process understanding that results in addition, elimination or adjustments of unit operations.

Documentation should capture these changes and the supporting justifications. This information should be archived in the Knowledge Management System. Development and documentation of the commercial manufacturing process in Development Reports should precede formal process characterization studies.

Increased knowledge gained during process characterization may require additional changes to the process description. All changes to the process should be approved through change control procedures as defined by the Quality System.

Design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function, or as a combination of variables such as components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can contribute to the establishment of a design space. Regardless of how a design space is developed, it is expected that operations within the design space will result in a product meeting the defined quality.

4.5 Analytical methods

Analyses of raw materials, in-process samples, drug substance, and drug product are important aspects of the Control Strategy (Section 4.8) and process characterization studies. Analytical methods used for such studies should be appropriate for their intended use, scientifically sound, reliable, and reproducible. Strategies for qualification/validation of the analytical methods used during development have been published, and provide approaches for evaluating tests used at this stage of the lifecycle[18].

Information on the analytical methods used during process characterization studies should be included in the Process Characterization Plan, and documented in the study reports. Qualification of the methods should also be documented. Since process characterization studies may be performed in development laboratories, instruments must be adequately calibrated and maintained.

4.6 Risk assessment and parameter criticality designation

Risk assessment plays an important role in the development of a commercial control strategy. Risk assessments are performed by interdisciplinary teams at several points during stage 1 of the lifecycle, and serve a number of purposes.

Risk assessment tools provide a structured means for documenting data and rationale associated with the risk assessment outcome, and becomes part of the documented process development history.

As shown in Figure 4.0-1, the initial identification of critical quality attributes is followed by a quality risk assessment in stage 1. The initial quality risk assessment is a cause and effect type of analysis to identify process input parameters where variability is likely to have the greatest impact to product quality or process performance. This assessment is based primarily on prior knowledge or early development work, and the outcome of this assessment provides the foundation for process characterization studies that follow.

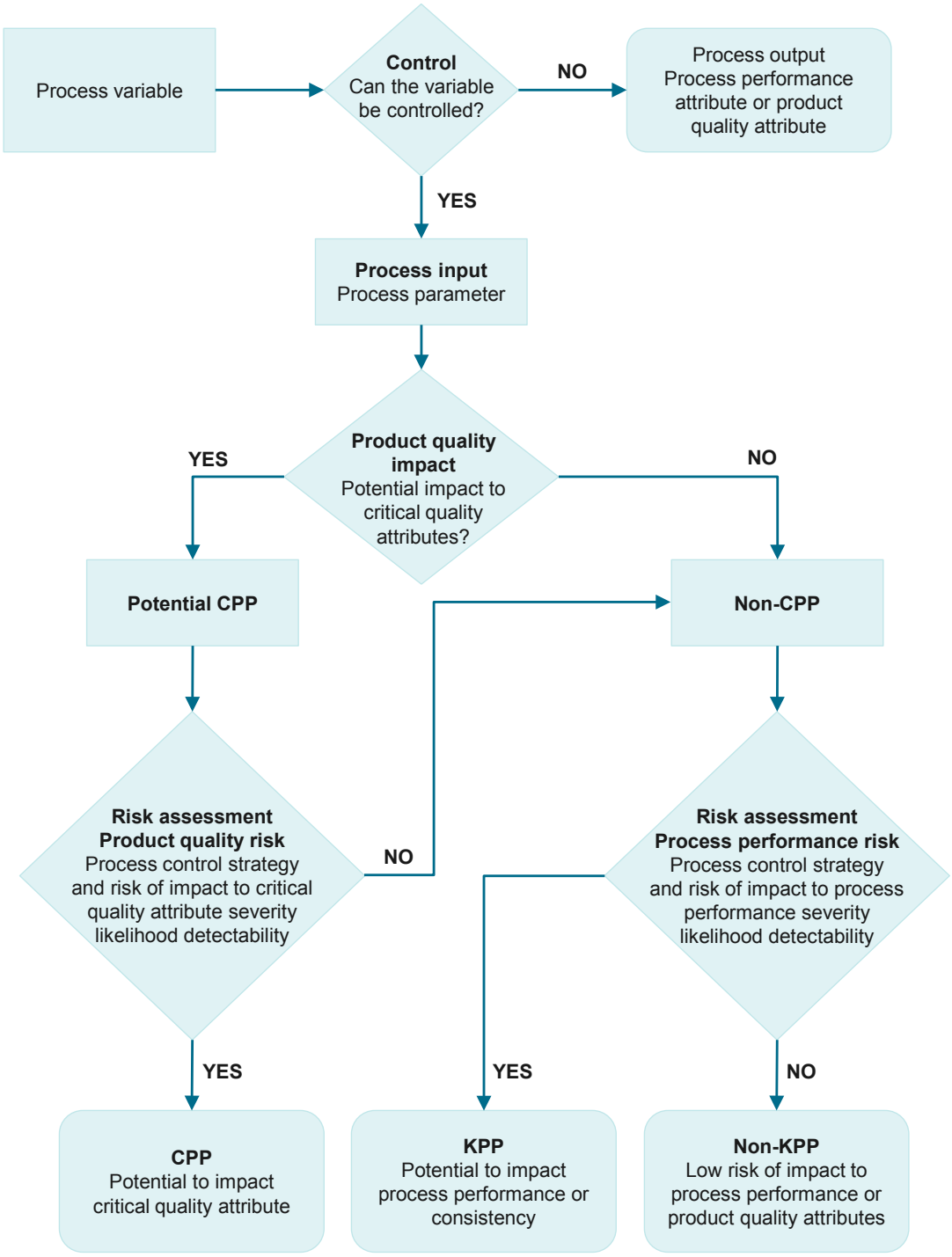
Understanding the impact of process parameter variability and applying the appropriate controls is a fundamental element in development of the commercial control strategy.

Figure 4.6-1 provides an example of a decision tree developed to guide the assignment of parameter designations in conjunction with the quality risk assessments. The decision tree facilitates categorization of process parameters as critical, key, or non-key (see definitions). Decision making tools can facilitate common understanding among participants, and have the advantage of increasing consistency in the decision making process as well as consistent documentation of rationales as part of the risk assessment process.

The decision tree can be used for risk assessments both before and after the supporting data from process characterizations studies are available.

- **Parameter or attribute:** Process variables can be outputs from one-unit operation and inputs to another. For a given unit operation, each variable is initially established as a parameter or an attribute on the basis of direct controllability.
  - **Yes** — directly controllable process input parameters can theoretically contribute to process variability.
  - **No** — process outputs that are not directly controllable are attributes that are monitored and may be indicative of process performance or product quality
- **Process parameters:** Potential impact to critical quality attributes.
  - **Yes** — if impact is suspected, or if data show that variability in a parameter could impact a CQA, the parameter is designated as a CPP. Although a parameter may be initially classified as a CPP, data from robustness studies conducted during process characterization may show that CQAs are not impacted despite exaggerated variations in the parameter. In these cases, the second risk assessment serves to change the assessment to non-CPP.
  - **No** — parameter is a non-CPP and is further evaluated.
- **Non-CPP:** potential to impact process performance or consistency if run outside of defined range.
  - **Yes** — parameter designated a KPP.
  - **No** — parameter has little impact to the process over a wide range. The parameter is designated a non-KPP.

Figure 4.6.1 Decision tree for designating parameter criticality



Refer to examples of decision trees addressing routine changes in process as given in Annexure 2 for details.

Risk assessment shall be applied to the material attributes of the input materials, process parameters and quality attributes of the final product (DS/DP) to arrive at conclusions on the Critical Material Attributes (CMAs) of incoming materials, Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) of the final product. Steps involved in the Risk Assessment strategy and approach are outlined in Annexure 3.

Risk assessment may also be used to screen potential variables for DOE studies, as applicable, to minimize the total number of experiments conducted while maximizing knowledge gained.

4.7 Process characterization and product characterization testing plan

Process characterization is a set of documented studies in which operational parameters are purposely varied to determine their effect on product quality attributes and process performance.

The approach uses the knowledge and information from the risk assessments to determine a set of process characterization studies to examine proposed ranges and interactions for process parameters. The resulting information is used to define the PPQ ranges and acceptance criteria. It can also be used to set the final parameter ranges and can be used to develop a Design Space if using an enhanced approach, i.e., incorporating advanced analytical and/or manufacturing control technologies, to process development.

Experiments can be designed to examine proposed ranges and explore ones wider than those that will normally be used in operation. An element of process characterization may include multivariate designed experiments to define process design space. While univariate approaches are appropriate for some variables to establish a proven acceptable range (PAR), multivariate studies account for interactions between process parameters/material attributes[1].

Since studies designed to characterize the process and setting acceptable ranges for process parameters are usually performed at laboratory scale, the ability of the laboratory-scale studies to predict process performance is desirable. When a laboratory scale model is used in development, the adequacy of the model should be verified and justified. When there are differences between actual and expected performance, laboratory models and model predictions should be appropriately modified. In that the conclusions drawn from the studies are applied directly to the commercial-scale process, qualification of laboratory-scale models is essential.

Qualification of the scaled down models should confirm that they perform in a manner that is representative of the full-scale process. This is shown by comparing operational parameters and inputs and outputs, including product quality attributes.

Pilot-scale models of small molecules that are representative of the commercial manufacturing process may be used for supportive PPQ data. In solid and liquid oral dosage forms, 10% of the commercial batch size and/or 100,000 units have been considered a representative scale[1]. Scale-up effects for certain processes, such as mixing freely soluble substances, tablet compression, or liquid filling may be well-known.

Batch sizes at 10% of bulk size or run times of 100,000 dosage units provide a sufficient duration to determine a degree of control and process characterization, while uncovering any preliminary major problems. Full-scale confirmation/evaluation may be carried out when small-scale studies are used to support PPQ. For scale-down studies, the raw materials, component attributes, equipment, and process parameters should be comparable and indicative of the process intended for the commercial product.

4.8 Control strategy

Establishing an effective and appropriate process control strategy is one of the most important outcomes of pharmaceutical development in Stage 1. An appropriate control strategy is based on knowledge and experience gained in Stage 1 and its effectiveness will dictate the extent to which a manufacturing process remains in a state of control.

Strategies for process control consisting of material analysis and equipment monitoring at significant processing points as well as defined settings in process equipment, shall be designed to reduce input

variation and adjust for input variation within defined specification range during manufacturing (and hence, reduce its impact on the output), or combine both approaches to assure quality of the product.

As with the other aspects of stage 1 discussed above, the development of an effective process control strategy is an iterative process. It starts early in development and evolves as process and product knowledge increase. A robust control strategy encompasses all elements of individual unit operations in the process. All product quality attributes and process parameters, regardless of whether they are classified as critical, are included in a complete process control strategy which includes the following elements:

Raw material controls

The ability to manage the quality of the inputs (raw materials and components) to assure a consistent output is an essential aspect of a process control strategy. Inputs should be categorized based on their potential risk for introducing variability or contaminants into the product and/or process.

Product variability may include changes to CQAs, whereas process variability may include inconsistencies in yield, reaction kinetics, filterability, or other non-product, quality-related effects.

For many raw materials used in the manufacturing process, selection of appropriate grades (based on purity, chemical and physical characteristics, and/or microbial specifications, such as endotoxin) may be an adequate level of control.

For higher risk raw materials, understanding the contribution to product and process variability may be essential to establishing specifications for those materials. Once the relationships are understood, appropriate risk reduction steps can be made part of the control strategy.

In-process and release specifications

In-process and product specifications may be related to product safety and efficacy or may assure product consistency. Confirmed failure to meet a product specification (in-process or product) disqualifies material from clinical or commercial use. Guidance on setting specifications is provided in ICH guidance documents Q6a and Q6b.

In-process controls

In-Process Controls (IPCs) are inputs to the process and are checks performed during production to monitor and, if appropriate, to adjust the process, and/or to ensure that the intermediates or product conform to specifications or other defined quality criteria.

Performance parameters

Performance parameters (e.g., tablet/capsule disintegration; harvest or peak growth cell densities/viability) are process outputs that cannot be directly controlled but are indicators that the process has performed as expected.

Process parameter set points and ranges

Knowledge of the effects of process parameter variability on the output of each Unit Operation and on the final product evolves during Process Development and Process Characterization (Section 4.7).

This information, along with process equipment capability (Section 5.1), is used to establish parameter set points and ranges (including ranges for alarms and deviations). It may also be used to assess the severity of process deviations caused by parameter excursions. Parameter ranges may be designated as normal operating ranges (NORs), or where proven by supportive data, as proven acceptable ranges (PARs).

Process monitoring (data review, sampling, testing)

Process monitoring includes measurement data (e.g., flow rates, temperatures, volumes, pH), in-process sampling plans, and appropriate analytical assays. Data collection and analysis begins in Stage1 and are integral parts of Stage 2, Process Performance Qualification. The data collection effort eventually evolves into the continued process monitoring program described for Stage 3, Continued Process Verification (see Section 6.0, "Continued Process Verification, Stage 3").

Processing and hold times

Hold conditions and times are an essential part of the process control strategy for all process intermediates (or in-process materials), drug substance, bulk drug product, and prepared solutions. Studies should be performed to support these limits. Time limits for processing steps should also be part of the control strategy.

Process Analytical Technology (PAT)

Process Analytical Technology (PAT) is one approach to implement the Control Strategy[19]. Using PAT, CQAs are monitored in real-time (using on-line or at-line analytics), and results are used to adjust CPPs during production to decrease product variability (CQAs) or achieve consistent CQAs at desired ranges with low variability.

PAT uses product and process knowledge as well as equipment automation and analytical instrumentation technologies. Successful application of PAT requires a thoroughly characterized process (Section 4.7) in which the relationship between CPPs and CQAs is explored using mathematical models, such as multivariate analysis. Application of this understanding to the Control Strategy (Section 4.8) also affects the design and qualification of the instrumentation and control systems in the manufacturing process.

To support implementation of PAT, Stage 1 deliverables must describe the CQA monitoring scheme and the algorithm for adjusting CPPs based on the process response. Qualification of the equipment, measurement system, and process (Stage 2) must demonstrate the capability to adjust CPPs according to the established algorithm and confirm that these adjustments result in acceptable and predictable outputs. Therefore, PAT-based control methods need to be qualified[20].

Process Control Strategies and Specifications shall be mandatorily designed for all CPPs and CMAs respectively. The type and extent of process controls shall be aided by the risk assessment and these may be further enhanced and improved as process experience is gained.

Such process controls shall be thereby established in the master production/packaging records which can help to take the process to the next stage of confirmation.

4.9 Process design report

The process design report is also a Stage 1 output. As a living document that describes in detail the intended commercial process, it may have various titles in internal procedures. Stage 1 study data are used to support this document and to justify the ranges, and process control strategy. Additional data and process knowledge are gained and gathered as the manufacturing process changes, and are incorporated during Stages 2 and 3.

The process design report should be updated to include this new information. This comprehensive document includes:

- Reference to CQAs and supporting risk assessments.
- Process flow diagrams.
- Process description tables.
- Inputs (in-process controls).
- Outputs (in-process tests and limits, in-process specifications).
- Process parameters and ranges.
- Classification of parameters for risk of impact to CQAs and process performance.
- Design space, as appropriate.
- Justification and data supporting all parameter ranges (e.g., characterization data, development studies, clinical manufacturing history).

Product life cycle management (PLM) document as per Annexure IV shall be initiated by compiling the manufacturing history of development batch, pilot bio batch, exhibit batches, pre-validation batches (but not limited to) and reviewed prior to initiation of PPQ batches by incorporating the following details (but not limited to) and shall be updated as various stage of product life:

1. General information.
2. Product composition.
3. Process flow diagrams.
4. Equipment gaps.
5. Quality target product profile information (QTPP).
6. Critical manufacturing attributes (CMA).
7. Critical process parameters (CPP).
8. History of challenges and/or problems faced.
9. Deviations and out-of-specifications details.
10. Change history details.
11. Stability failure and rejection/recall history.
12. Learning and risk assessment.

4.10 Process validation master plan

A process validation master plan should be initiated during Stage 1 to prepare for Stage 2 activities. It should outline the validation strategy and supporting rationale, and should typically include the following:

- Process characterization plan.
- Description of the manufacturing process and control strategy.
- Functions and responsibilities.
- PQ or PPQ plan.
- PPQ strategy (e.g., single unit operations or a combination of unit operations, bracketing, family, or matrix approaches) and a list of individual protocols, and applicable ancillary studies, (e.g., mixing, media preparation, in-process pool hold time, resin lifetime, etc.).
- List of equipment and facilities to be used.
- List of analytical methods and their status.
- Sampling plan.
- List of protocols to be executed under the plan.
- Proposed timeline and schedule of deliverables.
- Procedures for handling deviations and revisions.
- Continued Process Verification plan.

4.11 Stage 1 manufacturing and technology considerations

The capability of the production equipment and procedures has a significant influence on the ability to maintain process parameters within pre-set limits. The measurement and control capability of the process equipment is one of the subjects of Stage 2 (Process Qualification), and can be found in Section 5.1. Equipment qualification exercises should confirm the suitability of equipment for its intended use.

The functionality and limitations of commercial manufacturing equipment as well as predicted contributions to variability posed by different component lots, production operations, environmental conditions and measurement systems in the production setting shall be considered during this assessment.

For facility, availability of space, required environmental conditions, and ventilation facilities based on product requirement, air filtration level, waste handling facilities, utilities, analytical testing facilities and statutory requirements shall be considered as per product and process requirements.

5. Process qualification (Stage 2)

Process Qualification (PQ) during Stage 2 demonstrates that the process works as intended and yields reproducible commercial product. It should be completed before release of commercial product lots, and covers the following elements:

- Design and qualification of the facility, equipment, and utilities (this should be completed prior to qualification of the process).
- Process Performance Qualification (PPQ), which demonstrates control of variability and the ability to produce product that meets predetermined quality attributes.

5.1 Strategies for system design and qualification

Facilities, equipment, utilities, and instruments (collectively referred to as systems) used in the manufacturing process should be suitable and capable for their intended process use, and their performance during the operation should be reliable. Systems that affect product quality should be qualified to reduce the equipment performance as a process variable.

The review and qualification of these systems should be performed according to a pre-defined project plan. System qualification should precede Stage 2 PPQ activities. Qualification studies should be completed, reviewed, and approved, with all deviations addressed, prior to the start of PPQ studies.

5.1.1 Engineering and design

Facility, equipment, and utilities should be designed to meet process requirements. The design of the facility and commissioning of the equipment and utilities should assure the capability of operating as required for routine manufacturing and should be based on process parameters, control strategies, and performance requirements developed or identified during Stage 1 Process Design. These activities and all commissioning-related tasks should be conducted according to Good Engineering Practices (GEP), and recorded according to Good Documentation Practices (GDP), with oversight by the Quality Unit. Risk-based approaches may be used to assure adequate controls and verification. This element shall comprise of the following important activities:

- Selecting appropriate utilities and equipment construction materials, operating principles and performance characteristics for Process Performance Qualification (PPQ).
- Verifying that utility systems and equipment are built and installed in compliance with the design specifications.
- Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges.

5.1.1.1 Risk assessment

Risk assessment determines which systems and system components have an impact on the establishment and maintenance of process parameters and conditions that affect product quality. This information helps develop system qualification plans, protocols, test functions, and acceptance criteria. The process

steps and systems that affect product quality, the mode of effects, and the correlation between system performance and control of process variables should be understood.

5.1.2 Qualification plan

The qualification plan may be developed at any time once the process requirements and correlation to process systems are understood. Early development of the qualification plans may provide valuable guidance to the design, installation, and commissioning efforts. However, to capture any changes that result from start-up and commissioning, it may be prudent to complete the qualification plans and protocols after all information from the commissioning has been transferred. This approach means that Stage 2 activities may be underway during and prior to completion of all Stage 1 activities.

5.1.3 Test functions and acceptance criteria

System qualification tests or studies should be based on knowledge gained from previous activities, including Stage 1 (Process Design), and engineering studies. Test functions should be based on good scientific and engineering principles designed to demonstrate and assure that anticipated operating parameters will be met throughout the manufacturing process in a consistent and predictable manner.

Acceptance criteria should be based on sound scientific rationale; the criteria should be useful, attainable, and where appropriate, quantifiable. If sufficient process understanding is not available, or the scale-up effect is unknown, existing knowledge may be used during design and commissioning to define user requirements. Formal system operating and maintenance procedures or instructions should be in place prior to the execution of test functions. All measuring and test instruments should be calibrated and traceable to appropriate standards.

Deviations in the execution of qualification testing should be documented, investigated, and addressed. Conclusions should be based on the suitability and capability of the system to meet the process requirements.

5.1.4 Maintaining systems in a state of control

Qualification studies ensure that the manufacturing systems, as designed and operated, are in a state of control. For the process to remain valid and controlled, the systems must be maintained in a state similar to that demonstrated during qualification. Periodic assessment and evaluation of the system to determine its control status are important. The assessment should include a review of information that indicates or supports assurance of control.

5.2 Process performance qualification

Process performance qualification marks the transition from development and clinical manufacturing to routine commercial production. Process Performance Qualification (PPQ) demonstrates the validity of the process design and the suitability of the process control strategy at the commercial manufacturing scale. PPQ provides confidence that the systems of monitoring, control, and procedures in routine manufacturing are capable of detecting and compensating for potential sources of process variability over the product lifecycle.

The type and amount of information should be based on understanding of the process, the impact of process variables on product quality, and the process control strategy developed during Stage 1. The number of batches needed to acquire this information and data may be based in part on a statistically sound sampling plan that supports the desired confidence level. It may also be influenced by the approach selected to demonstrate that the batch-to-batch variability of CQAs is acceptable.

5.2.1 PPQ readiness

The transition from Stage 1 to Stage 2 of the process validation lifecycle is not strictly sequential. Completion of some Stage 1 activities may overlap with a few of those from Stage 2. Likewise, some preparative Stage 2 activities could be initiated in parallel with a few from later Stage 1 activities. Although initiation of PPQ activities does not depend on completion of all Stage 1 activities, a readiness assessment should be conducted to determine the timing of sufficient information and completion of activities to support moving forward with PPQ batch manufacture.

The readiness assessment should include deliverables from Stage 1 (as outlined previously in Section 4.1) and other elements:

Quality target product profile: this is initiated at the start of Stage 1, but updated to reflect knowledge obtained from Stage 1 prior to initiating PPQ.

Critical quality attributes with criticality assessment: CQAs are identified early in Stage 1. They are confirmed to account for additional analytical characterization, clinical and/or non-clinical data and information gathered during Stage 1. CPPs that impact are reviewed and updated based on detectability and occurrence [11].

Commercial manufacturing process description: this is started in Stage 1 and updated to reflect the finalized commercial process supported by data from Stage 1 studies.

Analytical methods: these are appropriately validated or suitably qualified methods should be identified and their status documented. Methods for product release and stability should be fully validated according to ICH requirements prior to initiating PPQ batch testing. Additional tests beyond normal release testing used to support PPQ should be identified and suitably qualified/validated prior to being used to test PPQ batches.

Approved commercial batch records: changes that may be made to batch records during Stage 1 should enhance, clarify, or optimize manufacturing instructions and/or to reflect knowledge gained during process characterization.

Process design report: this report (as described in Section 4.11) is the repository for the process design justification, and includes parameter risk ranking, and ranges for the process that will undergo PPQ study. The data summarized in this report will support the selection of the elements of the PPQ studies and proposed PPQ acceptance criteria. It is a best practice for this information to be finalized prior to PPQ study design since it provides the scientific support to justify the PPQ acceptance criteria.

Process Validation Master Plan (PVMP): drafting of the process validation master should begin in Stage 1 and be finalized prior to PPQ study initiation.

Quality system and training: qualified and trained personnel will be integral to the PPQ studies. Detailed, documented training specific to the PPQ is recommended for functional groups directly involved in the execution of the study. Quality Unit approval of PPQ activities should be completed prior to PPQ study initiation, and all PPQ studies should be conducted within the quality system.

Approved protocols for PPQ Studies: protocols for each study should be approved and finalized prior to initiation of PPQ studies. Design and content of process performance qualification protocols is discussed in Section 5.4.

5.3 Design Strategy for Process Performance Qualification (PPQ)

5.3.1 Use of prior knowledge and stage 1 data to support PPQ

Prior knowledge is that which has been gained from similar products and processes. It may come from experience with a portfolio of similar molecules or from similar process and unit operations.

Products manufactured in new facilities/equipment will not have a similar depth of prior knowledge and data prior to development.

In these instances, increased emphasis on data gathering in Stage 1 may be applied to support PPQ readiness. To gather sufficient data to demonstrate an acceptable level of confidence in the commercial manufacturing process when little prior knowledge or Stage 1 data are available, the scope and extent of PPQ may be greater.

The rationale and scientific justification for the use of existing data (prior knowledge) to support the PPQ Stage should be documented in the process validation master plan. All prior knowledge and Stage 1 data used in to support PPQ must be retrievable, traceable, verified, and generated using good scientific practices.

Use of stage 1 data for PPQ

Processes and products for which there is little or no prior knowledge may require a greater emphasis on Stage 1 and PPQ activities to demonstrate an acceptable level of confidence in the process control strategy. Data from Stage 1 process characterization studies and clinical manufacturing are generally used to support the establishment of the control strategy for new products, as discussed in Section 4.0. Stage 1 data may be used to support PPQ if sufficient scientific evidence for its use is available.

Past experiences in clinical, and stability, and pilot batch manufacturing process evaluation batches help determine the amount of PPQ data.

5.3.2 PPQ study design

Process Performance Qualification is a means to demonstrate that all important elements of a process unit operation are under the appropriate degree of control, and that all important variables and elements of the unit operation have been considered (facility, utilities, equipment, personnel, process, control procedures, and components).

During PPQ, critical process parameters and critical quality attributes are monitored along with process performance parameters. Their evaluation is useful in demonstrating consistency and can enhance confidence in the overall process control strategy when included in the PPQ. All parameters and attributes intended for ongoing Continued Process Verification in Stage 3 should be included in the PPQ.

5.3.2.1 Number of batches

The PPQ should be viewed as a means to evaluate and confirm a sound process design, an effective control strategy, and operational proficiency at commercial scale. The number of batches in the PPQ study or studies will be influenced by many factors such as:

- The performance and acceptance criteria.
- The analyses to be performed and the type and amount of data necessary to perform those analyses.
- The level of process knowledge and understanding gained from Stage 1.

- The type and complexity of manufacturing technology employed in the various unit operations.
- Knowledge from previous experience with similar well controlled processes.
- The inherent/known variability of the process resulting from raw materials, age of the equipment, operator experience.

Using risk-based approaches allows a balance between the number of batches studied and the risk of the process. They can also be used in conjunction with objective approaches to determine the number of batches to include.

Statistical methods are recommended to guide the determination of the number of PPQ batches needed to achieve a desired level of statistical confidence (see Sections 8 on statistical approaches to determining the number of batches and sampling plans). However, this approach alone may not always be feasible or meaningful. Refer to the methodology for selection of number of PPQ batches on risk based approach is outlined in Annexure 5.

When it is not feasible or meaningful to use conventional statistical approaches, a practical, scientifically-based, holistic approach may be more appropriate. In this case, the following factors may be used to support the rationale for the number of PPQ batches selected:

- Prior knowledge and platform manufacturing information/data.
- Risk analysis of the process to factor the level of risk into the batch number selection.
- Increased reliance on Stage 1 data to support that the process is under control and to add to the data set.
- Continuation of heightened sampling/testing plans during continued process verification until a sufficient dataset has been accumulated to achieve statistical confidence.

When a combination of approaches and data are used, the rationale and justification should be clearly documented in the process validation master plan. Also, references to all supporting source data should be included.

5.3.2.2 PPQ at normal operating conditions

Process characterization (robustness) studies conducted during Stage 1 serve as the foundation for establishing normal operating ranges, proven acceptable ranges, and design space, if appropriate. Effects of scale should also be considered if scaled-down models are suitably qualified, well-planned, and executed.

Study data on robustness should support conducting commercial-scale PPQ under routine manufacturing conditions. Supplemental engineering studies at scale may be appropriate to evaluate extremes of the normal operating range (e.g., line speed or compression speed). The process validation master plan should provide the justification for the approach used and reference all source data.

5.3.2.3 PPQ using individual unit operation studies

PPQ of a manufacturing process can be achieved by performing PPQ studies on each individual unit operation (or related groups of operations). This approach calls for the writing of individual protocols that outline the studies to be conducted on each unit operation.

By emphasizing unit operations that have more variability, higher risk of impact on CQAs, or more limited Stage 1 data available to support assurance of process, this strategy may facilitate more flexibility in PPQ design.

Protocols should define the testing performed and acceptance criteria for the output of the unit operation (intermediate). They may also require that the final drug substance or drug product meets all specifications and predefined acceptance criteria.

5.3.2.4 PPQ using bracketing, matrix, and family approaches

Many operations involve similar or identical process operations or equipment. In these cases, designs where grouping is used may be considered. Some process variables that might be amenable to approaches using bracketing, matrix, or family grouping PPQ include:

- Batch sizes.
- Drug product dosage strength.
- Identical equipment.
- Different size vessels, tanks, or similar configurations of the same design and operating principle or in-kind equipment.
- Various vial sizes and/or fill volumes of the same drug product (e.g., smallest and largest vial size).
- Filling line speeds (e.g., fastest and slowest line speed).
- Product packaging (e.g., bottle heights or dosage counts).
- Transport validation for biological products.

5.3.2.5 Bracketing approach

Bracketing qualifies processes that represent the extremes of process variables under the premise that the extremes are fully representative of intermediate groups. The bracketing strategy is used when a single process element can be varied while all other variables remain fixed.

Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells).

A common example where the use of bracketing approaches may be considered. A blend concentration of 50 mg active ingredient /100 mg powder, could be compressed into a 100 mg active (per 200 mg tablet weight), 200 mg active (400 mg tablet weight), and 300 mg active (600 mg tablet weight). The same powder blend is common to the three tablet strengths. The rationale for selection of representative groups and numbers of batches should be scientifically justified, risk assessed, and outlined in the process validation master plan and PPQ protocols.

5.3.2.6 Matrix approach

A matrix approach is appropriate for commercial manufacturing PPQ when configurations of the same process and product have more than one variable. The approach is based on the assumption that the batch configurations selected for inclusion in the PPQ fully represent processes for all combinations. The rationale for the selection of combinations, and the number of batches representing each

combination, should be scientifically justified, risk assessed, and documented in the process validation master plan and PPQ protocols.

5.3.2.7 Family (grouping) approach

A family approach is appropriate when multiple related but different entities can be grouped so that a single one represents the common characteristics or worst case of each group. The rationale for family groups and justification for the representative selection should be included in the validation master plan and PPQ protocol.

An example of the use of the family approach for PPQ is provided here. The example taken is that of an 'Equipment Family.' In this case, each equipment train was evaluated for similarity of the equipment (identical equipment trains with duplicated equipment of the same model and manufacturer). Identical equipment trains reduce the number of batches needed to show that the process is reliable in each one.

In this case, there is ample prior knowledge on the performance of the process. Use of a reduced number of batches in a family approach should take into consideration the amount of prior knowledge of the process, the number and impact of the critical process parameters, and the ability to control the parameters within the ranges.

For a unit operation with no critical parameters, use of fewer batches may be appropriate. In these cases, the approach should be clearly justified with reference to supporting data in the validation protocol.

5.3.2.8 Concurrent approach

Concurrent approach for PPQ shall be used only under exceptional circumstances as listed below:

- For process infrequently used, due to various reasons, such as to manufacture drugs for which there is limited demand (e.g. orphan drugs, minor use drugs, etc.) or which have short half-lives (e.g., radio pharmaceuticals, etc.)
- For manufacturing processes of urgently needed drugs due to shortage/absence of supply.

Circumstance and rationale for concurrent release shall be fully documented in PPQ protocol and shall be done only after approval by Quality Management.

Minimum requirements for concurrently released batches are as listed below:

- Batches comply with all cGMP/regulatory requirements, PPQ acceptance and batch release criteria.
- When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback.

5.3.2.9 Process analytical technology

After developing a control strategy that incorporates PAT (Section 4.8), process qualification is performed to confirm that the monitoring, measurement, and process control or adjustment systems are suitable, capable, accurate, and reliable. The key to effective PAT process control is the reliable operation of instruments and equipment.

The use of PAT controls can provide an alternate approach to PPQ. Qualification of the equipment, measurement system, and process must demonstrate the capability to adjust CPPs according to the established algorithm and confirm that the adjustments result in acceptable and predictable outputs. In other words, a PAT-based control method needs to be qualified [12].

5.3.2.10 Sampling strategy

During the PPQ, increased sampling and analytical testing is expected to verify that the process is under control, and to demonstrate consistency at intermediate steps, as well as in the final product. Sampling plans for discrete units should include the statistical rationales that underlie the plans.

For processes or individual unit operations that yield a single homogenous pool of material, statistically based sampling plans may not be useful in ascertaining the level of intra-batch process variability. For example, analysis of multiple samples from a homogeneous blend provides information on the variability of the analytical method only, but does not cover intra-batch variability of the process. In these cases, extended characterization of intermediate pools and non-routine sampling performed at certain points in the process and comparison of the data between batches can demonstrate process control and reproducibility. Refer PPQ sampling plan and acceptance criteria for Drug product, Drug substances and packaging materials in Annexures 6 and 7 for blend uniformity and content uniformity sampling and testing plan as per ASTM guidelines for PPQ and post PPQ studies.

5.3.2.11 Setting PPQ acceptance criteria

The acceptance criteria for PPQ should be based on the body of data available from Stage 1, prior knowledge, and equipment capabilities. The approach used to determine the acceptance criteria should be outlined in the process validation master plan, and the justification of the individual acceptance criteria for each unit operation should be documented in the PPQ protocols.

Statistical approaches should be used where appropriate, and each product and process variable should be evaluated individually. Process justification documented in the Process Design Report (see Section 4.11) provides the scientific basis and reference to the data supporting the acceptance criteria for process parameter ranges, and product attributes. The rationale for PPQ acceptance criteria should be clearly described. When sufficient data are available and statistical methods are used, the method(s) used and the rationale for selection of that method should be described.

When establishing acceptance criteria for PPQ, the following considerations should be taken into account:

- Historical data/prior knowledge.
- Preclinical, development, clinical, and pre-commercial batches.
- Early analytical method suitability (if data is used from clinical lots).
- Amount of data available (level of process understanding).
- Sampling point in the process.
- Whether compendial requirements can be met with high confidence.

Acceptance criteria may include:

- Incoming material: these should meet designated criteria (may be raw material or the output of a preceding step).
- Process parameters: these are expected to remain within normal operating ranges (NORs); particular attention is focused on parameters which are designated ‘Critical’ or ‘Key’.

All product quality and process performance attributes should meet pre-defined acceptance criteria and include statistical criteria where appropriate.

- Process performance attributes: these may be impacted by KPPs (e.g., step yield or bioreactor titer) and demonstrate process consistency between batches.
- Critical quality attributes: these have the potential to impact safety or efficacy (e.g., impurities).
- Quality attributes: these do not necessarily impact safety or efficacy, but can be used as a surrogate at certain process steps to demonstrate process consistency (e.g., deamidation or oxidation that does not impact potency or safety/immunogenicity).

5.4 PPQ protocol

PPQ protocols are documented plans for executing the PPQ studies. Protocols are reviewed and approved by cross-functional groups that include the quality unit. Protocols must be approved prior to commencement of PPQ activities. PPQ protocols typically contain the sections described below.

Introduction

The introduction should include a description of the process and/or specific unit operations under qualification, including the intended purpose of the operations in the context of the overall manufacturing process. The introduction should provide an overview of the study or studies, and other important background information.

Purpose and scope

This section describes the objective of the study and provides an overview of the study strategy, i.e., how it will be performed, how data will be analyzed, and the expected outcome. Justifications or cross-referencing to documents that contain justifications, such as the process validation master plan, should be included.

References

References to relevant documents related to the study should be included in the protocol:

- Development and/or process characterization reports that provide supporting data for operational parameter and attribute ranges.
- Process design report.
- Process validation master plan.
- Commercial manufacturing batch records.
- Related qualification documents (facilities, utilities, equipment, other PPQ studies, etc.).
- Analytical methods.
- Specification documents.
- Approved batch records.

Equipment and materials

A list of equipment, instrumentation, and materials necessary to perform the study should be included. References to qualification of utilities and equipment should be provided as appropriate.

Responsibilities

This section shall include a designation of various functional groups and their responsibilities as they relate to execution of the study, and verification that appropriate training has been conducted for all contributors.

Description of unit operation/process

The objective of PPQ is to provide confidence that all elements of unit operation/process are under the appropriate degree of control. A comprehensive discussion of the control strategy similar to the level of detail provided in the commercial manufacturing control strategy is appropriate to demonstrate that all process elements have been considered. Although all elements are described, only a subset of the process variables will comprise PPQ acceptance criteria. (See Acceptance Criteria mentioned below.)

Methodology

This describes the step-by-step procedure needed to perform the study. This section clearly identifies the critical and key process parameters under qualification and the methods by which the operation will be monitored and recorded. A brief explanation of the relevance of these parameters and their potential relationship to process performance and quality attributes is useful to further describe the PPQ strategy. Documents containing the detailed rationale for critical and key parameter designations should be referenced.

A discussion of the number of batches planned should be included, and the rationale should be stated. The level of confidence expected at the conclusion of the PPQ study should be included as applicable.

Data collection

Roles and responsibilities for various functional groups as they relate to collection and analysis of PPQ data and documentation should be included. The list of process data to be collected and how it will be analyzed should be stated.

Sampling plan

This is the description of a defined prospective sampling plan and its operating characteristic curve with details on the number of samples, frequency of sampling, and sampling points supported by statistical justification, as applicable. The typical contents of such a plan should include:

- Sampling points.
- Number of samples and statistical basis for sampling, as appropriate.
- Sample volume.
- Non-routine sampling for extended characterization.
- Sample storage requirements.
- Analytical testing for each sample.

Analytical testing

The overall validation package includes the methods used for all analytical testing performed, from assessment of raw materials to extended characterization of the drug product. A listing of all analytical methods used in each protocol and the validation or qualification status of each (and references to source documents) should be included. Analytical method validation should also be included as part of the process validation master plan.

Deviations

All potential deviations cannot be anticipated regardless of the level of characterization and knowledge. A general framework for defining the boundaries of qualification is appropriate and, as an example, should describe the following:

- Out-of-specification or out-of-limits test results.
- Failure of a CPP to remain within normal operating range; a CPP is designated as such due to the potential impact on a corresponding CQA. Failure to control may indicate overconfidence in an immature control strategy. This would be grounds for protocol failure.
- Missed samples or samples held under incorrect storage conditions.
- How individual batches or lots failing to meet validation acceptance criteria will impact the study.

Acceptance criteria for PPQ

The objective of PPQ is to demonstrate that the commercial manufacturing process is in a state of control, and the elements of the process control strategy provide confidence that a state of control will be maintained. The protocol should clearly document the acceptance criteria to be met in order for the PPQ to be considered successful. Acceptance criteria may be shown in tabular format in the protocol (see the following example).

Table 5.4-1 Example of PPQ Acceptance Criteria Table

Process parameter	Designation	Normal operating range
Parameter 1	CPP	(X.XX-X.XX)
Parameter 2	CPP	(X.XX-X.XX)
Parameter 3	KPP	(X.XX-X.XX)
Parameter 4	KPP	(X.XX-X.XX)
…	…	…
Attributes		**Acceptance criteria**
Recovery	Process Performance	(X.XX-X.XX)
Quality Attribute 1	Quality Attribute	(X.XX-X.XX)
Quality Attribute 2	Quality Attribute	(X.XX-X.XX)
Critical Quality Attribute 1	Critical Quality Attribute	(X.XX-X.XX)
Critical Quality Attribute 2	Critical Quality Attribute	(X.XX-X.XX)
Critical Quality Attribute 3	Critical Quality Attribute	(X.XX-X.XX)
Critical Quality Attribute 4	Critical Quality Attribute	(X.XX-X.XX)
…	…	…

Refer Specimen Template of PPQ protocol as Annexure VIII

5.5 PPQ report

A report should be prepared for each study and should typically include the following sections:

Introduction

This section should include a concise description and outline of the unit operations or group of unit operations that have been qualified. It should summarize the overall results of the study, providing back ground information and explanations as necessary.

Methods and materials

This provides a clear and concise summary of how the study was performed. It should identify how the objectives of the study were accomplished using both methodology and references to appropriate procedures and protocol requirements.

Deviations

A summary of the deviations and corresponding root causes, as well as a discussion of the potential impact to the PPQ, should be included. Corrective actions resulting from deviations should be discussed. Their impact on the process, the PPQ, and on the affected batches should be provided.

Protocol excursions

Protocol excursions and unexpected results should be included and fully described in the report. A reference to the root cause analysis should be provided if documented separately from the PPQ report. Any corrective actions and their impact on PPQ should be outlined in the report.

Discussion: PPQ results

This section should restate the key and critical process parameters and give the actual range of values occurring during the PPQ. It should include how the data were collected as well as references for analytical methods used. Data summarized and compared with pre-defined acceptance criteria should be presented in tabular or graphical format whenever possible, and data used from Stage 1 studies should be clearly identified.

The discussion should provide support for any study conclusions. The impact of ranges and deviations should be discussed if they affect the study results. Risk assessment and any follow-up conclusions, including corrective actions, should be stated. Findings associated with batches or lots that fail to meet the acceptance criteria in the protocol should be referenced in the final PPQ package; likewise, with any corrective measures taken in response to the cause of failure.

Conclusions

Conclusions as to whether data demonstrate that the process is in a state of control should be provided. Pass or fail results should be stated for each acceptance criteria and corresponding results. When a unit operation approach is used, PPQ reports should be prepared for each unit operation study. A summary executive report that unifies all the study results to support the overall process PPQ should be written.

5.6 Transition to continued process verification

Following a successful PPQ, the CPV plan can be finalized and implemented. Any adjustments to be made on the basis of the PPQ should be in place prior to manufacture of post-PPQ batches and should be handled through the change control procedures. When appropriate, enhanced PPQ-level sampling is recommended for a period of time following PPQ. However, this may not be necessary in all cases. Further information is presented in Section 6.

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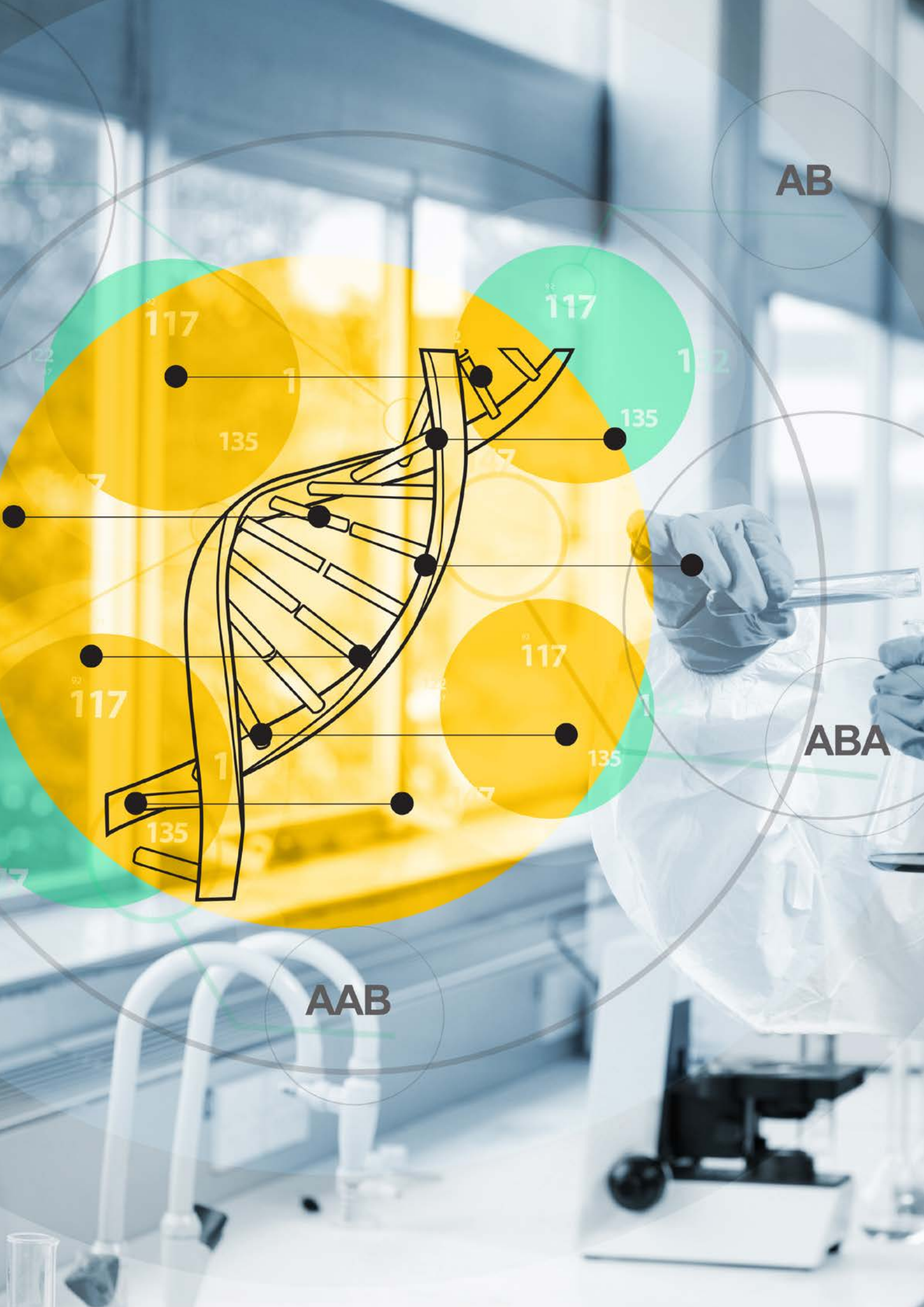
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6. Continued process verification (Stage 3)

6.1 Establishing a monitoring program

6.1.1 Purpose and strategy

A program of Continued Process Verification (CPV) provides a means to ensure that processes remain in a state of control following the successful Process Qualification stage. The information and data collected during Stages 1 and 2 set the stage for an effective control strategy in routine manufacturing and a meaningful CPV program.

The understanding of functional relationships between process inputs and corresponding outputs established in earlier stages is fundamental to the success of the CPV program.

Continued monitoring of process variables enables adjustments to inputs covered in the scope of a CPV plan. It compensates for process variability, to ensuring that outputs remain consistent. Since all sources of potential variability may not be anticipated and defined in Stages 1 and 2, unanticipated events or trends identified from continued process monitoring may indicate process control issues and/or highlight opportunities for process improvement.

Science and risk-based tools help achieve high levels of process understanding during the development phase, and subsequent knowledge management across the product life stages facilitates implementing continuous monitoring (see Sections 4.0 and 5.0).

6.1.2 Documenting the CPV program

Planning for CPV begins during the establishment of the commercial-scale control strategy in Stage 1. High-level quality system policies and documents should outline how various departments interact and how information is compiled and reviewed in order to ensure maintenance of the validated state.

Under such a policy document as well as a process validation master plan, a product-specific CPV plan should include the following elements:

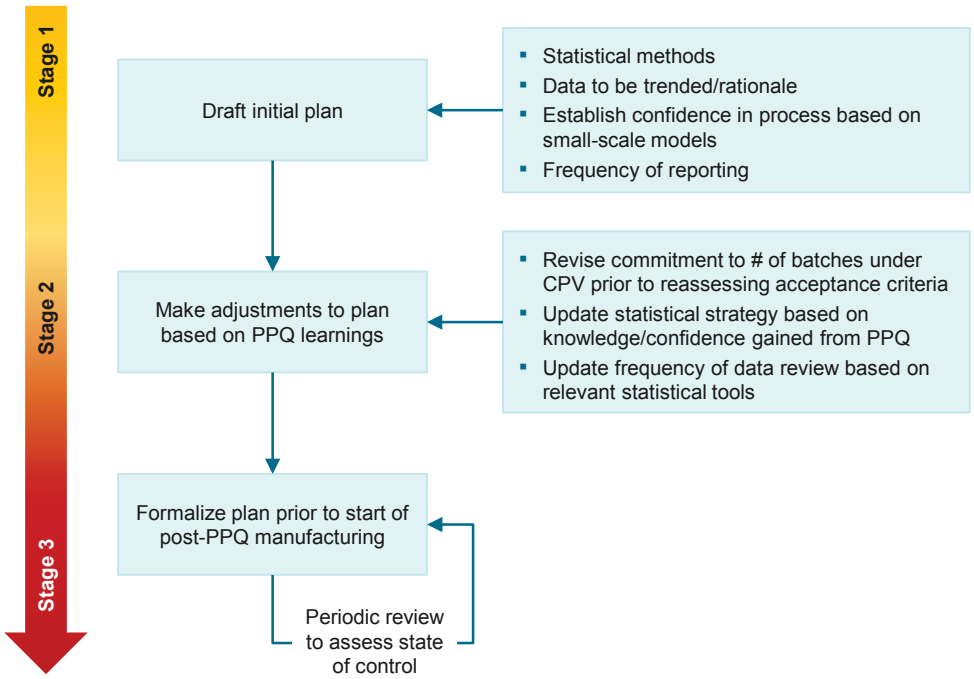
- Roles and responsibilities of various functional groups.
- Sampling and testing strategy.
- Data analysis methods (e.g., statistical process control methods).
- Acceptance criteria (where appropriate).
- Strategy for handling Out-of-Trend (OOT) and Out-of-Specification (OOS) results.
- Mechanism for determining what process changes and/or trends require going back to Stage 1 and/or Stage 2.
- Timing for re-evaluation of the CPV testing plan.

Figure 6.1.2-1 illustrates an example of the development of a CPV monitoring strategy throughout the lifecycle stages. Ideally, the majority of the control strategy is established prior to Stage 2, when PPQ is conducted. While adopting the concept of continued process verification for legacy products, the same general approach should be taken to document and execute the CPV program (see Section 6.1.3, Legacy Products and Continued Process Verification).

Since Stage 3 is part of the lifecycle validation approach, continued process verification should be governed by both an overarching quality system for validation practices and a process validation master plan.

At the minimum, the process validation master plan should make high-level commitments for both Process Design (Stage 1) and Continued Process Verification (Stage 3) in addition to Process Qualification (Stage 2). The specifics of the CPV sampling/testing strategy may not be finalized until completion of PPQ. Therefore, the process validation master plan may include general commitments to the planned CPV strategy. These are then further clarified in a separate CPV Plan referenced in the process validation master plan. It is still possible that a process validation master plan can be considered complete at the end of Stage 2 (i.e., not left open-ended for the entire commercial lifecycle) if the requirement that CPV activities, as required, are initiated as per the defined CPV Plan.

Figure 6.1.2-1 Development of a Continued Process Verification Plan



6.1.3 Legacy products and continued process verification

Figure 6.1.3-1 outlines one possible approach to assessing what is necessary to apply the lifecycle approach to a legacy product. It may be the case that a legacy process is well-controlled and monitored, and not much action is required. However, this decision should be based on an evaluation of the large body of historical process and monitoring data and an assessment of process variability. In this approach, the historical data is used to determine the current state of control of the process. Measures such as performance capability (Ppk) and other statistical approaches should be considered for assessment of the process.

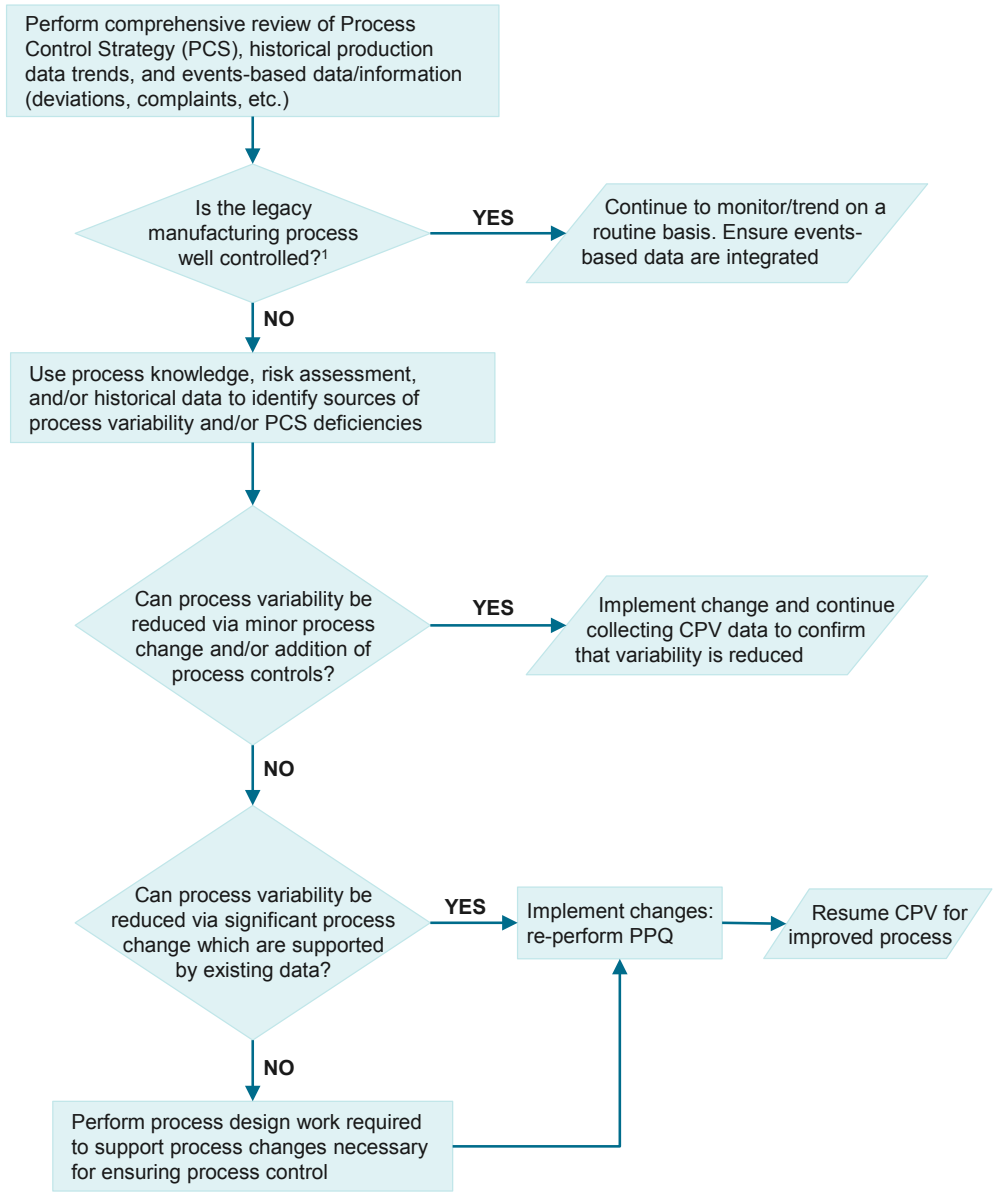
In addition to assessing process performance, the adequacy of the set of parameters being used to monitor the performance of the process should also be evaluated. Part of assessing the appropriateness

of the current process control strategy is to provide a foundation for determining what, if any, additional sampling/monitoring should be included during continued process verification for the legacy product.

A period of enhanced sampling will help generate significant variability estimates that can provide the basis for establishing levels and frequency of routine sampling and monitoring and should be considered. It is recommended that this ongoing monitoring also be captured under a formal plan as outlined in Section 6.1.2, documenting the CPV Program. CPV work flows for new and legacy products are outlined in Annexure 9 and Annexure 10.

In considering whether the sampling plans for legacy products are adequate, it may be determined that a statistically-driven approach should be applied. However, the amount and type of data may also lead to a decision that statistical justification of the sampling plan is unnecessary. This determination should be part of the initial assessment of the historical data and monitoring approach. Although statistically-derived models may not be required, the sampling plan should be scientifically sound and representative of the process and each batch sampled.

Figure 6.1.3-1 CPV Plan determination for Legacy Products



1 Is an appropriate process control strategy (demonstrating understanding of the impact of process parameters on CQAs) defined and does statistical of data show that variability is controlled?

6.1.4 Demonstrating continued process verification

Two primary sources of data that need to be included in a CPV plan are:

1. Process parameters (i.e., process performance and product quality indicators).

2. Potential sources of variability that are not defined process parameters. Examples of such sources of data/information may include:

   — Raw material quality.

   — Redundant equipment and instrumentation comparability.

   — Personnel impact on process (i.e., shift-to-shift consistency).

Critical and key input parameters and the corresponding outputs related to process performance and product quality attributes are established during process design (Stage 1).

At the commercial scale, process qualification (Stage 2) batches are produced to confirm that the process operates as intended and to verify that the process control strategy results in the consistent manufacture of a product that meets its predefined quality characteristics. The process control strategy should then also be used as the starting point for identifying the process data/information to be included in a CPV plan.

6.1.5 CPV monitoring plan

Routine sampling will generate some data for the CPV Program, but non-routine sampling should also be considered. The sampling/testing plan moving forward from Stage 2 into Stage 3 should be considered to be in a dynamic state; it needs to be updated and reviewed periodically. An enhanced sampling plan (that may include both off-line and on-line analyses) may be required to ensure that the appropriate data set is collected.

Since the PPQ protocols already specify those process parameters and attributes (inputs and outputs) that must be maintained within the specified ranges in order to make a product that meets predefined quality attributes, the PPQ sampling plan is a logical foundation for the CPV sampling plan.

PPQ may provide sufficient assurance that certain parameters are well-controlled at the commercial scale and do not need to be carried forward into a CPV plan. A biological process, for example, requires sufficient clearance of a process residual (e.g., antifoam) or a process-related impurity (e.g., DNA). These may be successfully demonstrated during PPQ batches, eliminating the need for ongoing sampling and testing during CPV.

In cases where either historical data are limited or where the data show a high degree of variability, testing and trending may be required after Stage 2 to ensure a high level of assurance that a particular impurity is well-controlled. This should be determined on a case-by-case basis via risk assessment and/or statistical assessment of historical data.

The prospective CPV plan should provide specific instructions for analysis conducted to a limited degree, and subsequently discontinued once a sufficient number of data points are accumulated to determine process control. The number of batches sampled and the frequency of sampling within a batch should be stated in a Stage 3 enhanced sampling plan.

Depending on the data generated, samples collected and analyzed 'for information only' (FIO) should have a designated end-point. A more open-ended approach, where no specific number of batches is identified, could be used to address data trends and results.

A plan that describes an approach to reduce (step-down) or increase (step-up) sampling and testing as a result of trending and results should be included as an option.

6.1.6 Data analysis and trending

The CPV plan should clearly state how the data collected will be analyzed. In some cases, it may be compared to pre-defined acceptance criteria, especially for those data that are tightly controlled (e.g., a gradient elution slope for a critical column chromatography step). In other cases, (e.g., unit operation yields), data may be statistically assessed to evaluate process trends.

In such cases, the statistical methods and rules used for continued process monitoring should be specified in the CPV plan. Control charts are commonly used to evaluate process control over time. They are appropriate for both evaluating statistical process control and for detecting process trends. Under CPV, control charts are generated and evaluated on a per batch basis.

It is necessary to establish prospective criteria to ensure that the process is in a state of control. However, there are states which describe "out of control" results (e.g., Out-of-Trend, Out-of-Control, Out-of-Specification), which should trigger actions per the Quality System (e.g., investigation, impact assessment to validated state, etc.). Specific actions will vary on a case-by-case basis, but the CPV plan should specify what types of action should be taken. A section on 'Tools for the Process Validation Lifecycle' should describe the tools available to address the statistical trending and SPC, along with risk-based evaluations.

Section 6.1.4 covers sources of process variability that may not be parameter-related (e.g., raw materials, personnel, and environment). As part of the overall CPV assessment, high-risk potential sources of variability should be risk-mitigated, and also assessed and demonstrated to be under control. Trends in purity for a critical raw material, for example, may indicate subtle differences between suppliers. Even seemingly innocuous changes by a supplier may lead to out-of-trend or out-of-specification events. These should be evaluated in light of overall process consistency and product quality.

6.2 Incorporation of feedback from CPV monitoring

6.2.1 Quality systems and CPV

The best tools for continued confirmation and refinement of process control are the quality system elements that provide feedback and objective measures of process control. The tools are based on product and process understanding, and are enabled by procedures that monitor, measure, analyze, and control the process performance [21].

Once in commercial production, maintenance of the validated state requires an events-based system of review, in addition to process trending described in Section 6.1, establishing a Monitoring Program.

Communication of review outcomes to the manufacturing, quality, and regulatory stakeholders to modify the control strategy (for improvement and/ or compliance reasons) is an iterative and essential part of the CPV. Feedback mechanisms can vary between immediate (intra-batch or real-time), after each batch, or after a series of batches or a defined time period. The CPV Plan should address when each of these mechanisms should be used.

6.3 CPV data review and reporting

The CPV plan needs to include a frequency of review of the information from data collection mechanisms as well as Quality Systems. It should also identify circumstances for, and a process to allow for, an immediate review based on significant issues identified with a process or product, and identify the participants in the review.

The frequency of data review will depend primarily on risk. The starting point for defining the review period will be the most recent process risk communication document. As more production data is generated, deeper process understanding is gained and control is likely to be more easily demonstrated. Thus, the period or intensity of review may be reduced.

An annual commercial data compilation effort in preparation for Annual Product Review (APR) may be sufficient. However, more frequent data reviews and comparisons to defined acceptance criteria may help manufacturers be more proactive and less reactive.

APR packages are necessary, as per regulatory guidelines. However, APR exercises are likely to become high-level reviews and summaries of multiple, more frequent CPV data reviews. The APR will identify any gaps in the CPV data reviews and will summarize long-term trends, but more frequent CPV data reviews should be performed by the manufacturer at defined intervals.

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7. Approach to process validation lifecycle of packaging process

The Process Validation Lifecycle for a packaging process shall be as described below.

The development/design studies of a new pack for a product may be divided into the following phases.

Process design (Stage 1)

Phase	Important activities
I	Feasibility studies, review of Product Information Form (if available), literature search, market search, marketable pack requirements, study of innovator/competitor pack
II	▪ Stability/compatibility/other tests and/or studies with various pack options, risk assessment and finalization of packaging configuration/s, preparation of Specification/STP, and preparation of Packaging Development Report (refer to relevant SOPs) ▪ Fitment assessment of packaging facility and equipment at the manufacturing site for the intended pack configuration, finalization of packaging change parts and/or machine/line setup, initiation of change part trials at manufacturing facility ▪ Qualification of packaging process and/or optimization of packaging machine process parameters (PAR finalization), etc. on scale-up batches and finalization of packaging process using risk assessment, trial results, etc., preparation of packaging process design Summary Report ▪ Packing of stability batches
III	▪ Conducting transit worthiness trials (if required) ▪ Finalization of pack design based on the above-mentioned studies ▪ Creation of artworks/mock-ups for regulatory submission, incorporation of texts on pack on the basis of compilation of product information including regulatory and marketing requirements and release for procurement ▪ Verification of packaging process parameters during EB/Pre-validation batches and updating of the Packaging Process Design Summary Report, if needed

During development of pack and packaging process design, risks associated with the materials used and the processes should be identified to assess the magnitude that each risk possesses. Risk assessment, however, shall be a continual process, and updating of risk assessment shall be carried out with understanding of packaging process and material attribute of input materials at further stages of the pack and packaging process development.

Process control strategies and specifications shall be mandatorily designed for all CPPs and CMAs respectively. The type and extent of process controls shall be aided by risk assessment as discussed previously and these may be further enhanced and improved as process experience is gained.

Qualification of packaging process/optimization of packaging process parameters

Overview

- Qualification of the packaging process shall be carried out for all packaging processes during scale-up studies conducted for the product.
- The qualified ranges of the process parameters should be used during packaging of Exhibit Batches and Pre-Validation Batches. The qualified ranges may be revised, if needed, based on Exhibit Batches/Pre-Validation batch experience and the revised ranges and/or reason(s) for revisions shall be documented clearly in the Packaging Process Design Summary Report.
- The finalized ranges of packaging process parameters and packaging process controls shall be used and further established during the PPQ batches of the product (i.e., during Stage 2 of PV).

Methodology

- Primary packaging process qualification shall be done for individual pack types and shall be performed for all new products. However, qualification of the secondary packaging operation shall be based on the bracketing and integrated packing line validation, i.e. that it shall be done for the worst case configurations identified.

- The following are the pre-requisites for primary packaging process qualification activities:

  — Packaging equipment shall be qualified to cover the ranges of the pack sizes and layouts as per the product's pack design.

  — Availability of relevant SOPs for packaging operation.

  — Change parts shall be qualified for the applicable primary packaging material configuration based on the applicable variables, for example, PVC-Alu bottles with screw caps, Alu-Alu strips, etc.

- This activity may be carried out through a separate packaging process qualification protocol or may be included in the scale-up batch monitoring protocol as per relevant SOPs.

- The qualification protocol shall clearly state the variable(s) which impact the integrity of the primary pack and set parameters range. Examples of these variables could include the following (but not limited to):

  — Speed.

  — Pack sealing temperature.

  — Integrity of sealing.

  — Product flowability.

  — Control on feeding quality/quantity.

  — Container closure system.

  — Challenge tests for rejection mechanism.

  — Challenge tests for detection of missing product units (e.g. cameras, etc.).

  — Power Intensity (in case of Induction Sealers).

- The Packaging Process Qualification activity shall start with documenting the numbers of the change parts and establishing the Proven Acceptable Range (PAR) for the process parameters which need to be studied. For example:

  — Blister sealing temperature and speed of conveyor in blister packs and/or strip packs.

  — Speed of conveyor and sealing torque for bottles used for dry syrups and liquid orals.

  — Torque for tablets and/or capsules bulk packed in HDPE bottles.

  — Speed, induction sealing, power wattage and conveyor speed, crimping parameters for topical ointments filled in collapsible tubes.

  — Speed and sealing torque in vials of sterile products.

- PARs shall be established for all such parameters for each configuration, primary packing materials, etc. with respect to each change part(s). While establishing the ranges, product filling is not a must.
- Once the PARs are established, they shall be validated with product filling, and running the batch with the optimized parameters.
- The number of samples withdrawn for qualification of packaging operation shall be representative of the batch under the qualification and the sampling plan shall be such that the results are in statistical confidence both within a batch and between batches. A Sampling Plan is given as guidance in Annexure 6.
- The packaging process length shall also be considered while drawing samples for packaging process qualification in order to verify the variability of parameters at different stages of a process, e.g., the start, middle and end of a blistering process.
- In-process checks on primary packs, like fill weight or fill volume or fill value, pack integrity checks to ensure product does not undergo physical damages during packaging operation, batch coding details and controls on un-authorized changes during runs, performance of camera systems to detect missing product, etc. shall be performed and established during packaging process qualification.
- Successful transport of the primary packs, to secondary packing magazines and/or conveyors shall be observed and documented, and the optimum speed shall be established.
- Wherever the Master Risk Analysis directs the conducting of a study with respect to the impact of heat on product, edge failure study shall be done by generating samples; e.g., in case of blister packs, samples shall be generated under low speed and high temperature settings. Such packs shall be subjected to stability study on specific parameters that are likely to be affected.
- Data once generated for specific change part(s) on PAR, may be considered as representative for other packs too, as long as primary packaging material and configuration is same.

At the end of Stage 1 of packaging PV, a Packaging Process Design Summary Report shall be prepared by the concerned personnel of packaging capturing the optimized packaging process details, risk assessment summary, process control strategy, etc. and may be given either as a part of the product TTD or attached separately as a supporting document.

Transition to stage 2 of process validation lifecycle

Qualified ranges of the process parameters, as finalized through the Stage 1 packaging process qualification activities, should be used during packaging of Exhibit Batches and Pre-Validation Batches.

The Packaging Process Design Summary Report and Risk Assessment Summary/Process Control Strategies shall be reviewed for the need for updates based on conclusions of packaging process verification activities during Exhibit/Pre-Validation batches, and updated, if required, with justifications. The qualified ranges may be revised, if needed, and the revised ranges/reason for revisions shall be documented clearly in the Packaging Process Design Summary Report which shall be updated thereof.

The intended Batch Packaging Record shall be prepared based on the conclusion of the above-mentioned batches by the relevant technology transfer team in consultation with other relevant stakeholders.

Stage 2 (process qualification):

The following activities shall be conducted as a part of Stage 2 of Packaging PV:

Phase	Important activities
IV	▪ Approval of proofs for production run of printed components ▪ Procurement of components as per approved proofs/specifications ▪ Smooth run of components on production shop floor during PPQ batches

During Stage 2, the finalized ranges of packaging process parameters and packaging process controls shall be used for verification, and established during the PPQ batches of the product.

The packaging process length shall also be specifically considered while drawing samples in order to verify the variability of parameters at different stages of the packaging process, e.g., the start, middle and end of a blistering process.

The Packaging Process Design Summary Report, Risk Assessment Summary/Process Control Strategies and Intended PI shall be reviewed for the need for any updates based on conclusions of packaging process verification activities during PPQ batches, and updated, if required, with justifications. The qualified ranges may be revised, if needed, and the revised ranges/reason for revisions shall be documented clearly in the Packaging Process Design Summary Report which shall be updated thereof.

Stage 3 of PV (CPV)

CPV of the Packaging Process shall be carried out as explained in Section 6.1-6.3.

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8. Process validation enabling systems and technology

This section presents tools and methods to assist in the planning and performance of the process validation program.

It includes sections on risk and knowledge management, statistical methodology, process analytical technology, and technology transfer. These tools can be used to identify, capture, and communicate information needed for the design and assurance of process control. They facilitate informed decision making, prioritization of activities, and interpretation of results related to the process validation effort.

8.1 Application of risk management

This section addresses aspects of risk management specific to the process validation lifecycle approach.

The application of risk management principles and approaches is instrumental to effective decision-making in the process validation lifecycle.

Management of variability is one example of applying risk management in the validation lifecycle. The level of control required to manage variability is directly related to the level of risk that variability imparts to the process and the product. The use of risk management to address variability requires understanding of:

- The origin of the variability.
- The potential range of the variability.
- The impact of the variability on the process, product, and ultimately, the patient.

Risk assessment should occur early in the lifecycle, be controlled appropriately, and effectively communicated. Risk Management increases product and process knowledge, which translates into greater control of product and process variability, and a lower residual risk to patients.

The process validation lifecycle provides continued assurance that processes will manufacture product in a predictable and consistent manner, where decisions related to product quality or process performances are made, risk can be assessed at several points throughout the process validation lifecycle.

Quality Risk Management applications throughout the process validation lifecycle include the following (see Figure 8.1-1):

Stage 1 — process design

- Identification of product attributes that may affect quality and patient safety.
- Criticality analysis of product quality attributes (CQA identification).
- Cause and Effect Analysis or Risk Ranking and Filtering, which link the process steps and parameters to process performance or product quality attributes. These can be used to screen potential variables for future process characterization (e.g., DoE) and testing.
- Preliminary Hazards Analysis (PHA) or early FMEA.

Stage 1-2 — transition from process design to process qualification

- Determining process control strategies that address the risk of failure for each process step
- Evaluation of residual risk remaining or created as a result of risk mitigation, process improvement, and process knowledge.

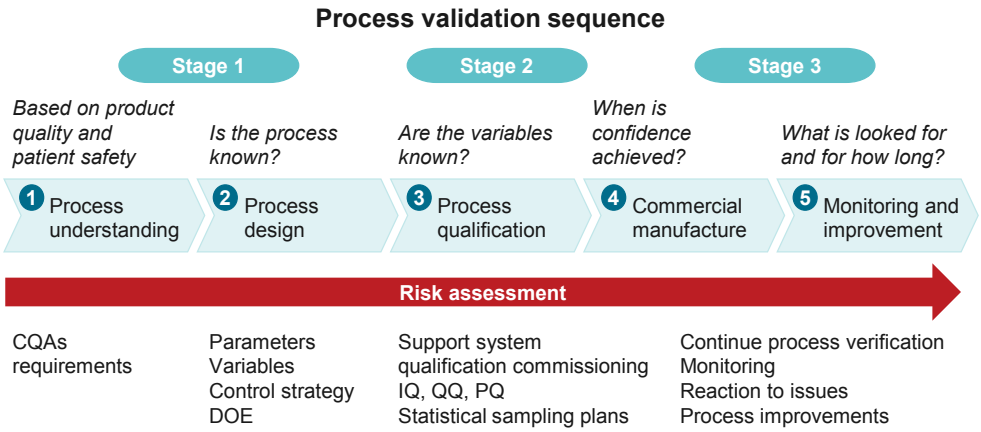
Stage 2 — process qualification

- Determination of process steps and parameters to test in PPQ, including sampling plans and the confidence and coverage they provide.
- Facility and equipment impact assessments.
- Determination of effective acceptance criteria for each test function.
- Analytical test results and deviations.

Stage 3 — continued process verification

- Determination of parameters that should be monitored as well as how they should be sampled and analyzed (e.g., sampling plans, confidence required and length of enhanced sampling).
- Evaluation of commercial manufacturing data to determine the best course for process improvement.

Figure 8.1-1 Depicts a quality risk management lifecycle tool for process development and validation[21]



8.1.1 Risk management in stage 1 (process design)

Conducting risk assessments during Stage 1 lays the groundwork for variables to be controlled and monitored. It also determines the extent to which continued monitoring will ensure a state of control during routine manufacturing. This begins with a criticality analysis: an initial definition of product quality attributes and an assessment of their relative importance.

Inputs for the criticality analysis are all relevant prior knowledge about the product being evaluated.

Outputs from the criticality analyses are:

- Initial CQA list.
- Initial relative severity listing of the CQAs.

Criticality of product attributes is assessed along a continuum – it not a 'yes' or 'no' question. This is accomplished by performing a risk assessment analysis that uses Severity and Uncertainty as variables, rather than the usual Severity and Occurrence. The process, which is iterative, is based on building product and process knowledge.

The level of severity assigned is based on the potential patient impact, while uncertainty is based on how much information (product knowledge and clinical experience) is available to determine the potential severity level for the specific attribute. Part of the output of this assessment will be further scientific studies to reduce the amount of uncertainty for higher risk attributes [21].

(See Figure 8.1-2, Example of Product Attribute Criticality Risk Assessment)

Figure 8.1-2 Example of Product Attribute Criticality Risk Assessment

		Uncertainty		
		Low	**Medium**	**High**
		Large amount of in-house knowledge, large body of knowledge in literature	Some in-house knowledge and literature	No/little in-house knowledge, very limited information in scientific literature
Severity	**High** (catastrophic patient impact)	Critical	Critical	Critical
	Medium (moderate patient impact)	Potential	Potential	Potential
	Low (marginal patient impact)	Non-critical	Non-critical	Potential

8.1.2 Risk management in stage 2 (process qualification)

Risk Management in Stage 2, the process qualification stage of the process validation lifecycle, is much more tactical. They are used to fine-tune the control strategies drafted in the Process Design stage.

Risk management is commonly applied during the facilities, utilities, and equipment qualification phase of Stage 2. Functional specifications are reviewed to help plan qualification activities. Higher-risk items require a higher level of performance output, while lower-risk items can be satisfied by use of commissioning activities with appropriate risk reviews and control.

Risk assessment output ratings can be applied against standard criteria to create the plan (see Table 8.1-1).

Table 8.1-1 Risk-based qualification planning

Risk assessment output ratings	Qualification planning
High	Testing to satisfy validation requirements will occur during qualification. Documentation and sampling requirements are high
Medium	A blend of qualification and commissioning activities can be used to satisfy validation requirements. Sampling requirements are moderate, given appropriate controls and risk reviews
Low	Testing to satisfy validation requirements can occur during commissioning phases. Appropriate controls and risk reviews should be in place

Risk assessments performed during Stage 2 not only help prioritize qualification activities, but also aid in the ongoing collection of knowledge and the planning of statistical sampling.

Generally, three factors – severity, occurrence, and detection (also known as controls) – are evaluated to determine the relative risk of specific failure modes. Each factor contributes to the validation plan in a different way.

Severity: this determines the level of testing required during Stage 2. The higher the severity rating for a particular attribute, the higher the statistical confidence required (see Table 8.1-2).

Occurrence: high occurrence rates may require further testing or development to reduce variation and increase process knowledge. Testing at this stage reduces additional and more costly testing during Stage 3. When the true occurrence rate is unknown, additional development or engineering studies may be required. When testing is complete, the occurrence ranking and overall risk rating for the failure mode can be updated with the new process knowledge.

Detection (controls): if the level of assessed controls is zero, the control strategy may need to be updated or new controls created. Controls do not have to be technology-based. The HACCP system is an example of a control, as are procedures and training.

Table 8.1-2 Severity rating and sampling requirements

Risk severity rating	Statistical and sampling requirements	Example confidence level required
High	+++	99%
Medium	++	95%
Low	+	90%

8.1.3 Risk management in stage 3 (continued process verification)

The continued process verification stage is the longest segment of the process validation lifecycle. It starts with an assessment of process capabilities and continues through a review of the output from process characterization, PPQ, and historical data.

The level of enhanced sampling that may be in place when commercial manufacturing commences can be determined by a statistical review of the PPQ data.

The capabilities of the processes help determine the level of enhanced sampling for an attribute and the length of time that sampling should continue at that level (see Section 8.2).

The statistical capability of the process is directly tied to the occurrence rating in the risk assessments. The more robust a process, the lower the occurrence rate for a potential failure and the lower the overall risk to the process. The level of risk can also determine the review period for certain product and process attributes[14].

8.1.4 Raw material risk management considerations

Sources of variation should be understood, and where possible, mitigated for process validation to succeed. In this context, using quality risk management to assess raw material quality and the potential impact on the process is important [22].

Risk identification through focused risk assessments is the first step toward attaining the desired level of process control from both a risk-to-patient and risk-to-business perspective.

The assessment identifies risk in relation to the raw material, and how it could impact the process and quality of product. The number and complexity of raw materials used in pharmaceutical manufacturing is quite large, and all potential issues (e.g., fraud or counterfeiting) should be addressed in the management of raw materials and components.

Risks-to-patient should also be addressed during commercial production. This can be done, through a risk assessment process that builds on current understanding of risk and process knowledge, combined with the Continuous Process Verification Program. QRM is a lifecycle process, with assessments that occur throughout the lifecycle of the product.

8.2 Statistical analysis tools

Successful process validation depends on sound, scientific data and information. Table 8.2-1 illustrates where various statistical methods are most commonly used in the validation lifecycle process.

Three of the methods – design of experiments, statistical process control, and process capability – are described in more detail in the sections that follow.

Table 8.2-1 Statistical methods and the typical stages at which they are used

Statistical tool	Stage 1 process design	Stage 2 PQ	Stage 3 CPV
Descriptive Statistics – mean, standard deviation, etc.	X	X	X
Statistical process control charts	X	X	X
Statistical power and sample size determination	X	X	X
Process capability study and capability indices	X	X	X
Design of Experiments	X	-	-
Measurement system Analysis (Gauge R&R)	X	-	-
Robust process design/Tolerance analysis/Taguchi methods	X	-	-
Multi-vari chart	X	-	-
Regression and correlation analysis	X	-	-
Analysis of Variance [ANOVA]	X	X	X
Levene, Brown–Forsythe, Bartlett, F_{max} Tests for Variation	X	X	X
Hypothesis tests/Confidence intervals	X	X	X
Pareto analysis	X		X
Acceptance sampling plans	-	X	X
Normal and nonparametric tolerance intervals	-	X	X

8.2.1 Design of Experiments (DoE)

The statistical design of experiments (DoE) is a powerful tool often used during Stage 1. Goals of DoE are to:

- Determine which process input parameters have a significant effect on the output quality attributes.
- Help determine the 'design space' levels of the input parameters that will produce acceptable output quality attributes results.
- Optimize the output of quality attributes, such as yield and acceptable levels of impurities.
- Determine the levels of input parameters that will result in a robust process that reduces its sensitivity to parameter variability.

DoE differs from the classical approach to experimentation, where only one parameter is varied while all others are held constant.

This "one-factor-at-a-time" type of experimentation cannot determine process parameter interactions, where the effect of one parameter on a quality attribute differs depending on the level of the other parameters.

The basic steps for the DoE approach are summarized below:

1. Determine the input parameters and output quality attributes to study.

   — This is best done as part of a team approach to identify potential critical process parameters and quality attributes; in many cases, the process may be well-understood and the parameters and attributes for experimentation readily determined.

   — If there are a large number of input parameters, an initial screening design, such as a fractional factorial or Plackett-Burman design, may be used[23]. The purpose of a screening experiment is to identify the critical parameters that have the most important statistical effect on the quality attributes. Since screening designs do not always clearly identify interactions, the reduced number of parameters identified by the screening experiment will be included in further experiments.

   — If the change is to an existing process, it is often valuable to construct a Multi-vari chart or SPC chart from current process data[24].

A Multi-varichart can be used to identify if the biggest sources of variation are within-batch variation, between-batch variation, or positional variation (e.g., between fill heads on a multi-head filler). Variance components can also be calculated from the data to determine the largest component of variance.

Process parameters that could be causing the largest sources of variation are then identified and included in subsequent experiments.

For example, if within-batch variation appears to be the largest source of variation, then charge-in of components done once at the beginning of the batch is not likely to be a key contributor to this variation. Charge-in differences due to inadequate weighing, for example, could cause between-batch variation rather than, within-batch variation.

This simple but powerful tool can sometimes discover important yet unsuspected critical parameters or 'lurking variables' that contribute to process variation, even if they are not initially on the list of parameters.

The same data may also be used to create SPC charts to determine if the process is in statistical control. Since a lack of statistical control will contribute to experimental error variation, it will be more difficult to understand the results of an experiment if the process is not in statistical control. Lack of statistical control may also mean that there are 'lurking variables' not in the list of process parameters that are contributing to process variation.

2. Conduct experiment(s) to determine which parameters have a significant main or interaction effect on the quality attributes.

   — This will usually be a full factorial design for two to four parameters. A full 2-level factorial design has a low (–) and high (+) level selected for each factor (parameter). At least one experiment is run at each combination of the factor levels.

For two factors, $2^2 = 4$ combinations exist; for three factors, $2^3 = 8$ combinations exist; for four factors, $2^4 = 16$ combinations exist.

Full factorial designs are seldom used for more than four factors since so many experiments are required. Fractional factorial experiments, where only one-half or one-quarter of the combinations are used, are often done for four to six parameters.

— If possible, control runs at the nominal midpoints (0) between the low (–) and high (+) levels of the factors should be included in the experimental design.

Using control runs at the beginning and the end of the factorial experiment, and ideally also during the factorial experiment, will allow detection of any process drift during the experiments.

Control runs at the beginning and end of experiments that do not give similar results indicate the presence of another uncontrolled variable.

Replicate control runs at the nominal values also provide a true estimate of inherent process variation (called experimental error). In addition, these can serve as a basic check for a non-linear curvature effect between the parameters and quality attributes.

— If possible, the parameter effects on both the mean and variation of the quality attributes should be determined. Some parameters may affect the mean only, variation only, or both. This information can be used to minimize the variation while optimizing the mean, which results in a robust process. Standard DoE approaches may be used for this as well as the Taguchi method[25].

3. Optimize with response surface experiments and determine design space.

— Occasionally, the science behind a process will be understood well enough to skip screening and 2-level factorial experiments and start with response surface experiments. If enough information is learned from 2-level factorial studies, no additional experiments will be required and this step can be skipped.

The goal of response surface experiments is to develop an equation that accurately models the relationship between the input parameters and output quality attributes. This equation is then used to determine the design space region of the input parameters where the output quality attributes will meet specifications.

The most common response surface experimental designs are Box-Behnken, central composite, 3-level full factorial, and computer-generated D- and G-optimal designs[23].

All of these experiments where at least three levels of the parameters are included in order to estimate curvature (quadratic) effects. The results are analyzed to determine regression equations to model the process with such computer programs as Minitab, JMP, and SAS[24].

— Another aspect of optimization is to develop a robust process. The regression equations already developed can be used to locate input parameter settings that are "forgiving;" i.e., when the process is run at these settings, variation in the input parameters will not result in unacceptable variation in the quality attributes. The idea is to stay away from boundaries or areas in the parameter design space where variation in the parameter will result in rapid quality deterioration.

This is accomplished by using the quadratic and interaction effects to minimize variation. The Taguchi method of experimental design mentioned earlier uses a slightly different approach to also develop robust processes.

— The results may also be used to calculate the percent of total variation attributable to each parameter. This is called a variance components analysis. The input parameters contributing the most to the output quality attribute variation can be controlled the most tightly, made robust by running the process at a particular level of the other parameters, or improved by a process design change to reduce the impact of the parameter.

4. Confirm DoE results

Once the design space region for the input parameters that result in quality attributes meeting specifications has been determined, additional experiments can be used to confirm the expected DoE results. This may consist of running a few experiments at various parameter combinations to verify that the DoE equation adequately predicts the results. In some cases, where there is already good confidence in the DoE results, Stage 2 PPQ results may be used. For further information on DoE, see Montgomery[26] or Box, Hunter, and Hunter[27].

8.2.2 Statistical process control and process capability

Statistical Process Control (SPC) may be used to determine if a process is stable, predictable, and in statistical control. Process capability is used to determine if the process is capable of consistently meeting specifications. A process is considered stable or 'in statistical control' when only random variation around a stable process mean is observed, i.e., only natural, common causes of variation are present.

Figure 8.2.2-1 Illustrates a stable process that is in classical statistical control

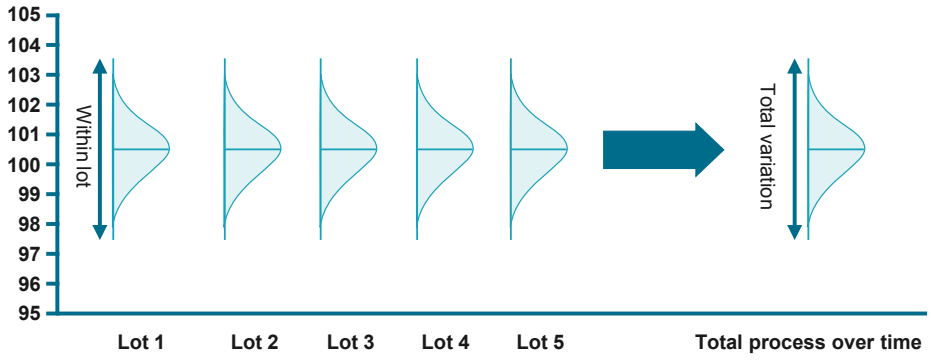
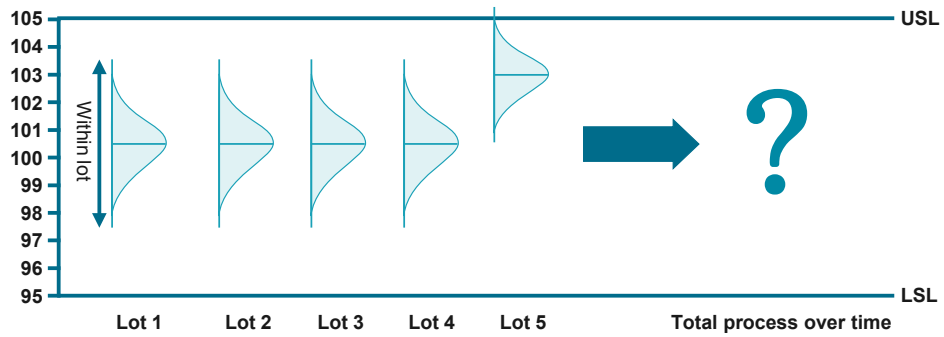


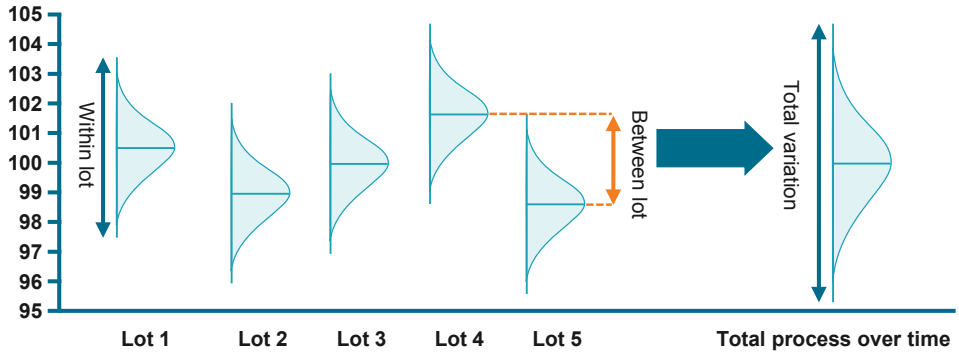
Figure 8.2.2-2 Shows a process that is not in statistical control and has a special cause of variation occur at lot 5



A more complex form of a process that is also stable and in control is shown in Figure 8.2.2-3. This pattern is typical of many processes where there is variation both within and between lots, but the

variation between lots is in control. One purpose of validation and CPV is to determine both within-lot and between-lot variations.

Figure 8.2.2-3 A Process with both Within-lot and Between-lot Variations



8.2.2.1 Statistical process control charts

Statistical process control charts are used to determine if a process is stable and in statistical control, or if there are special causes of variation present in the process. The basic procedure to construct a Statistical Process Control (SPC) chart to assess process stability is as described below:

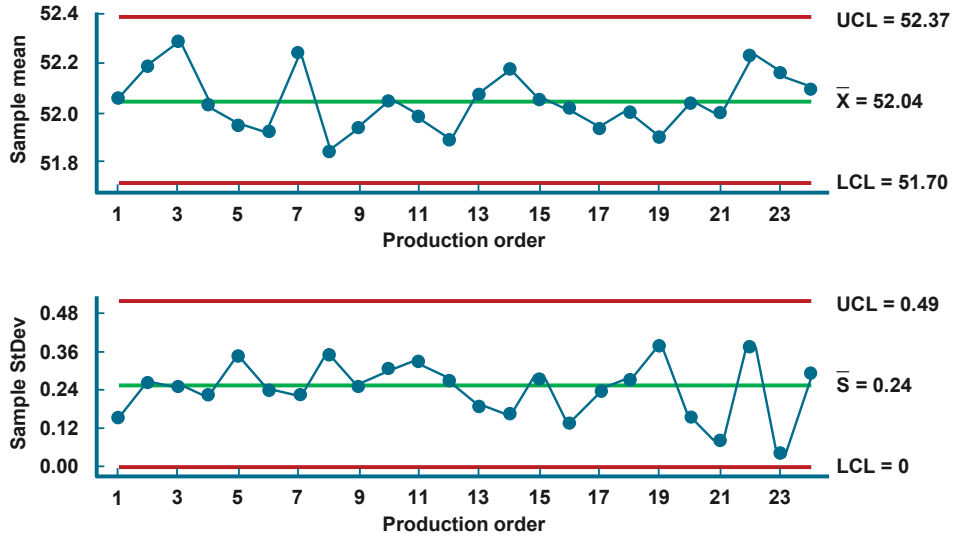
- Data from the process is collected over time. Ideally, at least 20 subgroups should be collected, but preliminary limits may be made with less data and updated as more data become available[23]. Other references, such as ASTM E2587[28], have more detailed recommendations for the amount of data to collect initially. The summary statistics from each subgroup is plotted over time, such as mean (Xbar), standard deviation (S), percent nonconforming, or individuals.
- Centerlines are drawn at the grand average of the statistic being plotted.
- The standard error is calculated of the plotted statistics and control limits are drawn at three standard errors on either side of the centerlines. These limits are called '3-sigma' control limits.

Values that fall outside the control limits indicate that special cause variation is likely to be present, and the causes for these excursions should be investigated. In addition to a single value beyond the 3-sigma limits, there are many other rules that may be used to check for process stability. Of these, the most commonly used are:

- 8 in a row above or below the mean.
- 2 out of 3 beyond 2-sigma limits.
- 4 out of 5 beyond 1-sigma limits.
- 6 in a row increasing or decreasing.

Figure 8.2.2.1-1 shows an example of an Xbar/S-chart for fill weight, where five vials from single-head filler were sampled every 15 minutes over a six hour production order or lot, for 24 samples. Both the mean and standard deviation appear to be stable, with no values exceeding the 3-sigma control limits. The process appears to be stable and in a reasonable state of statistical control.

Figure 8.2.2.1-1 Xbar/S Control Chart for Fill Weight, n=5 per group



Control charts can be used during all three validation stages for within- or between-lot data. During Stages 1 and 2, they can be used to determine if the process is stable and in control in order to commence commercial production.

Control charts are particularly useful during Stage 3 (CPV Stage). Special causes of variation affect almost every process at some point. Control charts help identify when such a special cause has occurred and when an investigation may be needed.

As special causes are identified and corrective actions taken, process variability is reduced and quality improved. Control charts are easy to construct and can be used by operators for ongoing process control.

8.2.2.1.1 Factors to consider in designing a control chart

There are many factors to take into consideration when designing control charts, including:

- Characteristic(s) to chart.
- Type of control chart to use.
- Sample size and frequency of sampling.
- How quickly the chart will detect a problem of a given magnitude.
- Economic factors (costs of sampling and testing, costs associated with investigating out-of-control signals, costs of allowing defective units to reach the customer).
- Production rate.

8.2.2.1.2 Types of control charts

Control charts may be used for both variables and attributes data. Variables data are those that are measured quantitatively, such as potency, weight, and pH. Attributes data are those obtained by counting, such as number of rejected lots per month and percent of tablets rejected.

For variables data, it is important to control both the process mean and variation, and both should be charted. A change in either indicates special causes acting on the process that should be investigated.

For attributes data, such as percent nonconforming units or number of cosmetic flaws in 100 glass vials, only a single chart for the variable of interest might be kept. A separate chart for variation is not necessary because the variation of attributes data is related to the mean value.

When possible, it is preferable to use variables data rather than attributes data. A measured value contains more information than an attributes value, such as conforming/nonconforming. Control charts for variables data have more statistical power and can use smaller sample sizes than attributes data charts.

Although the underlying theory for control charts assumes normally distributed and uncorrelated data, control charts are robust and generally work well even when these assumptions are not met[23].

One exception is for attributes data with low values, which have a highly skewed non-normal distribution. Bioburden monitoring is an example of a process with low attributes data values, where many or most of the data are zeroes. Exact probability control limits use of the negative binomial, Poisson, or other suitable distribution that might be used to prevent too high of a false alarm rate; see *"Understanding Statistical Process Control, 2nd ed."*[25].

8.2.2.1.3 Process capability

Statistical process control charts answer the question, "Is the process stable and consistent?"

Process capability statistics answer the question, "Is the process capable of meeting specifications?"

Process capability is the ability of a process to manufacture product that meets pre-defined requirements. It can be assessed using a variety of tools, including histograms and process capability statistics.

The two most common process capability statistics, Cp and Cpk, are shown in Figure 8.2.2.1.3-1.

Cp measures the capability of a process to meet specifications if it is centered between the specification limits. Cpk assesses if the process is actually meeting specifications when any lack of centering is considered.

Examples of normally distributed processes with various values of Cp and Cpk are shown in Figure 8.2.2.1.3-2.

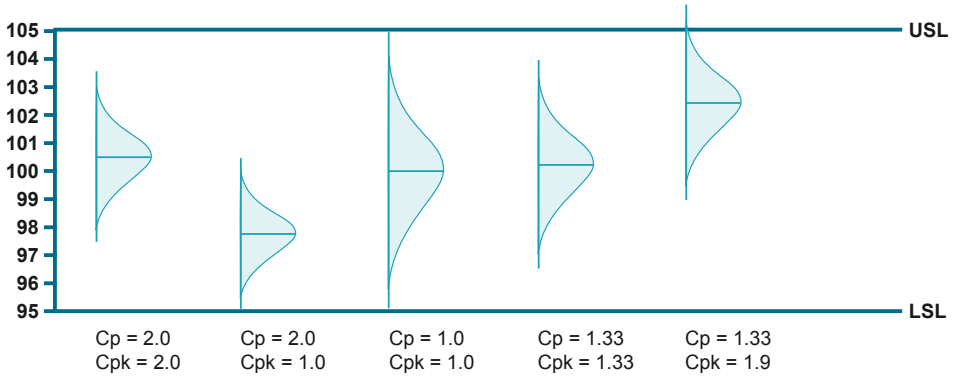
Figure 8.2.2.1.3-1 Process Capability Statistics Cp and Cpk

$$C_p = \frac{(USL - LSL)}{6s}$$

$$C_{pk} = \text{Min}\left[\frac{(\bar{\bar{x}} - LSL)}{3s}, \frac{(USL - \bar{\bar{x}})}{3s}\right], \text{ where}$$

USL = Upper specification limit
LSL = Lower specification limit
$\bar{\bar{x}}$ = Grand average of all the data
s = Standard deviation

Figure 8.2.2.1.3-2 Examples of Process Capability Statistics Cp and Cpk



If the process is in statistical control, the standard deviation (s) used to calculate Cp and Cpk in Figure 8.2.2.1.3-1 is usually based on estimates derived from the control chart for the standard deviation or range.

If a process is in statistical control, there will be little difference between Cp and Pp or between Cpk and Ppk.

If a process is not in statistical control, it is difficult to determine process capability because of the lack of process stability; see Figure 8.2.2-2.

If a process is not in statistical control, Pp and Ppk are preferred as they include variation due to lack of stability.

Figure 8.2.2.1.3-2 shows the relationship between the process capability index Cpk and the probability that the process output will be out-of-specification. The table assumes the process is in statistical control, normally distributed, and centered between the lower specification limits (LSL) and upper two-sided specification limits (USL). If the process is not normally distributed, process capability methods for non-normal distributions should be used.

Table 8.2.2.1.3-2 Relationship between capability and % or per million nonconforming

USL-LSL	±2σ	±3σ	±4σ	±5σ	±6σ
Cpk	0.67	1.00	1.33	1.67	2.00
Non-conforming	4.6%	0.27%	63 ppm	0.6 ppm	2 ppb
% of specification used (±3σ limits)	150	100	75	60	50

Acceptable values for Cpk depend on the criticality of the characteristic, but 1.0 and 1.33 are commonly selected minimum values. Six-sigma quality is usually defined as Cp≥ 2.0 and Cpk ≥ 1.5 for a normally distributed process in statistical control.

See Wheeler[23] or Montgomery[26] for more complete treatments of SPC and process capability.

8.2.3 Statistical acceptance sampling

Statistical acceptance sampling is another commonly used statistical tool for validation.

The general principle is that the sampling used for validation should provide higher confidence than sampling used during routine production. In validation, larger sample sizes, more replicates, and other such factors are typically used.

Commonly used acceptance sampling plans for validation to ensure that a high percentage of individual units (e.g., tablets, vials) are conforming are:

- Single sampling for attributes data.
- Double sampling for attributes data.
- Variables sampling for quantitative data.

Samples should be representative of the entire population being sampled. Random, stratified, and periodic/systematic sampling are the most commonly used approaches.

Targeted sampling to include suspected worst-case locations within the batch or process may be used when appropriate. For example, samples from the very beginning and end of the batch may be selected to assure that these potential trouble spots are included, while the rest of the required samples are randomly selected from throughout the batch.

Reaching at least 90% confidence at the end of PPQ is desirable when using statistical acceptance sampling for validation with little prior confidence. This means that the combined information from the PPQ runs shows that there is at least 90% confidence that the validation performance level has been met; 90% confidence is recommended as the minimum because it is the traditional confidence associated with detecting unacceptable quality levels (called the Rejection Quality Level [RQL], Lot Tolerance Percent Defective [LTPD], or Limiting Quality [LQ])[29].

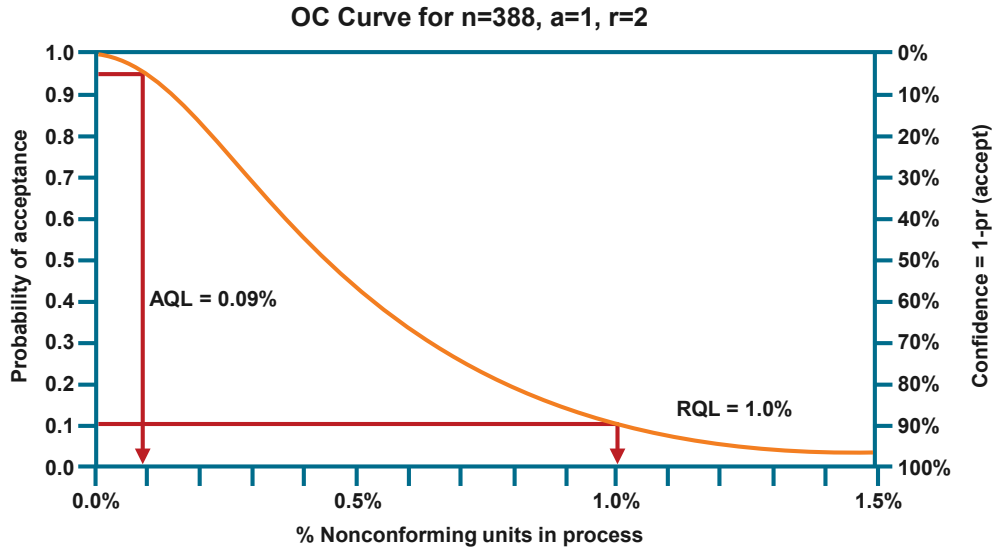
Note that this use of the term "confidence" is different than the traditional 95% confidence of acceptance associated with the Acceptance Quality Limit (AQL) in routine lot acceptance sampling.

The AQL relates to the Type I error of incorrectly rejecting an acceptable lot, while the 90% minimum confidence recommended here refers to the Type II error of incorrectly accepting an unacceptable process.

- Single sampling for attributes is the simplest type of sampling. For example, a sampling plan of n=388 units, accept on 1 non-conformance, reject on 2, would detect a 1% non-conformance rate with 90% confidence.

The statistical operating characteristic curve for this sampling plan is shown in Figure 8.2.3-1.

Figure 8.2.3-1 Example of an Operating Characteristic Curve



- Double sampling plans for attributes may take a second set of samples depending on the results of the first set.

  For example, the double sampling plan n1=250, a1=0, r1=2; n2=250, a2=1, r2=2 will also detect a 1% non-conformance rate with 90% confidence.

  The values n1 and n2 are the stage 1 and stage 2 sample sizes; a1 and a2 are the accept numbers; r1 and r2 are the reject numbers. If a1=0 non-conformances are found in the first set of n1=250 samples, the sampling plan is passed. If exactly 1 nonconformance is found in the first sample of n1=250 units, an additional n2=250 units are sampled.

  If the total number of non-conformances found in the combined 500 samples is no more than a2=1, the sampling plan is passed.

  If the total number of non-conformances found in the combined 500 samples is r2=2 or greater, the sampling plan is failed. One advantage of double sampling plans is that they often have lower false reject rates; i.e., good processes will not fail the sampling plan as often.

- Several types of variables sampling plans may be used for validation, one of the most common being the normal tolerance interval.

  For example, one normal tolerance interval sampling plan for two sided specifications is n=30, k=3.17. If the average ± 3.17 standard deviation is contained within the specification limits, the sampling plan is passed. This plan also provides 90% confidence in detecting a 1% non-conformance rate.

- Variables sampling plans assume the data are normally distributed, and this assumption should be confirmed with a suitable normality test. An advantage of variables sampling plans is that they often are able to use much smaller sample sizes than attributes plans to provide the same confidence.

  Example: *The validation will show with 90% confidence that the process averages ≤0.1% leaking containers after simulated shipping. This requires an attributes sampling plan of n=2300, accept=0, reject=1.Three lots will be used for the Stage 2 PPQ, so n = 2300/3 = 767 containers per lot will be inspected for leakage after simulated shipping. If no leakers are found in the combined n=2300 samples, the sampling plan is passed.*

ANSI/ASQ Z1.4 "Sampling Procedures and Tables for Inspection by Attributes" and ANSI/ASQ Z1.9 "Sampling Procedures and Tables for Inspection by Variables" are commonly used sampling plans for routine production[47, 48].

They should be used with care for validation, since they may not provide a high enough level of confidence.

For example, one Z1.4 tightened sampling plan for AQL 0.4% is n=315, a=2, r=3. If a validation lot has 2 nonconforming units in a sample of n=315, the validation lot would pass the sampling plan. (However, note that 2/315 = 0.63% is substantially larger than the AQL of 0.4 %.)

Finding 0.63% nonconforming units in a sample does not provide high confidence that the process is ≤0.4% nonconforming, if that was the goal of the PPQ. If Z1.4 and Z1.9 are used for validation, the Operating Characteristic curves in the standards should be consulted to verify that the desired confidence is achieved.

Not all sampling plans used to make accept/reject decisions are for percent nonconforming units. For example, the USP test for content uniformity (of dosage units) is specified in terms of a two-stage sampling plan given in USP. In this case, validation sampling should provide confidence that the USP test can be passed with high confidence[30].

Example: *The sampling plan will show with 95% confidence that the routine USP content uniformity (of dosage units) test requirements can be met.*

8.2.4 Number of lots for stage 2 Process Performance Qualification (PPQ)

The number of lots required for Stage 2 PPQ depends on the following:

- Prior information about the process available from Stage 1 Process Design or quality history from similar processes. The more scientific evidence already available to establish that the process is capable of consistently delivering quality product, the fewer the number of PPQ lots required.
- Risk factors, including criticality of the product characteristics and extent of in-process quality control (e.g., PAT, 100% inspection).
- Type of data: attributes (pass/fail) or variables (quantitative).
- Statistical confidence desired.
- Production rate (i.e., how often lots are produced). If only one commercial lot is produced per year, it will not be feasible to require a PPQ with a large number of lots.

Depending on the prior information and/or risk involved, it may not be necessary to determine the number of PPQ lots using statistical methods.

Regardless of the number selected and acceptance criteria used, the data collected during PPQ should be statistically analyzed to help understand process stability, capability, and within (intra) and between (inter) lot variation.

Lots produced during Stage 1 under similar conditions as the PPQ lots may potentially be used to reduce the number of lots required at PPQ. This can be done using Bayesian statistical methods or by combining the Stage 1 data and Stage 2 PPQ results, if there are no significant differences in the data[31].

The criteria for combining Stage 1 data and PPQ data should be specified before the PPQ lots are produced. These criteria would typically include such statistical comparisons as ANOVA (analysis of variance) to compare lot means, Levene/Brown-Forsythe or Bartlett's test to compare the lot standard deviations, SPC charts, and equivalence tests to demonstrate that Stage 1 and PPQ data are similar[32].

8.3 Process Analytical Technology (PAT)

PAT is a method of process control, where the product or in-process material quality attributes are monitored and measured, and the process parameters and conditions are altered to maintain those quality attributes. PAT can provide high levels of product quality assurance through the analysis of material attributes and process adjustments so that process quality attributes do not vary outside of the prescribed ranges, and product and material quality is maintained[33].

It also relies on the proper design, use, and validation of the PAT monitoring, measurement, and control loop systems. The validation of the PAT system is based in part on the following principles:

1. Measurement of the correct product and in-process quality attributes.

2. Accuracy and understanding of the correlation between these quality attributes and the process parameters that would be adjusted.

3. Reliability, suitability, capability, and accuracy of the monitoring, measurement, and process control loop or adjustment systems.

4. Acceptable performance of the PAT system throughout commercial manufacturing, including the ability to identify opportunities for process improvement.

Prior to the selection of the PAT system, the product and manufacturing process must be developed and well understood. Selecting the right PAT system should be based on fitness for purpose, system ruggedness, and vendor customer service.

Selection criteria should include, but are not limited, to, specificity, sensitivity and accuracy, electronic integration requirements of information technology compatibility, data management, and communication.

Table 8.3.1-1 provides a partial list of PAT systems, each of which may provide information helpful to the understanding and validation of the respective drug manufacturing processes.

Table 8.3.1-1 Examples of PAT tools and their application

PAT tools	Process	Application
Laser-based particle size analyzers	Crystallization, granulation, milling	Particle size, particle shape
FT-Infra-Red	Chemical reactions	Reaction progress and completion
	Raw materials	Identification
Nuclear magnetic resonance (NMR)	Chemical reactions	Reaction progress and completion
Light induced fluorescence (LIF)	Blending	End-point determination
	Compression	Content uniformity, assay
Near infra-red spectroscopy (NIR)	Blending, granulation	End-point determination
	Drying	Water content
	Compression	Content uniformity, assay
	Fermentation	Nutrient content
	Raw materials	Identification
Raman spectroscopy	Blending	End-point determination
	Granulation	Water content, polymorphism
	Compression	Content uniformity, assay
	Raw materials	Identification
	Lyophilisation	Water content, polymorphism
Refractive Index (RI)	Blending or mixing	End-point determination
Turbidity	Blending or mixing	End-point determination
Microwave	Blending, granulation	End-point determination, water content
Acoustic absorption/ emission	Blending, granulation	End-point determination, water content
Effusivity	Blending, granulation	End-point determination, water content
pH, Conductivity, Dissolved oxygen (DO), Oxidation – reduction potential (ORP)	Fermentation	Reaction progress, end-point determination
Focused beam reflectance measurements (FBRM)	Formulation of suspensions and emulsions	Measure particles and droplets
Rapid high–performance liquid chromatography (Rapid HPLC)	Fermentation	Nutrient content, reaction progress, end-point determination
	Chemical reactions	Reaction progress and completion

During PAT system design, an understanding of how process parameter changes affect product attributes is established.

Process monitoring and control systems are designed and linked to specific product attributes. Ranges of acceptable process parameter variation are determined. PAT design efforts should include: risk assessment, system feasibility and selection, in-process application development, and consideration of regulatory requirements.

The Risk Assessment should identify product and in-process quality attributes that have an effect on final product quality. Quality attributes, and corresponding process steps and conditions that are not monitored by the PAT system, may require other means to assure or validate performance. Having PAT systems is expected to lower the risk to product quality, by having additional controls, timely responses, increased detectability, increased understanding, and information (e.g., identification, measurement, control of CQAs). These features enable a more informed risk assessment decision.

Tools for the assessment and evaluation of PAT processes and systems are discussed in Section 8.1, as well as PDA TR 54, ICH Q9 and other publications[12, 13, 30].

One key to effective PAT process control is the reliable operation of instruments and equipment. For implementation, an implementation and validation team should be assembled to categorize the validation requirements and propose acceptance criteria for each unit of operation, based on the application or intended use of the PAT system and method.

The Continued Process Verification Stage is where information is obtained to confirm that the PAT system performs at an acceptable level throughout commercial manufacturing. It also determines where product and in-process quality attributes, or process parameters fall out of expected ranges; those that do are identified, investigated for cause, and addressed.

Evaluation of PAT and or in-process derived data should be part of the quality system and review processes[11].

Where data trending shows excursions in anticipated monitoring results, analysis of the cause of the excursion should be conducted to determine if changes to the control system are needed or opportunities for process improvement can be identified.

When variables are found that are not being monitored adequately, changes to the monitoring methods may be needed.

8.4 Technology transfer

For a lifecycle approach to process validation to be effective, all information that is available to support the understanding of the process, including that from other sites and similar processes, should be considered. This information should be useful, accurate, and complete. The goal of technology transfer (TT) activities is to communicate product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization.

Technology transfer can occur at different stages of the process validation lifecycle. If a new process is being transferred from research and development to commercial manufacturing, the technology transfer may occur between Stages 1 and 2. However, if it occurs after a product has been launched and it is in the commercial manufacturing phase, then transfer will occur during Stages 2 and 3.

Refer to Table 8.4-1 below for distribution of technology transfer activities throughout the product lifecycle, which outlines the increasing knowledge and process understanding with each technology transfer.

Table 8.4-1 Technology transfer activities throughout product lifecycle

Process validation lifecycle stage	Activities	Knowledge development/data	Application
Stage 1	Process Design provides product and process development knowledge and data for technology transfer.	Development Report ▪ Development history, including criticality assessments and DoE with sources of variation ▪ Data and knowledge development from stability studies and development batches ▪ Rationale for specifications and methods ▪ Critical Process Parameters (CPPs) ▪ Critical Material Attributes (CMAs) ▪ Critical Quality Attributes (CQAs) ▪ KPPs, PARs, NORs ▪ Manufacturing process description, equipment train	Technology Transfer Batches manufactured during Stage 1are intended to establish comparability of product quality between sites and develop filing/market authorization data. Development Report summarizes activities from Stage 1.
Stage 2	Most technology transfer activities in a product lifecycle are carried out at Stage 2 ▪ Development of transfer strategy ▪ Manufacturing of commercial scale PPQ Batches. ▪ Site equivalency analysis (from receiving to sending unit). ▪ Transfer and validation of analytical methods ▪ Confirming CPPs at commercial scale. ▪ Conducting stability studies at commercial scale under commercial package. configurations. ▪ Confirming risk assessments, criticality analysis. ▪ Establish sampling plans and statistical methods at commercial scale. ▪ Evaluation of personnel qualifications and training.	Technology Transfer Strategy: ▪ Product and process description (as designed from Stage 1, and reported in the development report). ▪ Assessment of site change requirements; e.g., post-approval and, prior-approval with rationale. Category under SUPAC guidelines, if applicable. ▪ Number of batches required to meet transfer requirements, including validation/PPQ strategy/matrix approach. ▪ Specifications and methods transfer plan. ▪ Validation plan. ▪ Control strategy	Technology Transfer Batches manufactured during Stage 2 are intended to reproduce the manufacturing process, including components and composition configurations at the transfer site, and to conduct PPQ. Equivalency between sites is intended to compare equipment and facilities to assure that they are equivalent and qualified for commercial manufacturing.

Table 8.4-1 Technology transfer activities throughout product lifecycle

Process validation lifecycle stage	Activities	Knowledge development/data	Application
Stage 3	Technology Transfer activities at Stage 3 are most likely carried out for products that have already been validated and are on the market. These are known as post-approval changes under the SUPAC guidelines (for small molecules), and apply to changes to alternate manufacturing sites within a company or to contract manufacturers.	Similar to activities in Stage 2, a Technology Transfer Strategy is recommended. The Strategy would include data listed under Stage 2 of this Table. For products at Stage 3, additional data and knowledge will be available. This should be considered and evaluated prior to starting technology transfer activities. At Stage 3, technology transfer activities may pose opportunities for process improvement at the receiving site using historical control and quality systems data. Valuable data to evaluate include: ▪ Stage 2 Technology Transfer and Validation Reports ▪ Annual product reports, including process trending and process capability ▪ History of investigations, CAPA, change control, OOS, complaints reports, field alerts, stability studies, yield variations ▪ Executed batch records ▪ Sampling and test plans ▪ Analytical data ▪ Conduct gap analysis at current vs. transfer site to assess risks and variations, including – Manufacturing equipment train design and operating principle, as well as qualification status – Confirmation of CPPs, equipment operating ranges at new site – Suppliers – Personnel – New site state of compliance Technology Transfer Strategy ▪ Product and process description (as designed from Stage 1,and reported in development report and validation reports) Assessment of site change regulatory requirements, post-approval, with rationale ▪ Number of batches required to meet transfer requirements, including validation/PPQ strategy/Matrix Approach ▪ Specifications and methods transfer plan ▪ Validation plan and control strategy	Transfer to a new location within a manufacturing site, to an alternate site of the company, or to a contract manufacturer. Filing requirements are defined by SUPAC, as these have different implications from the regulatory standpoint. Validation requirements apply equally to any of the technology transfer scenarios.

8.5 Knowledge Management

The effective and efficient capture and analysis of process-related information is essential to process understanding and validation. Information that supports process validation should be identified, analyzed, communicated, maintained, and available.

It is important to recognize that knowledge management is not just data collection. It involves a strategic, systemic, and methodical approach that should include the acquisition of data at pivotal process steps, rigorous data analysis, easy access, and controlled storage and dissemination of information about the product, process, and components.

Knowledge management includes systems that capture review and feedback information in an effort to ensure correct decisions were made, and identify where process improvements can be implemented.

Knowledge management systems should be designed, installed, used, and maintained. They play a pivotal role in finding problems and preventing process shifts by providing feedback for continuous improvement efforts[4].

When changes are made in Stages 2 and 3, they should be communicated to all affected parties in an efficient, accurate, and timely manner. Formal Change Control procedures are recommended and required Quality System component[4]. Transparent interaction between teams collecting data, performing risk assessments, and transferring information is essential to the process validation effort. Joint reviews between teams responsible for process development, risk assessments, and data collection should be conducted throughout the lifecycle of the process.

These reviews enable the effective transfer of information from scale-up through full-scale manufacturing batches, and help to ensure that the process operates in a reliable and predictable manner.

9. References

This Guidance was drafted taking into account the inputs from the technical report No. 60 – process validation: a life cycle approach [PDA – Parenteral Drug Association, INC. 2013]. The references mentioned in each section are given below:

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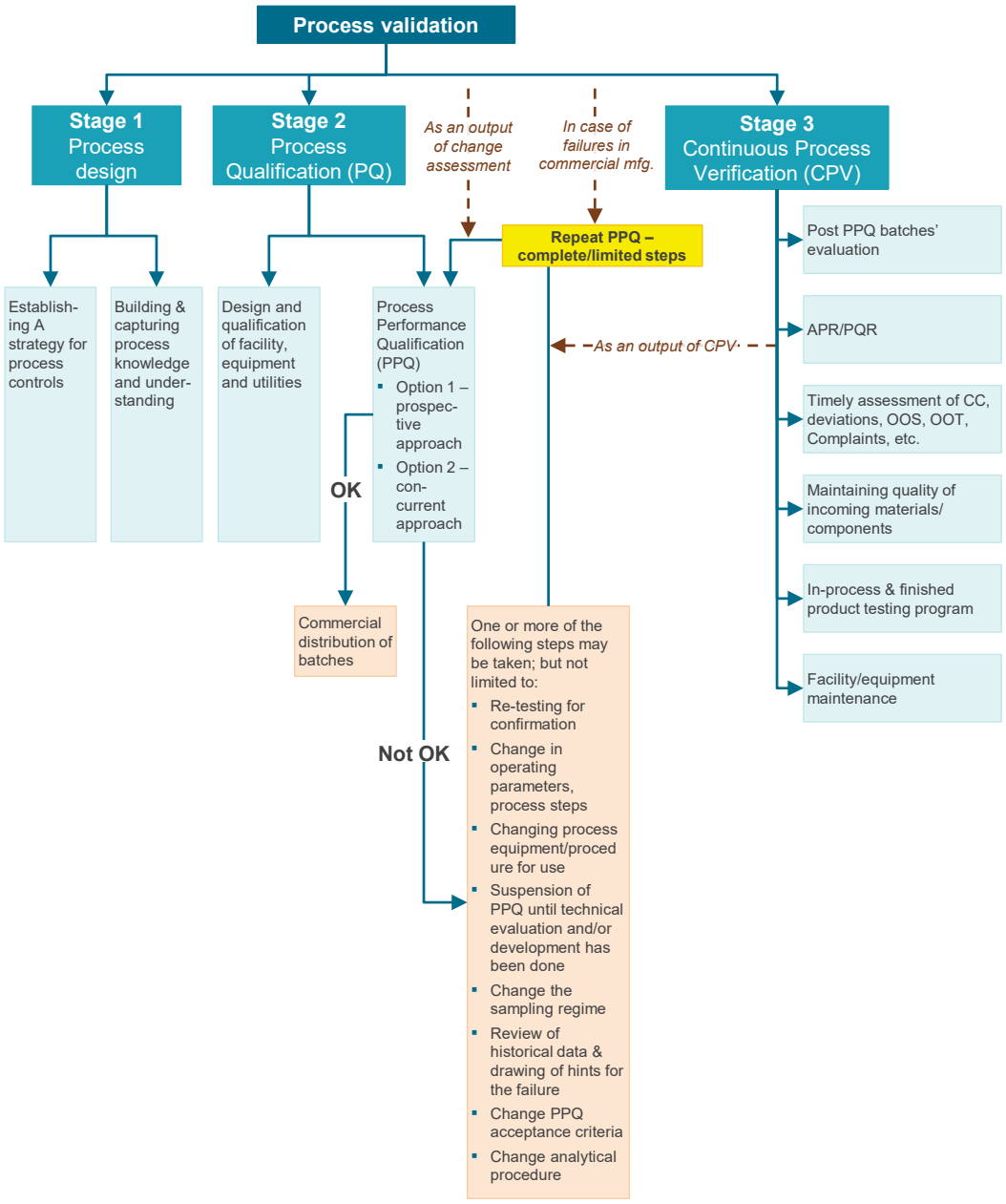
ANNEXURES

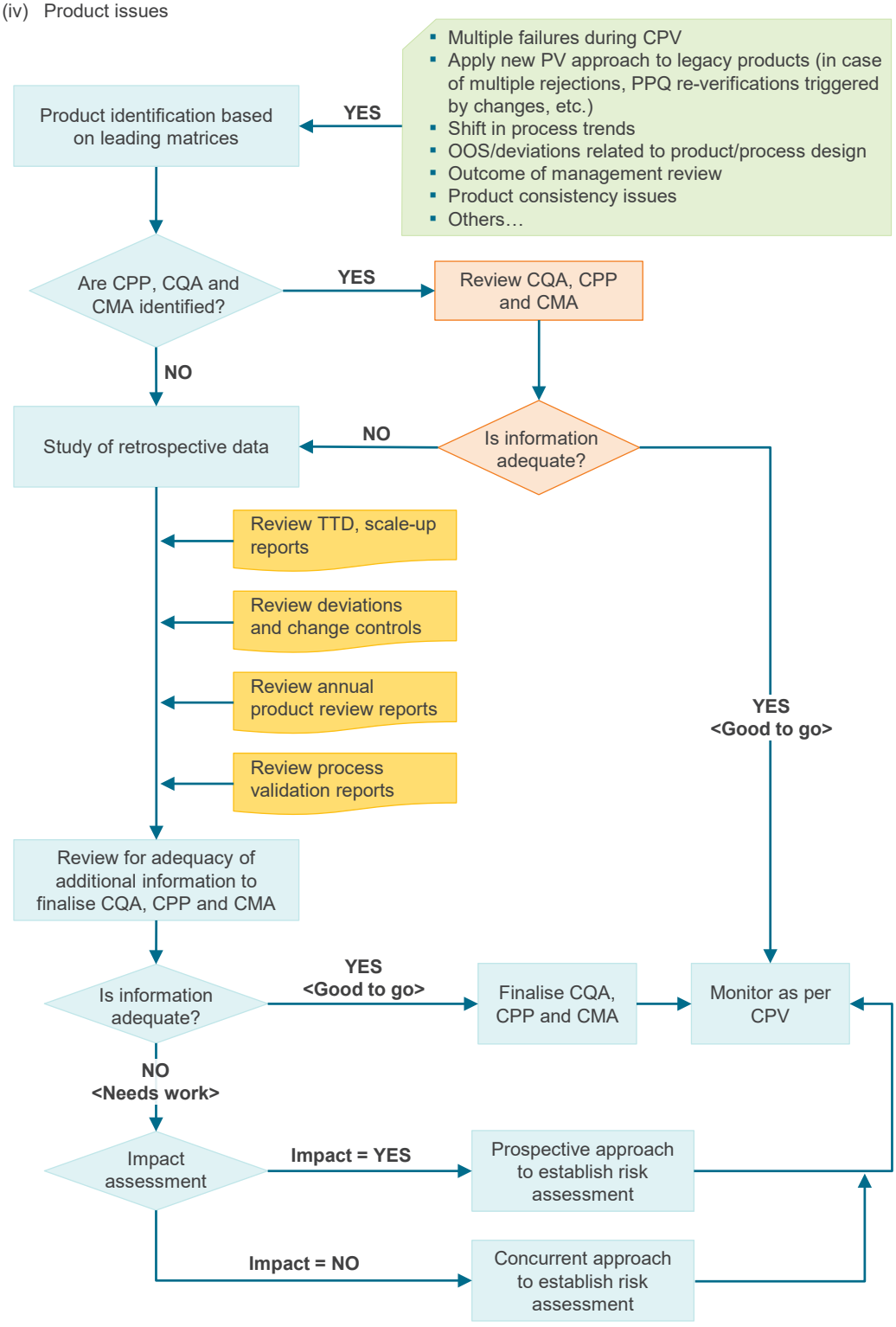
Annexure 1

A: Process validation lifecycle



B: Workflow to address the following issues

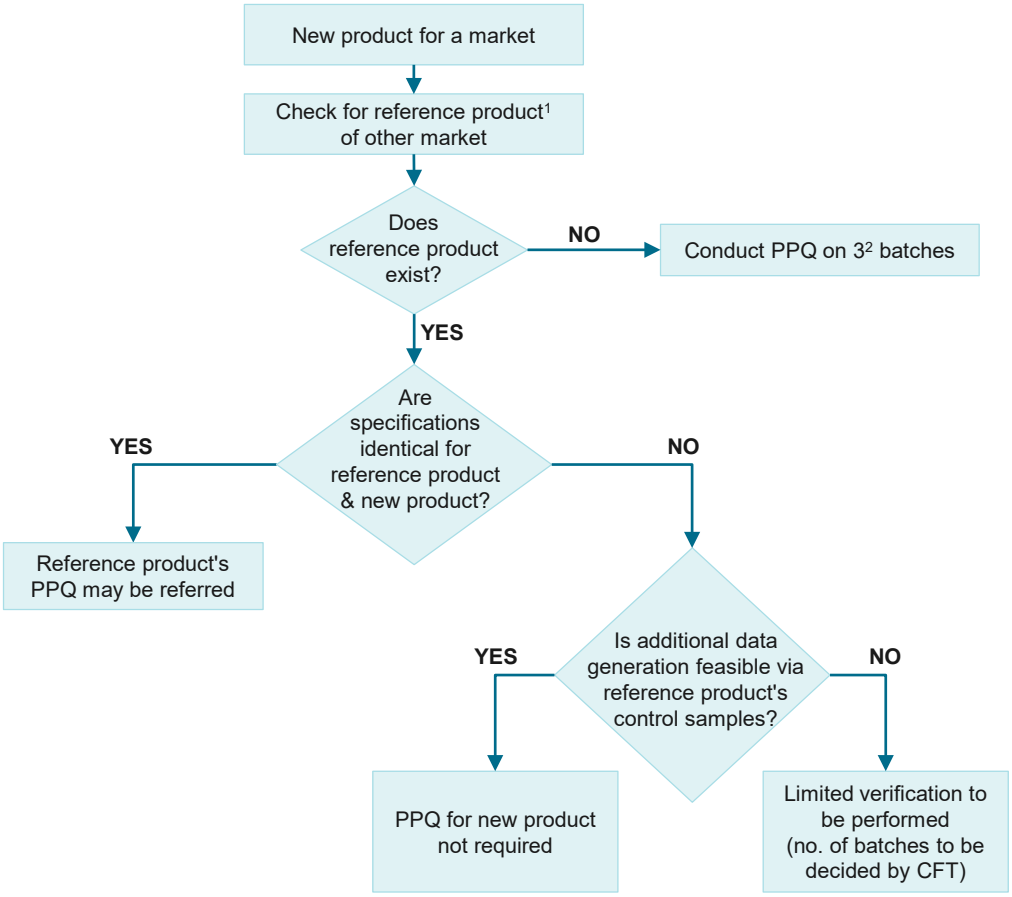
(i) Multiple failures during CPV
(ii) Application of the new PV approach to legacy products
(iii) Address shift in process trends/product consistency issues, and
(iv) Product issues



Annexure 2

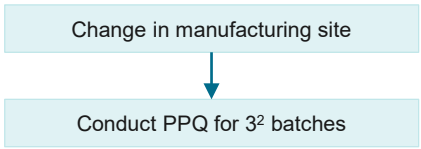
Decision trees: addressing routine changes in process

Decision tree no. 1 – PPQ for new products



1 Reference product means product with same batch size, same equipment used, same unit composition, same API source, same API/KRM specs. (as applicable) and same manufacturing process
2 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 2 – PPQ for change in manufacturing site of product[1]



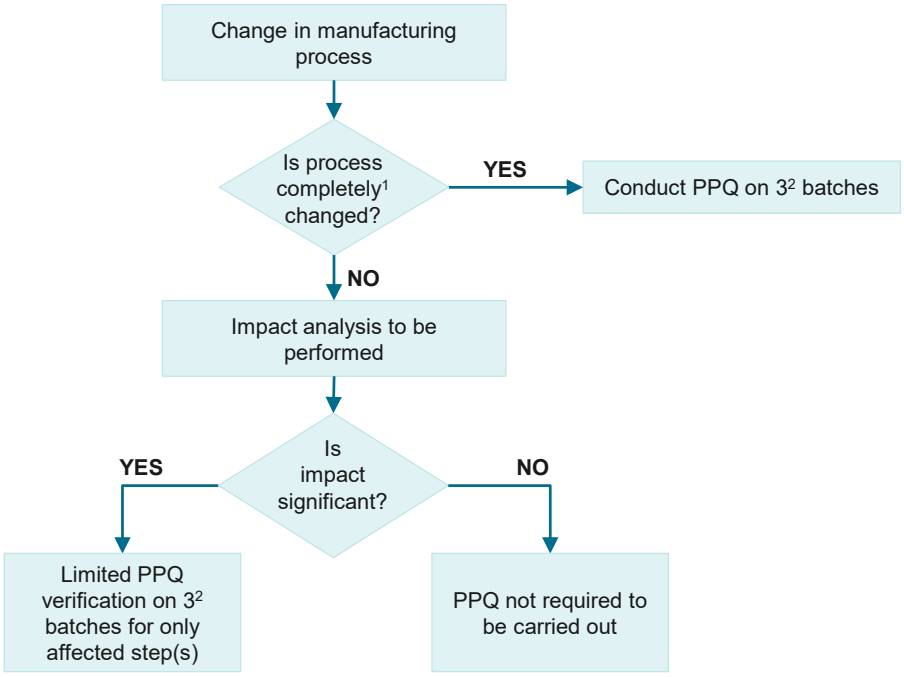
1 Change in manufacturing site means change in the equipment train of existing product (i.e., change in manufacturing site/module/unit, as applicable)
2 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Notes:

a. Reference product indicates existing product in the market.

b. Limited verification should be performed based on GAP and Impact Analysis.

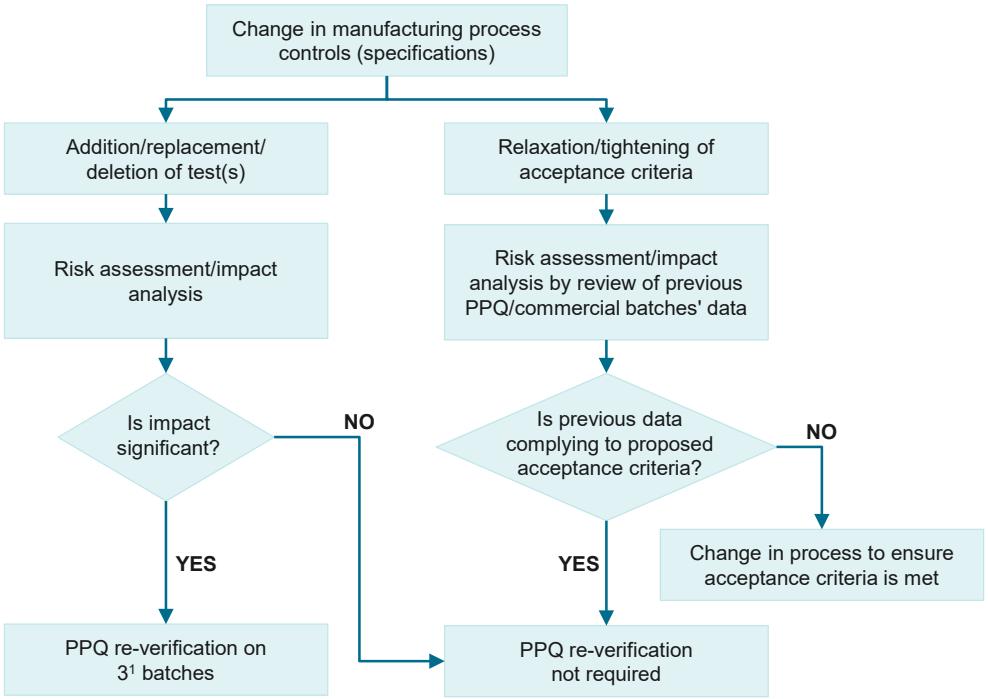
Decision tree no. 3 – PPQ for change in approved manufacturing process



1 Complete process change refers to change in all critical steps of the process
2 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

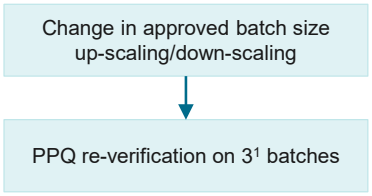
Note: Limited verification should be performed based on GAP and impact analysis.

Decision tree no. 4 – PPQ for change in manufacturing process controls (specs.)



1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

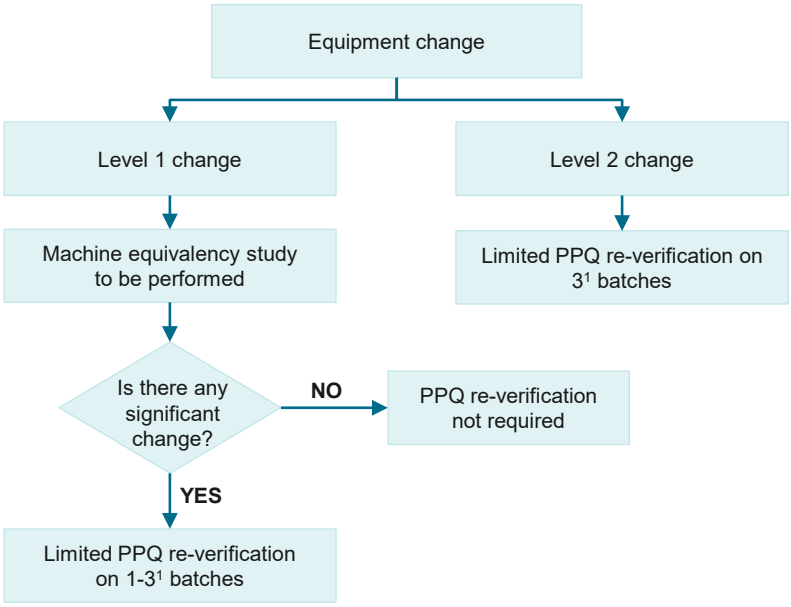
Decision tree no. 5 – PPQ for change in batch size



Note: Changes in previously approved batch size shall include only changes required for scale-up & scale-down; changes in operating principles, process controls and equipment shall not be considered under this category.

1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

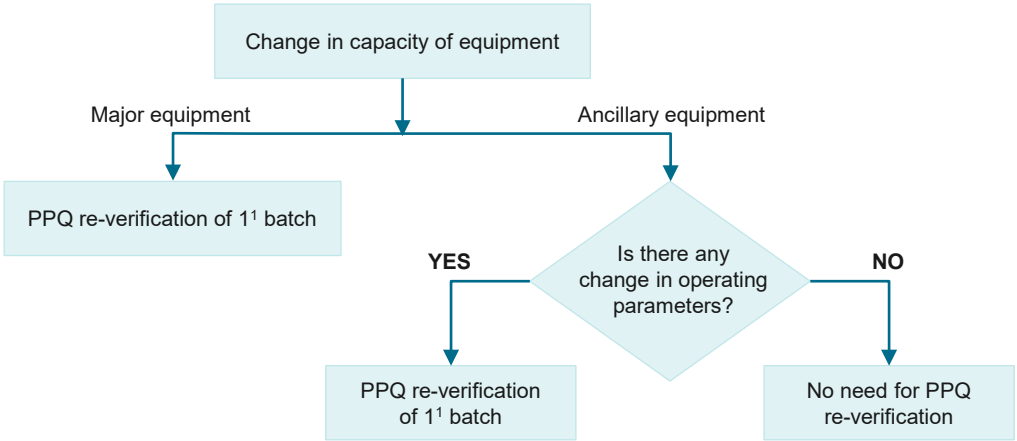
Decision tree no. 6 – PPQ for equipment change



Note: Level 1 change refers to changing with an equipment which has similar operating principle and design; Level 2 change refers to changing with an equipment which has different operating principle and design. *change in the size of the equipment shall not be considered for use of this decision tree*

1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

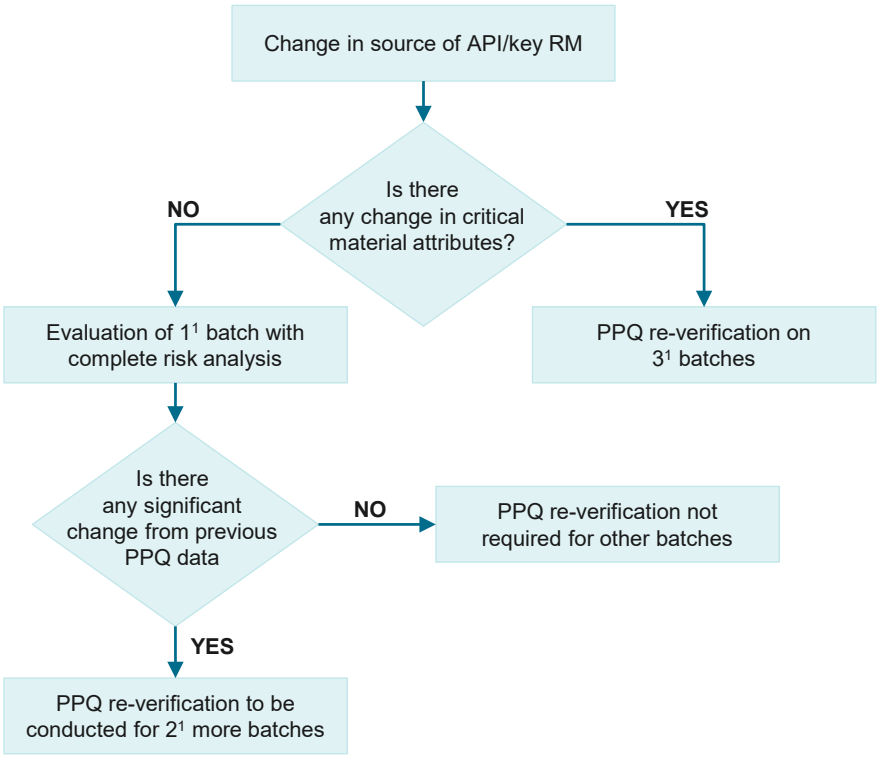
Decision tree no. 7 – PPQ for change in capacity of an equipment



1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc. This decision tree is based on the assumption that there is no change in batch size of the product

Note: Limited verification should be performed based on GAP and Impact Analysis.

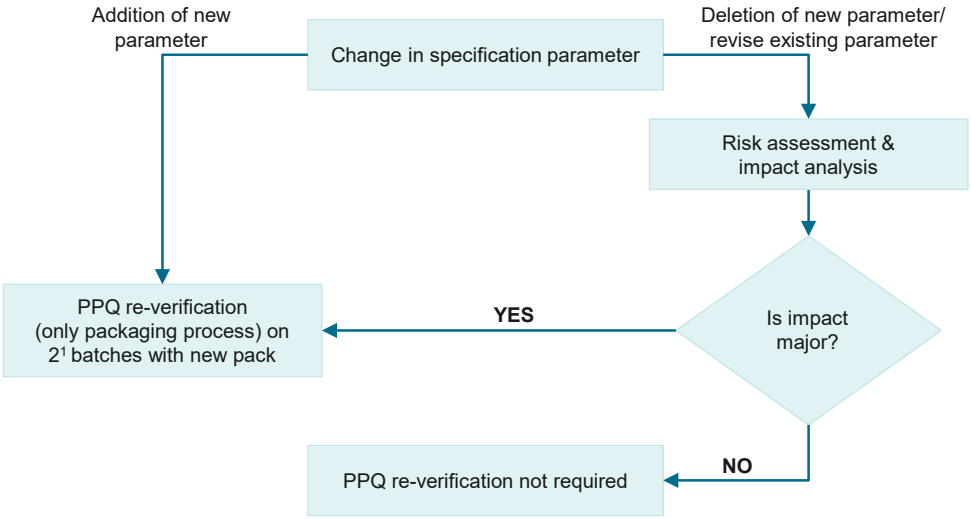
Decision tree no. 8 – PPQ for change in source of API/key RM



1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

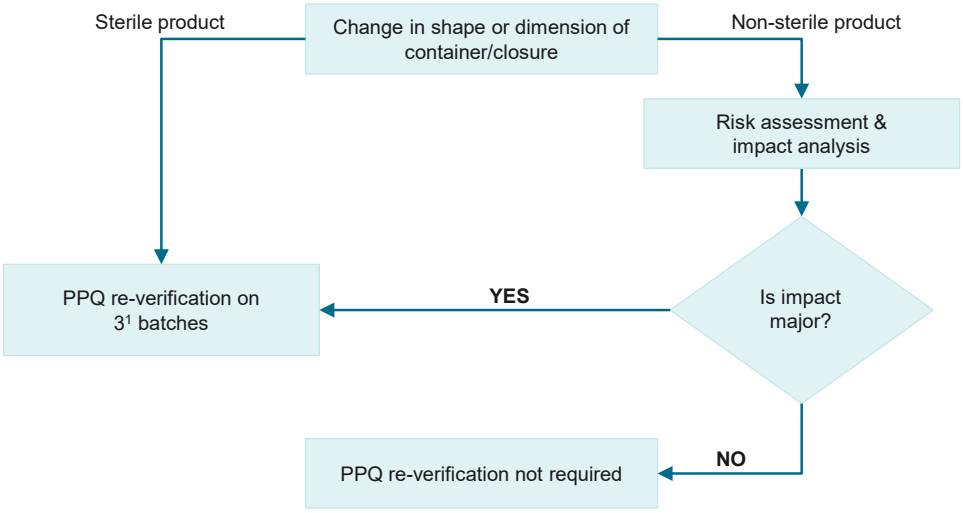
Note: Limited verification should be performed based on GAP and impact analysis.

Decision tree no. 9 – PPQ for change in specification of primary pack of finished product



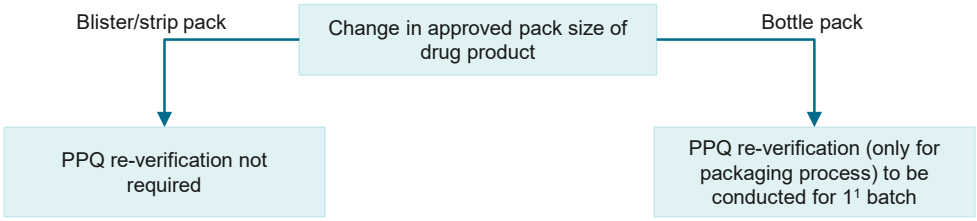
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 10 – PPQ for change in shape/dimension of container/closure of finished product



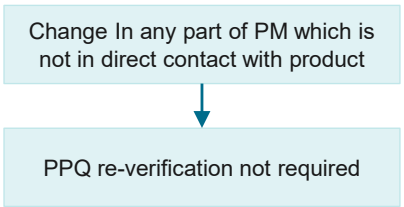
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 11 – PPQ for change in approved primary pack size of finished product



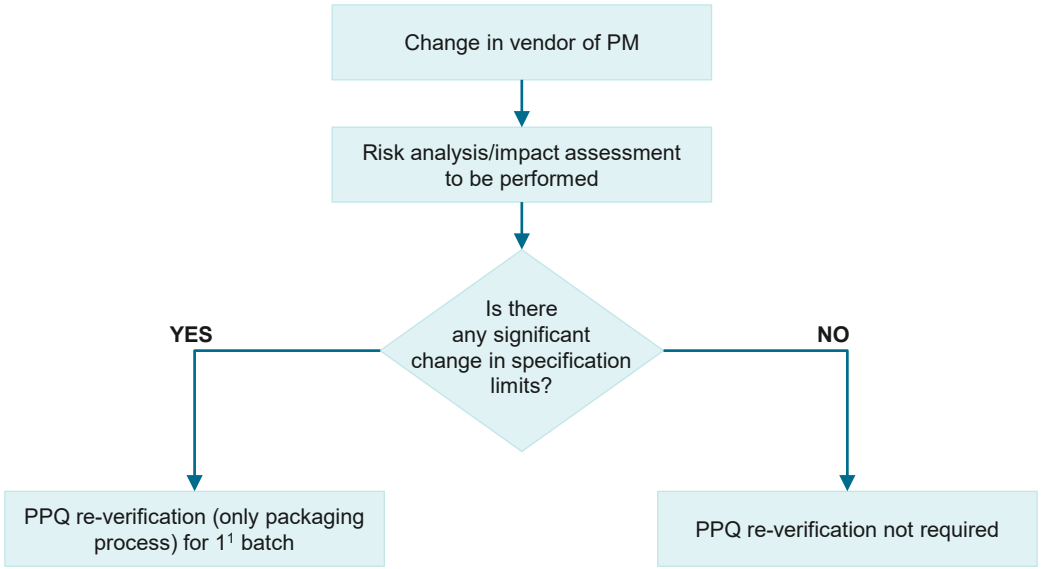
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 12 – PPQ for change in pm which is not in direct contact with product



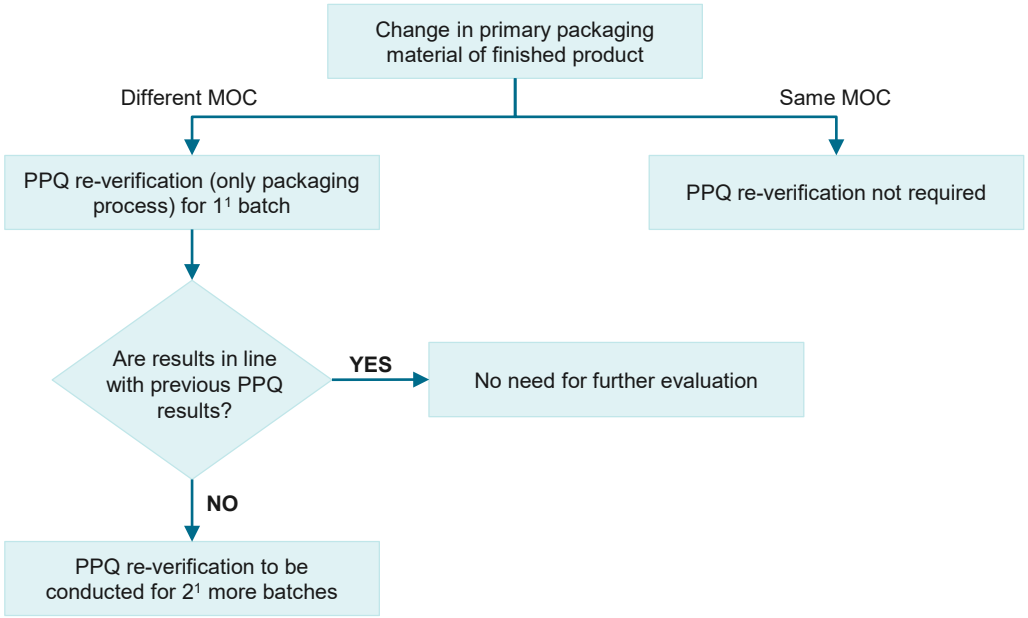
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 13 – PPQ for change in vendor of PM



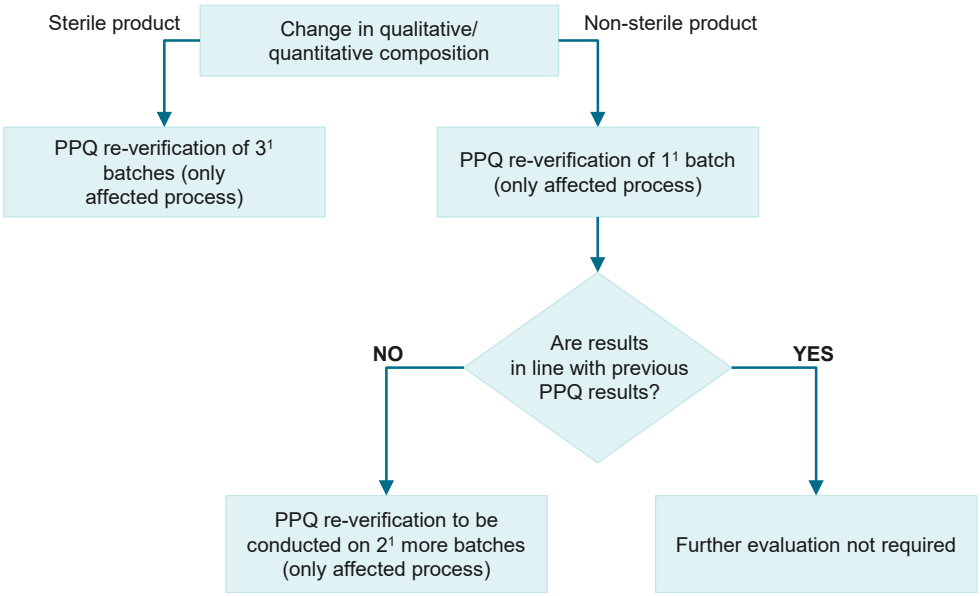
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 14 – PPQ for change in primary packaging material of finished product



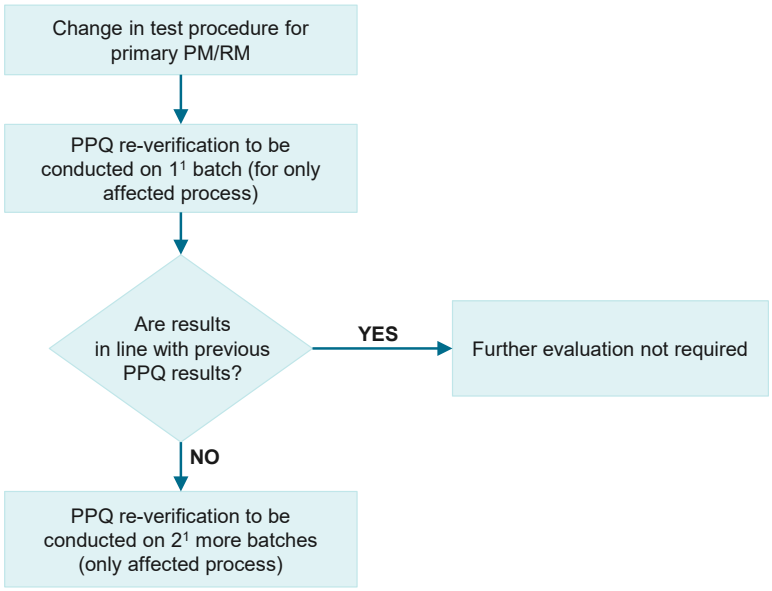
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 15 – PPQ for change in qualitative/quantitative composition of primary or functional secondary pack of finished product



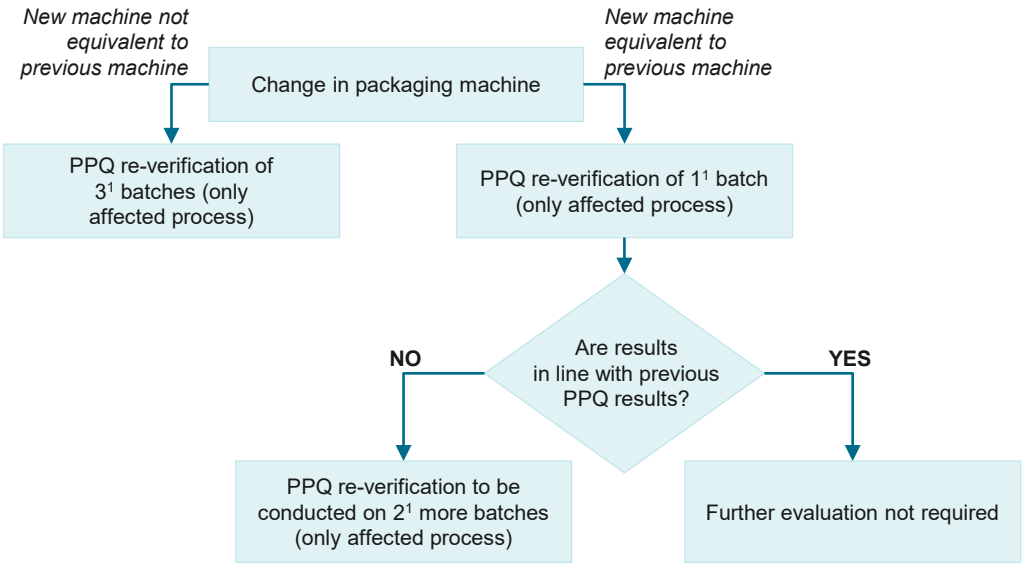
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 16 – PPQ for change in test procedure for primary PM and RM



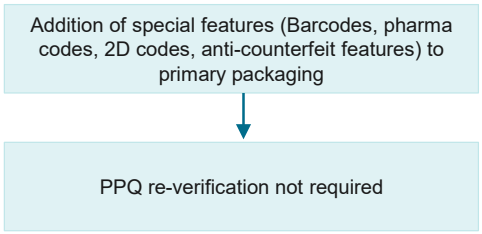
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 17 – PPQ for change in packaging machine



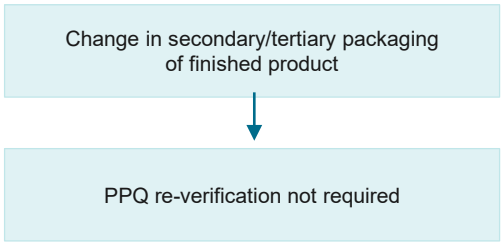
1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 18 – PPQ for change in special features of packaging material



1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Decision tree no. 19 – PPQ for change in secondary/tertiary packaging



1 No. of batches is for guidance purpose only, CFT may change the same based on regulatory requirements, product specific requirements, change control evaluation, etc.

Annexure 3

Risk assessment strategy and approach

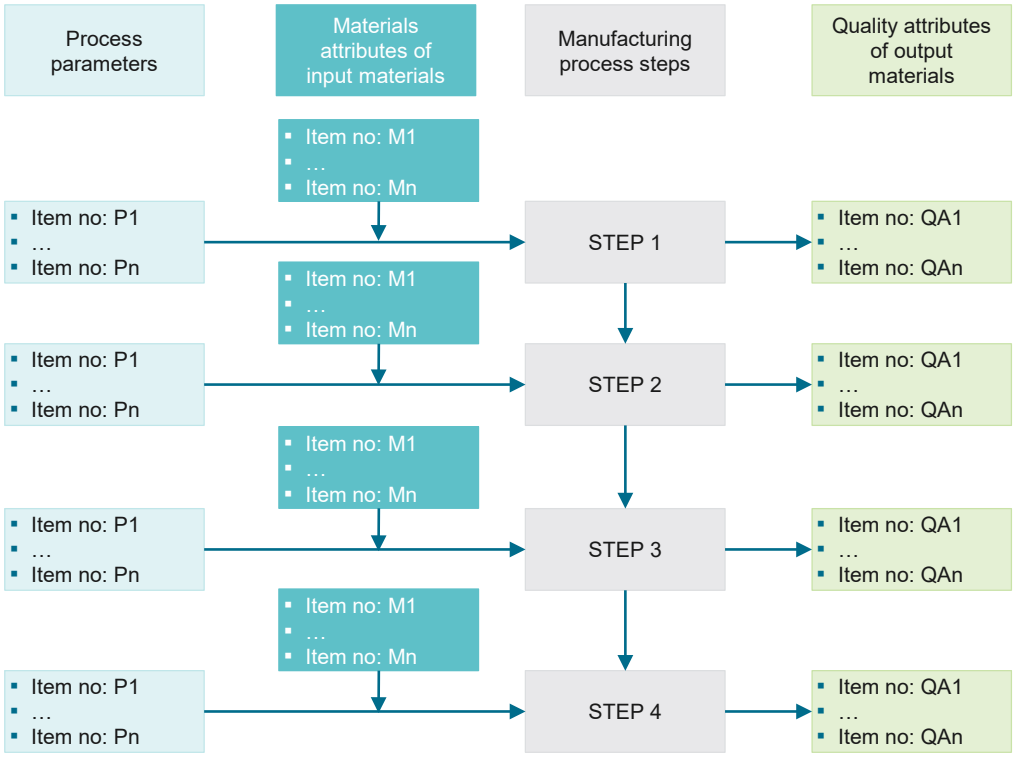
1.0 Scope

This Annexure details a basic strategy to perform risk assessment during product/process development in order to identify the risks associated with the materials used, formulation and processes, and to assess the magnitude of each risk. Based on the identified risks, a control strategy may be developed and processed during the development stages so that the risks can be mitigated.

2.0 Manufacturing process map, Process Parameters (PP), Material Attributes (MA), and Quality Attributes (QA)

(A process map is given in this section, representing the major steps in the process, step-wise process parameters, quality attributes and input material attributes deduced from sound science and risk management principles. A skeleton of this process map is shown below.)

Process map skeleton



Note: Parameters as applicable to the product shall be inserted in the skeleton above

3.0 Risk assessment for identification of Critical Quality Attributes (CQA), Critical Process Parameters (CPP), Critical Material Attributes (CMA) and Process Control Strategy

3.1 Procedure

3.1.1 Step A

- Drug Product: Risk assessment at the process design stage is performed on the quality attributes to deduce the critical quality attributes based on the impact of each attribute on patient safety and product efficacy.

  Note: These quality attributes are based on the Quality Target Product Profile (QTPP) of the drug product. In an ANDA, the QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy to the drug product.

- Drug Substance: Risk assessment at the process design stage is performed on the quality attributes to deduce the critical quality attributes based on the impact of each drug substance attribute on the drug product CQA.

3.1.2 Step B

- Each process parameter and material attribute is assessed for its risk to CQAs, and based on the risk assessment each is classified as a critical process parameter and critical material attribute respectively.

3.1.3 Step C

- Based on the identified CPP and CMA, appropriate control strategy is built in the manufacturing process and testing processes for the same.

3.2 Risk assessment for deducing CQA for drug substances and drug products

3.2.1 Drug products

Overview of relative risk ranking system based on patient safety and product efficacy

Risk rating	Criteria
Low	▪ Low impact on product identity, strength, purity and quality ▪ Low patient impact
Medium	▪ Likely impact on product identity, strength, purity and quality ▪ Potential patient harm
High	▪ Direct impact on product identity, strength, purity and quality ▪ Potential patient harm

Risk assessment summary with justification

(The risk ranking based on the table shown above should be identified and justification for each ranking should be provided.)

Drug product quality attributes	Target	Impact on patient safety/product efficacy High/medium/low	Justification (identify the risk and then provide justification for the risk level)	Summary – is it CQA?
QA_1				
QA_2				
……..				
QA_n				
The DP QAs coming under 'High' risk shall be mandatorily considered as a CQA; those assessed as 'Medium' and 'Low' risk may be reviewed for identification as CQA				

3.2.2 Drug substances

Risk assessment of the drug substance attributes is performed to evaluate the impact that each drug substance attribute could have on the drug product CQAs.

Drug product CQAs	Drug substance quality attributes (Risk ranking, i.e., high/medium/low, should be given based on impact of drug substance quality attribute on each drug product CQA)			
	DS QA1	**DS QA2**	**DS QA….**	**DS QAn**
DP CQA1				
DP CQA2				
DP CQA….				
DP CQAn				
The DS QAs coming under 'High' risk shall be mandatorily considered as a CQA of the DS; those assessed as 'Medium' and 'Low' risk may be reviewed for identification as CQA.				

Risk assessment summary with justification

(Justification is to be provided for risk ranking given to each drug substance quality attribute based on its impact on the drug product CQA.)

Drug substance quality attributes	Drug product CQAs (on which impact is being justified)	Justification
QA1	CQA1	
	CQA…	
	CQAn	
QA2	CQA1	
	CQA…	
	CQAn	
QA…	CQA1	
	CQA…	
	CQAn	
QAn	CQA1	
	CQA…	
	CQAn	

Prepared by:

Name:

Signature:

Date:

_____

Verified by:

Name:

Signature:

Date:

_____

3.3 Risk assessment for deducing CPP for drug substances and drug products

Overview of relative risk ranking system

Risk rating	Criteria
Low	Realistic change in the process parameter can have no impact on the quality of the output material (this shall be studied for each identified CQA)
Medium	Realistic change in the process parameter can have a likely impact on the quality of the output material (this shall be studied for each identified CQA)
High	Realistic change in the process parameter can significantly impact the quality of the output material (this shall be studied for each identified CQA)

Risk assessment summary with justification

Drug product/drug substance CQAs	Process parameters (Identify the risk ranking based on the table above and provide justification for each)					
	P1		P2		P…n	
	Risk category	Justification	Risk category	Justification	Risk category	Justification
CQA_1						
CQA_2						
……..						
CQA_n						
Conclusion (for each parameter)						
Process control strategy (mandatory for 'high' risk process parameters)						
The process parameters coming under 'High' risk shall be mandatorily considered as a CPP of the DS/DP (as applicable); those assessed as 'Medium' and 'Low' risk may be reviewed for identification as CPP						

Note:

- The analysis as shown above shall be done for all process parameters identified for the various process stages.
- Based on the risk conclusion of each process parameter, process control strategy, e.g., in-process monitoring, operational range setting etc., shall be finalised and summarised in the table above.

Prepared by:

Name:

Signature:

Date:

Verified by:

Name:

Signature:

Date:

Risk assessment for deducing CMA for drug substances and drug products

Overview of Relative Risk Ranking System

Risk rating	Criteria
Low	Realistic change in the input material attribute can have no impact on the quality of the output material (this shall be studied for each identified CQA)
Medium	Realistic change in the input material attribute can have a likely impact on the quality of the output material (this shall be studied for each identified. CQA)
High	Realistic change in the input material attribute can significantly impact the quality of the output material (this shall be studied for each identified CQA)

Risk assessment summary with justification

(The risk ranking should be identified based on the table above and justification for each should be provided.)

Drug product/ drug substance CQAs	Name of input material: _____					
	Input material attribute					
	M1		M2		M…n	
	Risk category	Justification	Risk category	Justification	Risk category	Justification
CQA_1						
CQA_2						
……..						
CQA_n						
Conclusion (for each attribute)						
Control Strategy (Mandatory for 'High' Risk Material Attributes)						
The material attributes coming under 'High' risk shall be mandatorily considered as a CMA of the DS/DP (as applicable); those assessed as 'Medium' and 'Low' risk may be reviewed for identification as CMA.						

Note:

- The analysis as shown above shall be done for all input materials during the various process stages.
- Based on the risk conclusion of each material attribute, control strategy, e.g., specification setting of input materials, etc. shall be finalised and summarised in the table above

---

Prepared by:

Name:

Signature:

Date:

Verified by:

Name:

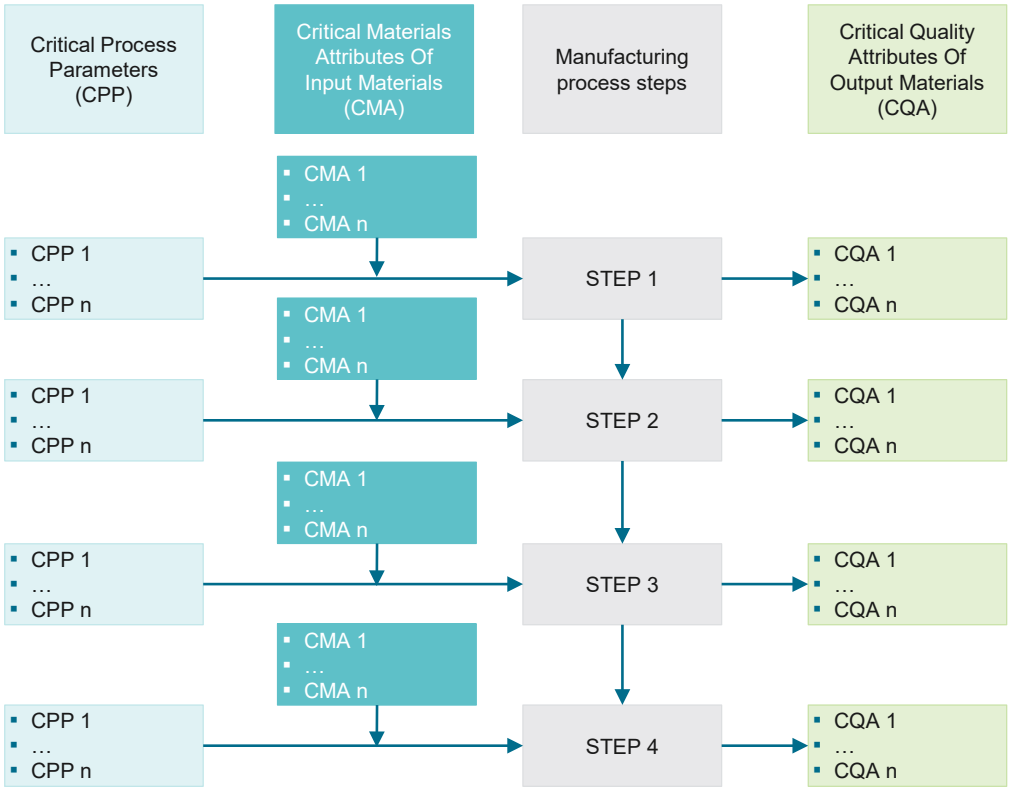
Signature:

Date:

4.0 Manufacturing process map showing Critical Quality Attributes (CQA), Critical Process Parameters (CPP) and Critical Material Attributes (CMA)

(Based on the conclusions drawn from the risk analyses of Quality Attributes, Process Parameters and Input Material Attributes as given in Section 3.0, a process map representing major steps in the process, CQA, CPP and CMA shall be given in this section. A skeleton for such a process map is shown below.)

Process map skeleton showing CPPs, CMAs & CQAs



Note: Parameters as applicable to the product shall be inserted in the skeleton above

5.0 Manufacturing process risk map showing inter-relationships between CQA, CPP and CMA based on impact assessment

5.1 Inter-relationships between CQA and CPP

CQA	Impacted by	Justification
CQA 1	CPP 1	----------
	CPP….	----------
	CPPn	----------
CQA…	CPP 1	----------
	CPP….	----------
	CPPn	----------
CQAn	CPP 1	----------
	CPP….	----------
	CPPn	----------

Prepared by:

Name:

Signature:

Date:

_____

Verified by:

Name:

Signature:

Date:

_____

6.2 Inter-relationships between CPP and CMA

CPP	Impacted by	Justification
CPP 1	CMA 1	----------
	CMA….	----------
	CMAn	----------
CPP..	CMA 1	----------
	CMA….	----------
	CMAn	_____
CPPn	CMA 1	----------
	CMA….	----------
	CMAn	_____

_____

Prepared by:

Name:

Signature:

Date:

_____

Verified by:

Name:

Signature:

Date:

_____

Annexure 4

Product lifecycle management

Name of Product	
SFG Code	
Strength	
Label Claim	
Dosage Form	
Storage Condition	
Market	

1) Background of product:

2) Composition:

Sr. No.	Material	Role of Excipient	Quantity/Unit	% W/W	SU		RU	
					Item Code	Batch Size Quantity/Batch	Item Code	Batch Size Quantity/Batch

3) General information:

Batch Details	Exhibit Batch	Engineering Batch	Validation Batch	Commercial Batch	Site Shift/ Further Validation
Batch Number					
Batch Size					
Manufacturing Location					
Person Involved/Designation					
Technology Transfer Team					
Technology Receiving Team					
Production					
Others					

Product Development History

PDR Summary

Yield Data of Previous Batches

4) CMAs of Input Materials (Raw Materials and Packing Materials):

Name of Materials	SAP Code	Vendor	CMAs	Limit	Exhibit Batch		Validation Batch		Commercial Batch		Site Shift/ Further Validation	
					AR No.	CMA Value	AR No.	CMA Value	AR No.	CMA Value	AR No.	CMA Value

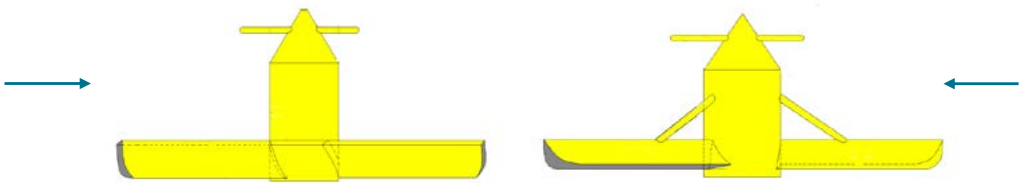
5) Manufacturing Process Flow diagram

(This page intentionally left blank – product specific process flow)

6) Detailed Technical GAP of Equipment:

RMG scale-up or Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/ Exhibit/ Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Capacity (litre)			
Bowl Height (m)			
Bowl Diameter (m)			
Bowl Height/Diameter Ratio			
Impeller Blade(Tangential/Radial)			
Impeller Type (Type I/Type II)			
No. of Impeller Blades			
Chopper Design			
Number of Chopper Blades			
Impeller Height (m)			
Impeller Direction			
Chopper Centre Height from Bowl Bottom (m)			
Chopper Diameter (m)			
Chopper Direction			
Ratio of Chopper Centre Height to Total Height			
Sprinkler Availability			
Impeller Motor Capacity (HP)			
(B) Kinematic Detail			
VFD Availability			
Available Impeller RPM			
Available Chopper RPM			
Qualified Impeller RPM			
Qualified Chopper RPM			
Target Impeller RPM (Slow/Fast)			
Target Tip Speed (m/sec)*			
(C) Process Detail			
Weight of Dry Mix (Kg)			
Dry Mix BD (gm/ml)			
Dry Mix Volume (m^3)			
Bed Height (m)*			

RMG scale-up or Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Bed Height/Diameter Ratio			
Occupancy (%)			
Impeller Height			
Impeller Height/Bed Height			
Approx. Change in Volume after Granulation (Amount of Densification/Swelling)			
End Point Current (Amp) (Range)			
End Point Torque (Nm) (Range)			
Peristaltic Pump Availability			
MOC of Tube			
Thickness of Tube (mm)			
Tube Diameter (mm)			
Weighing Balance Availability			
Mass Flow Meter Availability			
Bed Height = Dry mix vol / (TT*d^2/4)			
*Tip Speed (m/sec)= 3.14*D*N			



Side View (A) **Side View (B)**

Type I **Type II**

FBP Scale-up/Site Transfer Checklist – Top Spray			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/ Scale-up/Exhibit/Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Model			
Capacity (Litre)			
Bowl Height (m) (H)			
Bowl Base Diameter (m) (d)			
Base Plate area (m^2)#			
Base Plate Ratio (Scale 2/Scale 1)			
Bowl Top Diameter (m) (D)			
Ratio (Bowl Height/Base Diameter)			
Height of Expansion Chamber (m)			
Spray gun Height from Base Plate (m)			
MOC and Type of Filter Bag			
Number of Finger Bags			
Base Plate Category (Sieve-size) used			
High-speed Spray-gun available or not			
Spray-gun Nozzle size (mm)			
Number of Nozzles			
*Bowl Wall angle from vertical			
(B) Process Detail			
Weight of Input Material (Kg)			
Dry Mix BD (gm/ml)			
Volume of Dry Mix (L)			
Input Occupancy (%)			
Weight of Output (dried) Material (Kg)			
BD of Dried Mass			
Volume of Dried Mass (L)			
Output Occupancy (%)			
Base Plate Category (Sieve-size) used			
Maximum Available Air Flow Rate (CFM)			

FBP Scale-up/Site Transfer Checklist – Top Spray			
	Scale 1	**Scale 2**	**Remarks**
Target Air Flow Rate (CFM)$			
Maximum Available Blower RPM			
Atomization Pressure (bar) (Available Range)			
Atomization Target Pressure (bar)			
Mass Flow-meter Availability			
Humidifier Availability			
Dehumidifier Availability			
Air Absolute Humidity (g/Kg) (Available Range)			
Target Air Absolute Humidity (g/Kg)			
Dew Point (^oC) (Available Range)			
Target Dew Point (^oC)			
Pump RPM Range			
Target Spray Rate (g/min)$			
MOC of Tube			
Thickness of Tube Wall (mm)			
Tube Inner Diameter (mm)			
*Bowl Angle from Vertical = **$TAN^{-1}((D-d)/(2*H))$**			
#Base Plate Area (m^2) = $3.14*d^2/4$			
$Air Flow rate and Spray rate to be calculated on the basis of base plate area ratio			

FBP Scale-up/Site Transfer Checklist – Bottom spray			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/Exhibit/ Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Model			
Capacity (Litre)			
Bowl Height (m) (H)			
Bowl Base Diameter (m) (d)			
Base Plate area (m^2)#			
Base Plate Ratio (Scale2 / Scale 1)			
Bowl Top Diameter (m) (D)			
Ratio (Bowl Height / Base Diameter)			
Height of Expansion Chamber (m)			
Spray-gun Height from Base Plate (m)			
MOC and Type of Filter Bag			
Number of Finger Bags			
Base Plate Category (Sieve size) used			
High-speed Spray-gun available or not			
Spray-gun Nozzle Size (mm)			
Number of Nozzles			
*Bowl Wall angle from vertical			
(B) Process Detail			
Weight of Input material (Kg)			
Dry Mix BD (gm/ml)			
Volume of Dry Mix (L)			
Input Occupancy (%)			
Weight of Output (dried) Material (Kg)			
BD of Dried Mass			
Volume of Dried Mass (L)			
Output Occupancy (%)			
Base Plate Category (Sieve size) used			
Maximum Available Air-flow Rate (CFM)			

FBP Scale-up/Site Transfer Checklist – Bottom spray			
	Scale 1	**Scale 2**	**Remarks**
Target Air flow Rate (CFM)[$]			
Maximum Available Blower RPM			
Atomization Pressure (bar) (Available range)			
Atomization Target Pressure (bar)			
Mass Flow-meter availability			
Humidifier Availability			
Dehumidifier Availability			
Air Absolute Humidity (g/Kg) (available range)			
Target Air Absolute Humidity (g/Kg)			
Dew Point (^{o}C) (available range)			
Target Dew Point (^{o}C)			
Pump RPM Range			
Target Spray Rate (g/min)[$]			
MOC of Tube			
Thickness of Tube Wall (mm)			
Tube Inner Diameter (mm)			
[*]Bowl Angle from Vertical = **$TAN^{-1}((D-d)/(2*H))$**			
[#]Base Plate Area (m^2) = 3.14* $d^2/4$			
[$]Air Flow rate and Spray rate to be calculated on the basis of base plate area ratio.			

Roll Compactor Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/Exhibit/ Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Model			
Roll type			
Feeder Screw Type			
Roller Type			
Roll Diameter, D (mm)			
Roller Thickness (mm)			
Pre-granulator Screen Size (Available Range)			
Fine Granulator Screen Size (Available Range)			
(B) Kinematic Detail			
Roller Speed (RPM) (Available Range)			
Target Roller Speed, N (RPM)			
Stirrer Speed (RPM) (Available Range)			
Target Stirrer Speed (RPM)			
Target Roller Tip Speed (m/s)*			
Screw Speed (RPM) (Available Range)			
Target Screw Speed (RPM)			
Auger Speed (RPM) (Available Range)			
Target Auger RPM			
Pre granulator RPM (Available Range)			
Target Pre-granulator RPM			
Fine Granulator RPM (Available Range)			
Target Fine Granulator RPM			
(C) Process Detail			
Weight of Dry Mix (Kg)			
Dry Mix BD (gm/ml)			
Maximum Roller Pressure (bar) (Available Range)			
Target Roller Pressure (bar)			
Linear Load (Ton/cm)			
Roll gap (available range in mm)			
Target Roller gap (mm)			
Ribbon Density (gm/ml)			
Ribbon Thickness (mm)			

Roll Compactor Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Granules to Fine Ratio			
Maximum Throughput (kg/h)			
Number of Cycles			
Maximum Deaeration (Vacuum) Attained (bar)			
* Tip Speed (m/s) = 3.14 * D * N/60000			

Blender Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/ Exhibit/ Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Capacity (Litre)			
Blender Height (m) (H)			
Blender type (Octa, Conta, etc.)			
NIR Availability			
(B) Kinematic Detail			
VFD Availability			
Available Blender RPM Range			
Qualified Blender RPM			
Target Blender RPM (N)			
Tip Speed*			
Froude Number*			
Total Number of Rotation*			
(C) Process Detail			
Weight of RFC (Kg)			
RFC BD (gm/ml)			
RFC Volume (m^3)			
Occupancy (%)			
Blending Time (sec)			
Lubrication Time (sec)			
* Total number of rotations = Blender RPM * Total time (to be kept constant)			
* Froude Number = HN^2/g (to be kept constant)			
* Tip Speed = πHN			

Compression Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/Exhibit/ Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Model			
No. of Stations			
Tooling type (B/D)			
Tooling MOC			
Hopper Shape			
Hopper Angle (Degree)			
Number of Punches used (n)			
Pre-compression Roller Diameter (mm)			
Main Compression Roller Diameter (mm)			
Pitch Circle Diameter (mm) (PCD)			
Force Feeder/Gravity Feeder			
Feeder Volume (litre)			
Punch-head Flat Diameter (mm) (PHF)			
(B) Process Detail			
Weight of Blend (Kg)			
Blend BD (gm/ml)			
Weight of Unit Tablet, W (mg)			
Target Turret RPM (N)			
Target Force Feeder RPM			
Turret RPM/Feeder RPM ratio			
Dwell Time (millisec)*			
Blend Consumption Rate (gm/min)#			
Blend Residence Time in Feeder (min)##			
Target Pre-compression Force (kN)			
Target Main Compression Force (kN)			
AWC Availability (Y/N)			
* Dwell Time (millisec) =	$\frac{PHF * 60000}{3.14 * PCD * N}$		
# Blend Consumption Rate (gm/min) =	n*W*N/1000		
## Blend Residence Time (min) =	$\frac{\text{Feeder volume (L)} * 1000 * \text{BD (g/ml)}}{\text{Blend consumption rate}}$		

Coater Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Product			
Strength (mg)			
Manufacturing Site			
Type of Batch (Development/Scale-up/ Exhibit/Validation)			
Area			
Area RH (%)			
Area Dry Bulb Temperature (°C)			
(A) Geometrical Detail			
Make			
Model			
Brim Volume (Litre)			
Pan Diameter, D (m)			
Pan Depth (m)			
Pan RPM			
Brim Volume (Litre)			
Number of Guns			
Type of Gun			
Spray-gun Nozzle Size (mm)			
Individual or Combined Pump for each Gun			
Pan Depth/Pan Diameter			
(B) Process Detail			
Weight of Tablet, W (Pan Load) (Kg)			
Tablet Bulk Density (gm/ml)			
Volume of Bed (L)			
Input Occupancy (%)			
Maximum Available Air flow Rate (CFM)			
Target Air Flow Rate (CFM)$			
Available Pan RPM (range)			
Target Pan RPM			
Atomization Pressure (bar) (Available range)			
Target Atomization Pressure (bar)##			
Mass Flow-meter Availability			
Mass Flow-meter Number (Single/Multiple)			
Humidifier Availability			
Dehumidifier Availability			
Target Absolute Humidity (g/kg)			
Gun to Bed Distance (cm)			
Pump RPM Range			
Target Spray Rate, SR (g/min)#			
MOC of Tube			

Coater Scale-up/Site Transfer Checklist			
	Scale 1	**Scale 2**	**Remarks**
Wall Thickness of Tube (mm)			
Tube Diameter (mm)			
# Spray rate (Scale 2) should be calculated as per following formula: $(SR)_2 = (SR)_1 * (W_2/W_1)*(D_1/D_2)$			
$ Air flow rate should be increased in the ratio of spray rate increase.			
## Atomization to be scaled as per same droplet size.			

7) Critical Process Parameters

Manufacturing Process	Process Parameters	Exhibit Batch		Validation Batch		Commercial batch		Site shift/ Further Validation		Remarks
		Batch Size		Batch Size		Batch Size		Batch Size		
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
Wet Granulation										
Manufacturing Condition	Temperature									
	RH									
	Specific recommendation									
Sifting/Milling	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	x									
	x									
	Yield									
	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Impeller Speed (RPM)									
Dry Mixing	Impeller Tip Speed (m/s)									
	Chopper Speed									
	Binder Addition Time									
	Ampere Load									
	BD of Dry Mix									
	LOD of Dry Mix									
	Occupancy %									
	Bed H/D									
Binder Preparation	Area Temperature									
	Area RH									
	Binder Quantity									
	Solvent Quantity									
	Stirring Time									
	Stirring Speed									
	Stirrer ID									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
Binder Addition	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Impeller speed (RPM)									
	Impeller Tip Speed (m/s)									
	Chopper Speed									
	Time									
	Ampere Load									
	Peristaltic Pump/ Sprinkler									
	RPM of Peristaltic Pump									
	Binder Addition Rate (gm/min)									
	Extra Solvent Quantity (if any)									
Wet Mixing and/or Kneading	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Impeller Speed (RPM)									
	Impeller Tip Speed (m/s)									
	Chopper Speed									
	Ampere Load									
	Torque									
	Time									
	Extra Solvent Quantity (if any)									
	Wet Mass LOD									
Wet Milling	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Screen Size									
	Speed (RPM)									
Drying	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Air Drying Time									
	Inlet Temperature									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Inlet Air CFM									
	Outlet Temperature									
	Drying Time									
	Racking/Other Requirement									
	LOD									
	Yield									
Sizing	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Screen Size									
	Speed (RPM)									
	Yield									
Blending and Lubrication										
Manufacturing Condition	Temperature									
	RH									
	Specific recommendation									
Blending and Lubrication	Area Temperature									
	Area RH									
	Equipment and Capacity									
	Equipment ID									
	Occupancy %									
	Blender RPM									
	No of Rotations									
	Blending time									
	Lubrication Time									
	Yield									
Compression										
Manufacturing Condition	Temperature									
	RH									
	Specific recommendation									
Compression	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	No of station									
	No of punches									
	Type of tooling (D/B/BB)									
	Tooling MOC/ Coating									
	Turret RPM									
	Type of feeder									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Feeder RPM									
	Compaction force (Main Roller)									
	Compaction force (Pre-compression)									
	Ejection force									
	Dwell Time									
	Average Weight									
	Weight Variation									
	Hardness									
	Thickness									
	Friability									
	DT									
Coating										
Manufacturing Condition	Temperature									
	RH									
	Specific recommendation									
Coating Solution Preparation	Area Temperature									
	Area RH									
	Binder Quantity									
	Solvent Quantity									
	Stirring Time									
	Stirring Speed									
	Stirrer ID									
	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	Pan Load									
	Occupancy %									
	Pan Diameter									
	No of Guns									
	Type of Gun									
	Bed- to- gun Distance									
	Pan Coating and/ or other requirements									
	Inlet Temperature									
	Inlet Air RH									
	Inlet air Dew Point									
	Outlet Temperature									
	Product Temperature									
	Spray Rate (Gm/Min)									
	Atomization									
	Pan RPM									
	Pan DP									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Drying Temperature									
	Drying Time									
	Drying Pan RPM									
	Pan Coating and/ or other requirements									
	Average Weight									
	Hardness									
	Thickness									
	DT									
	Weight Gain									
	Yield									
FBP –Top Spraying										
Manufacturing Condition	Temperature									
	RH									
	Specific Recommendation									
Top Spray Granulation	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	Screen Type									
	Filter Bag Type									
	Inlet Temperature									
	Outlet Temperature									
	Product Temperature									
Preheating	Inlet air CFM									
	Dew point									
	Inlet RH									
	Mode of Shaking									
	Shaking Interval									
	Pre-heating Time									
	LOD of Preheating material									
	Occupancy %									
Solution Preparation	Area Temp									
	Area RH									
	Solid Quantity									
	Solvent Quantity									
	Stirring Time									
	Stirring Speed									
	Stirrer ID									
	Filter Screen Size									
Spraying	Solution Holding Tank Details									
	Stirring RPM									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Product Temperature									
	Inlet Air CFM									
	No. of Spray Guns									
	Spray Rate									
	Spray Rate/Gun									
	Nozzle Diameter									
	Atomization									
	Spray Gun Position									
	Filter Bag DP									
	Dew Point									
	Inlet RH									
	Mode of Shaking									
	% LOD after Spraying									
Drying	Inlet Temperature									
	Outlet Temperature									
	Product Temperature									
	Inlet Air CFM									
	Dew Point									
	Inlet RH									
	Mode of Shaking									
	Shaking Interval									
	Drying Time									
	LOD after drying									
FBP – Bottom Spraying										
Manufacturing Condition	Temperature									
	RH									
	Specific Recommendation									
Bottom Spray (Wurster Coating)	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	Screen Type									
	Base Plate Type									
	Filter Bag Type									
	Filter Bag Mesh Size									
Preheating	Sifting Details (before Loading)									
	Inlet Temperature									
	Outlet Temperature									
	Product Temperature									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Inlet Air CFM									
	Dew Point									
	Inlet RH									
	Mode of Shaking									
	Shaking Interval									
	Drying Time									
	Partition Column Height									
	LOD of Preheating Material									
	% Occupancy									
Solution Preparation	Area Temperature									
	Area RH									
	Binder Quantity									
	Solvent Quantity									
	Stirring Time									
	Stirring Speed									
	Stirrer ID									
	Filter Screen Size									
Spraying	Solution Holding Tank Details									
	Stirring RPM									
	Inlet Temperature									
	Outlet Temperature									
	Product Temperature									
	Inlet Air CFM									
	No. of Spray Guns									
	Spray Rate									
	Spray Rate/Gun									
	Nozzle Diameter									
	Atomization									
	Partition Column Height									
	Dew Point									
	Inlet RH									
	Mode of Shaking									
	Sifting Details (During Process)									
	Total Spray Solution Consume									
	% Weight Gain									
Drying/Curing	Inlet Temperature									
	Outlet Temperature									
	Product Temperature									
	Inlet Air CFM									

Manufacturing Process	Process Parameters	Exhibit Batch Batch Size		Validation Batch Batch Size		Commercial batch Batch Size		Site shift/ Further Validation Batch Size		Remarks
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Dew Point									
	Inlet RH									
	Mode of Shaking									
	Shaking Interval									
	Drying Time									
	LOD after Drying									
	Yield									
	Sifting Screen									
	Yield after Sifting									
	No of Pellets/gm.									
Roll Compaction										
Manufacturing Condition	Temperature									
	RH									
	Specific recommendation									
Roller Compaction	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	Roller RPM									
	Auger RPM									
	Roller Gap									
	Compaction Pressure									
	Screw RPM									
	Hardness of Slug									
	No. of Compaction Cycles									
	Granules to Fines Ratio									
	Yield									
Capsule Filling										
Manufacturing Condition	Temperature									
	RH									
	Specific Recommendation									
Capsule Filling	Area Temperature									
	Area RH									
	Equipment									
	Equipment ID									
	Filling Speed									
	Filling Setting									
	Average weight									
	Weight Variation									
	Locking Length									
	Disintegration Time									

Manufacturing Process	Process Parameters	Exhibit Batch		Validation Batch		Commercial batch		Site shift/ Further Validation		Remarks
		Batch Size		Batch Size		Batch Size		Batch Size		
		Proposed	Actual	Proposed	Actual	Proposed	Actual	Proposed	Actual	
	Polishing Machine ID									
	Metal Detector ID									
	Weight Checker Detail									
	Yield									
Visual Inspection										
Manufacturing Condition	Temperature									
	RH									
	Specific Recommendation									
Visual Inspection	Type of Rejection									
	Rejected Quantity									
	Yield after Inspection									

8) Challenges faced and remedies

Type of batch	Stage	Challenge faced	Remedies and/or Corrective Action
Demo Batch			
Pilot Bio Batch			
Scale-up Batch			
Exhibit Batch			
Engineering Batch			
Validation Batch			
Commercial Batch			
Site shift /Further validation			

9) Quality Target Product Profile Information (QTPP)

QTPP	Acceptance Criteria	Exhibit Batch	Validation Batch	Commercial Batch	Site shift/ Further Validation

10) Change History of CMA/CPP/QTPP or Regulatory Query

Date	Stage	Impacted CPP/CQA/QTPP	Existing System	Proposed System	Justification for Change

11) Deviation/OOS/OOT History

Date	Details of Deviation/OOS/OOT	Reference document number	Root Cause	Corrective Action	Preventive Action

12) Stability Failure and Rejection or Recall History

Date	Details of Stability Failure and Rejection or Recall	Reference document number	Root Cause	Corrective Action	Preventive Action

13) Way Forward and Learning

Risk Assessment		
Process Stages	**Risk identified**	**Risk mitigation measures/Justification for risk acceptance**
Raw Materials		
Equipment		
Equipment 1		
Equipment 2		
Equipment 3		
Equipment 4		
Equipment 5		
Manufacturing Process		
Unit Operation 1		
Unit Operation 2		
Unit Operation 3		
Unit Operation 4		
Unit Operation 5		
Analytical Parameters		

Annexure 5

Determining and justifying the number of process performance qualification batches

This section describes a framework for assessing the level of product knowledge and process understanding, and how well the control strategies are linked to the Critical Quality Attributes (CQAs). The residual risk identified from this assessment may then be translated to a number of validation batches.

Risk-based approach

Risk assessment should be performed periodically during development in order to highlight the extent of understanding and the extent of impact on the PPQ program.

If high risk(s) is/are identified from the assessment, it may be prudent to increase knowledge before starting the Stage 2 PPQ activities, in order to reduce the risk and, subsequently, the number of PPQ batches required to demonstrate process reproducibility.

Risk assessment is primarily focused on the following aspects:

- Assessing product and process knowledge and understanding risks.
- Assessing control strategy risk.
- Determining residual risk level.
- Approaches to determine the number of validation batches.

Assessing product and process knowledge and understanding risks

Quality target product profiles (QTPP) are related to the critical quality attributes (CQAs) of the drug product or drug substance.

The evaluation of product knowledge focuses on the severity of harm to the patient and the probability that variability has an impact on safety, efficacy and quality of the product. The risk ranking level is assigned based on an evaluation of the methodology applied to identify CQAs and an evaluation of the extent of impact of variability as understood.

Process understanding can be established from the following:

- The development phase, by understanding the variability from development and product characterization.
- From prior knowledge, since for a mature product, data from annual product review, product quality review, deviation investigation, complaint investigation, and/or change control information can be used.
- From the degree of process understanding and/or unit operation, it is possible to judge the extent of knowledge gained and explored during the development of each unit operation and the depth

of understanding of the effects of inputs and process parameters on process results. Impact from personnel, selection of appropriate equipment and environmental conditions can be included.

- From process predictability and modeling, wherein the sophistication of the small-scale model and its ability to adequately predict the effects of input variability on output at commercial scale may be judged.

- Understanding the effect of changes to the scale on which the process is run.

Product knowledge risk ranking

Product knowledge factor	Relative risk ranking – characteristics of ranking assignments		
	Low risk	Medium risk	High risk
Identification of CQA and impact of CQA variation on patient	▪ Physiochemical and/or biological, pharmacokinetic knowledge, and QbD approach used to design the formulation of drug product ▪ Impact of variation on bioavailability explored and understood	▪ Critical quality attributes identified and justified ▪ Physicochemical and/or biological and pharmacokinetic properties identified ▪ Some exploration of impact of variation	▪ Product specifications established from development trial and error ▪ Impact of variation known only from evaluation of incidents
Product characterization	▪ Analytical method has direct measurable linkage to clinical performance ▪ Complete product physiochemical and/or biological characterization	▪ Analytical method development based on mechanism of action for the therapeutic agent, but linkage to clinical performance is hypothetical ▪ Product physiochemical and/or biological characterization identify categories of structural variants of a heterogeneous product	▪ Product characterization measures quality against established empirical limits ▪ Heterogeneous product not well defined by physiochemical and/or biological characterization

Process understanding risk ranking

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

Assess control strategy risk

Process control strategy evolves through the development of process and product knowledge in stage 1 of the product lifecycle. The main purpose of this approach is to control the impact of input variability from materials, environment, and operational practice, so that the output variability of the product attributes and process performance is appropriately monitored and controlled.

Factors to be considered for risk assessment of control strategy include the following:

- Raw material specification: impact of variability of critical material attributes, management of this variability, and potential impact of the raw material attributes on the process and product quality.
- Equipment capability: capabilities derived from qualification activities as compared with process requirements.
- Experiences with process performance: experiences with the process in managing variability, with appropriate control of scale effects and comparable process performance serving as indicators.

Control strategy risk ranking

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

Determining residual risk level

Residual risk level reflects the confidence in performance of the commercial process and can be used to determine the appropriate number of PPQ batches. The output of risk assessment will be determined from any quality risk management tool in alignment with QRM principles.

Overall residual risk levels are classified under five categories:

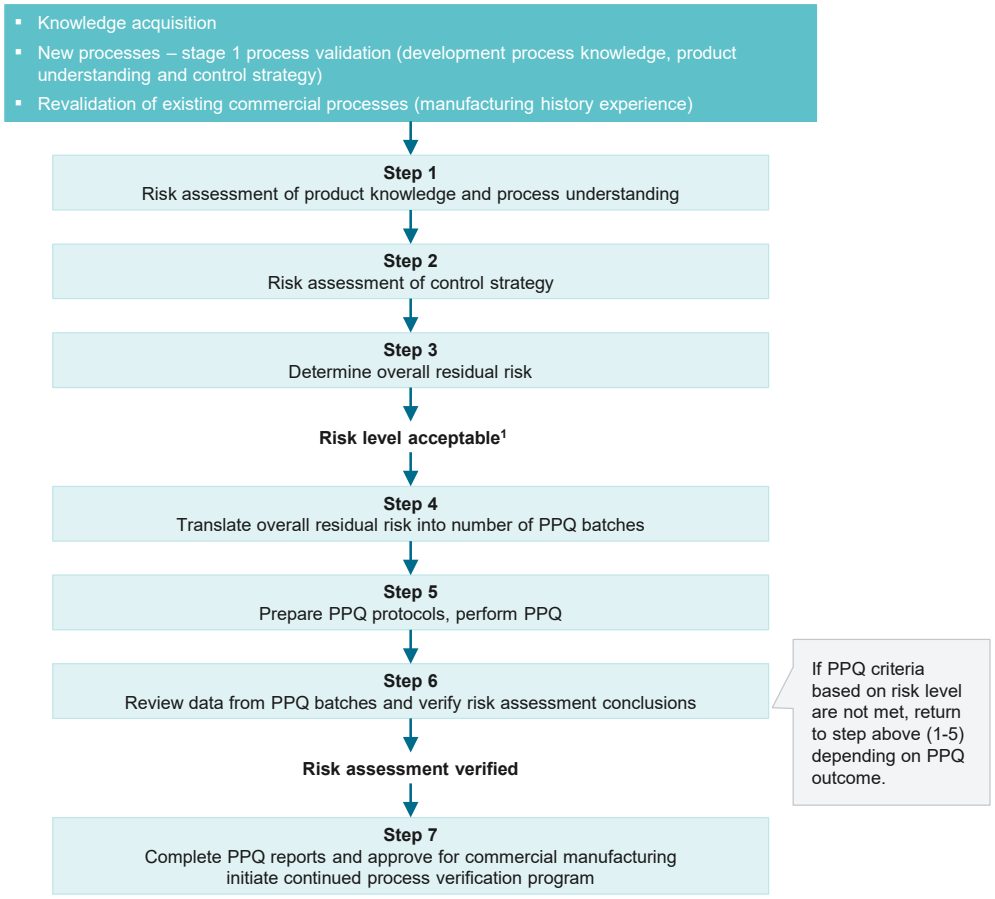
Residual risk level	Description	Product knowledge	Process understanding	Control strategy
Severe (5)	Multiple factors have high risk ratings.	H	H	H
High (4)	Few factors have high risk ratings or all have medium risk rating.	H	H	M
		M	H	H
		H	M	H
		M	M	M
Moderate (3)	Medium risk level for multiple factors or high risk level for one factor.	H	M	M
		M	H	M
		M	M	H
		M	M	L
		L	M	M
		M	L	M
Low (2)	Medium risk level for a few factors, the others are low risk.	M	L	L
		L	M	L
		L	L	M
Minimal (1)	Low risk level for all factors.	L	L	L

Residual risk level represent the level of remaining task revealed from the assessment of product knowledge, process understanding and control strategy effectiveness. A process that has higher residual risk requires more PPQ batches in order to provide enough assurance that the batch variability is appropriately controlled before commencing commercial distribution and vice-versa for low residual risks.

An example of rationales for number of batches for different residual risk levels is given below.

Residual risk level	Number of batches	Rationale
Severe (5)	Not ready for PPQ	Additional development should be pursued to identify processes or controls needed to reduce residual risk.
High (4)	10	Higher residual risk makes it unlikely that a small number of PPQ batches are adequate to show process consistency. A larger number of successful batches may show process consistency, but achieving this would be unlikely if controls are not adequate. A preferable course of action would be to perform additional development and/or knowledge acquisition to reduce residual risk so that fewer PPQ batches would be needed.
Moderate (3)	5	Increased residual risk can be addressed by preparing two additional PPQ batches to provide further demonstration of process consistency.
Low (2)	3	Knowledge and control strategy are regarded as sufficient. Three PPQ batches have been shown historically to be appropriate for demonstrating process consistency for many low-risk processes.
Minimal (1)	1-2	Strong knowledge and high degree of controls minimize risk. One situation where this may be appropriate is for verifying specific controls associated with a well-understood change to a process, or where process can rely on using a control strategy successfully shown for a similar product or process. Processes with PAT as a significant part of control strategy will be of minimal risk.

Workflow for determination of the number of stage 2 – PPQ Batches



1 Determination of an acceptable level of risk may be based on internal company standards.

The standards may be designed to encourage additional development work (increasing product and process understanding) rather than performing large number of PPQ batches.

Annexure 6

Sampling plan during PPQ

A) Sampling plan for PPQ of drug products

Manufacturing stage[1]	Process variables	Sampling stages	Tests to be performed	Approx. Sample Size *(Wherever applicable, pictorial representation of the sampling locations should be given in the PPQ Protocol)*	Acceptance criteria for quality attributes
Pre-mixing – granulation (tablets)	Mixing time Speed of chopper motor Speed of main motor	Time intervals to be fixed in PPQ Protocol	Blend uniformity	▪ Number of locations should be fixed based on equipment design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Wet-mixing – granulation (tablets)	Granulation time Speed of chopper motor Speed of main motor	Time intervals to be fixed in PPQ Protocol	Blend uniformity	▪ Number of locations should be fixed based on equipment design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Compaction (tablets)	Gap between rollers Screw feeder speed Roller speed Hydraulic pressure Pre-granulator speed Post-Granulator speed Granulator screen size	Time intervals to be fixed in PPQ Protocol	Appearance of compact Bulk density Tapped density	▪ Number of locations should be fixed based on equipment design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Drying (Tablets)	Drying time Inlet air temperature Air flow rate (CFM)	Time intervals to be fixed in PPQ Protocol	Loss on drying (LOD)	▪ Number of locations should be fixed based on dryer bowl design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Pre-mixing – blending (tablets, capsules, dry syrup, dry powder injections)	Blending time Speed (RPM)	Time intervals to be fixed in PPQ Protocol	Blend uniformity	▪ Number of locations should be fixed based on equipment design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Blending (tablets, capsules, dry syrup, dry injections)	Blending time Speed (RPM)	Time intervals to be fixed in PPQ Protocol	Blend uniformity	▪ Number of locations should be fixed based on equipment design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Storage container containing unloaded blend (tablets, capsules)	-	-	Blend uniformity Bulk density, tapped density, particle size	▪ Number of locations should be fixed based on container design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Capsule filling	Machine speed (capsules/min.) Vacuum pressure Tooling format or set-up	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of process - start of process at full hopper, middle of process at half hopper, end of process at low hopper)	Uniformity of weight Uniformity of content Dissolution rate Locked length (mm) Disintegration time (min.)	▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol. Each filling station should be considered for sampling at fixed duration	As per approved specification

1 Samples for hold-time study shall also be withdrawn at appropriate stages, as per requirement.

A) Sampling plan for PPQ of drug products

Manufacturing stage[1]	Process variables	Sampling stages	Tests to be performed	Approx. Sample Size *(Wherever applicable, pictorial representation of the sampling locations should be given in the PPQ Protocol)*	Acceptance criteria for quality attributes
Compression (tablets)	Compression speed Hopper level Main compression force Type of tooling	Time intervals to be fixed in PPQ Protocol (Guidance: Start, Middle and End of Compression -Start of compression at full hopper, middle of compression at half hopper, end of compression at low hopper)	Uniformity of content Description Average weight (mg) Individual weight variation (mg) Thickness (mm) Hardness Friability (%) Disintegration time (min)	▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol ▪ Samples from not less than one revolution of machine output at each stage ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Coating of tablets	Gun to bed distance (mm) Inlet air temperature (^{0}C) Bed temperature (^{0}C) Exhaust temperature (^{0}C) Pan speed (RPM) Solution spray rate (g/min) Atomizing air pressure (kg/cm2) Air flow rate (CFM)	Time intervals to be fixed in PPQ Protocol	Weight gain (% w/w) Physical appearance Dissolution rate profile	▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol ▪ Number of locations should be fixed based on equipment design	As per approved specification
Primary packaging (blister/strip) of tablets or capsules	Forming temperature (^{0}C) Sealing temperature (^{0}C) Machine speed	Time intervals to be fixed in PPQ Protocol (Guidance: Start, Middle and End of Blistering Process)	Leak test Assay (wherever needed)	▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Liquid injections – bulk manufacturing	Agitator speed Mixing time	Time intervals to be fixed in PPQ Protocol	Content uniformity	▪ Number of locations should be fixed based on manufacturing tank design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Vial or ampoule filling (dry powder or liquid injections)	Machine speed Fill weight/volume adjustment	Time intervals to be fixed in PPQ Protocol (Guidance: Start, Middle and End of Filling Process)	Fill volume and/or fill weight (as applicable) Uniformity of fill volume and/or fill weight (as applicable) Reconstitution time (for dry powder injection)	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Vial/ampoule after sealing	Machine speed Torque	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of a sealing cycle)	Uniformity of content, leak test	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Vial/ampoule after sterilization – in case of terminally sterilized product	Sterilization time Sterilization temperature (^{0}C)	Time intervals to be fixed in PPQ Protocol	Assay Sterility Leak test	▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification

1 Samples for hold-time study shall also be withdrawn at appropriate stages, as per requirement.

A) Sampling plan for PPQ of drug products

Manufacturing stage[1]	Process variables	Sampling stages	Tests to be performed	Approx. Sample Size *(Wherever applicable, pictorial representation of the sampling locations should be given in the PPQ Protocol)*	Acceptance criteria for quality attributes
Cream/ointment (after bulk preparation)	Temperature at which final mixing is done (^{0}C) Stirring speed Stirring time	Time intervals to be fixed in PPQ Protocol	Bulk uniformity/ Homogeneity of drug Viscosity pH	▪ Number of locations should be fixed based on mixing vessel design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Cream/ointment (filling operation)	Machine speed	Time intervals to be fixed in PPQ Protocol (Guidance: Start, middle and end of a filling cycle)	Average fill weight/weight variation Uniformity of content Leak test	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Liquid orals/ suspension (after bulk preparation)	Stirring time Stirring speed	Time intervals to be fixed in PPQ Protocol	Bulk uniformity/ Homogeneity of drug pH Weight per ml.	▪ Number of locations should be fixed based on mixing vessel design ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Liquid orals/ suspension (filling operation)	Machine speed Machine speed	Time intervals to be fixed in PPQ Protocol	Average fill volume/ Uniformity of volume Uniformity of content Leak test	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Dry syrup (filling and sealing)	Hopper level Machine speed	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of Filling/Sealing Process)	Average fill weight/uniformity of weight (as applicable) Reconstitution time Uniformity of content	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Primary packaging (bottles for dry syrup, suspension, liquid orals, tablets, capsules)	Power to induction sealer	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of Packaging)	Leak test Assay (in case of heat-sensitive product)	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification

Note: In case of direct blending in solid dosage forms, stratified sampling is preferable.
1 Samples for hold-time study shall also be withdrawn at appropriate stages, as per requirement.

B) Sampling plan for PPQ of drug substances (API) – critical operations

Manufac-turing stages	Process variables/ validation study	Sampling/ recording stages	Tests to be performed	Approx. sample size	Acceptance criteria
Addition of reagents and/or solvents	Order of addition	Charging	Order verification as per PPQ Protocol	Not applicable	As specified in PPQ Protocol
	Quantity of reagents and/or solvents	Charging	Verification as per load cell, actuator, flow meter, rotary charging valve, metering pump, calibrated charge vessels with orifice in the addition line, weighing balance	Not applicable	As specified in PPQ Protocol
	Rate of addition	As specified in PPQ Protocol, or at start, middle and near end stage of addition	Verification as per load cell, actuator, flow meter, rotary charging valve, metering pump	Monitor at each sampling stage	As specified in PPQ Protocol
	Temperature required at the time of addition	As specified in PPQ Protocol	Record temperature	Monitor temperature	As specified in PPQ Protocol
	Temperature of the reaction mass as well as the solvent and/or reagent				
Reaction procedure	Temperature	As specified in PPQ Protocol I	Physical verification	Monitor temperature at each stage	Specified temperature range in PPQ protocol
	Time of reaction	Start and end stage of reaction	Record time	Record start and end point of reaction	± X Minutes of total reaction time as specified in PPQ protocol
Reaction procedure	pH	As specified in PPQ Protocol	Record pH	Monitor pH at each stage	± X of value/range as specified PPQ protocol
	Pressure	As specified in PPQ Protocol	Record Pressure	Monitor pressure at each stage	± X bar as specified in PPQ protocol
	Reaction monitoring	As specified in PPQ Protocol	HPLC/GC/ analysis OR as per PPQ protocol	As specified in PPQ Protocol	As specified in PPQ Protocol
Recovery of solvent	Temperature	Start, middle and near end stage of recovery	Record temperature of reaction mass/utility	Monitor temperature at each sampling stage	± X°C or temperature range as specified PPQ protocol
	Vacuum	Start, middle and near end stage of recovery	Record pressure	Monitor at each sampling stage	± X bar or range as specified in PPQ protocol

B) Sampling plan for PPQ of drug substances (API) – critical operations

Manufac-turing stages	Process variables/ validation study	Sampling/ recording stages	Tests to be performed	Approx. sample size	Acceptance criteria
Crystalli-zation	Order of addition of solvents or reagents	As specified in PPQ protocol	Verification as per PPQ protocol	Not applicable	Order as specified in PPQ protocol
	Quantity of solvents or reagents	As specified in PPQ protocol	Verification as per load cell, actuator, flow meter, rotary charging valve, metering pump, weighing balance	Not applicable	Quantity as specified in PPQ protocol
	Rate of addition of solvents	As specified in PPQ Protocol, or at start, middle and near end stage of addition	Verification as per load cell, actuator/ flow meter/metering pump/calibrated charge vessels with orifice in the addition line	Monitor the rate of addition at each sampling stage	As specified in PPQ Protocol
	Temperature of addition of solvents	As specified in PPQ Protocol, or at start, middle and near end stage of addition	Temperature	Monitor temperature at each sampling stage	± X°C or temperature range as specified in PPQ Protocol
	Temperature of the reaction mass as well as the solvent and/or reagent				
	Agitation	Start, middle and near end stage of crystallization, or as per PPQ protocol	Record RPM	Monitor RPM of agitator at each stage	Range of RPM as specified in PPQ Protocol
Filtration	Temperature of slurry during filtration	Start, middle and near end stage of filtration, or as per PPQ protocol	Record temperature	Monitor temperature at each stage	± X°C or temperature range specified in PPQ Protocol
Drying	Drying temperature (utility)	Start, middle and near end stage of drying, or as per PPQ protocol	Record temperature	Monitor temperature at each stage	± X°C or temperature as specified in PPQ protocol
	Drying temperature (dryer chamber)	Start, middle and near end stage of drying, or as per PPQ protocol	Record temperature	Monitor temperature at each stage	± Y°C or temperature as specified in PPQ protocol

C) Sampling plan for packaging process qualification for bottles

Test condition	Summary - no. of samples
Low power to induction sealer (60-65%)	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
Optimum power to induction sealer (66-75%)	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
High power to induction sealer (75-90%)	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
Low speed of conveyor	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
Optimum speed of conveyor	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
High speed of conveyor	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
Distance between sealing head and the bottle cap **Distance =_____**	▪ Visual check of sealing quality: ____ bottles ▪ Leak test: _____ Nos.
Note: ▪ **Guidance: samples shall be withdrawn at the start, middle and end of the packaging process.** ▪ **Visual checks shall be performed based on relevant SOPs.**	

D) Sampling plan for packaging process qualification for blisters/strips

Test condition	Summary - no. of samples
Low sealing temperature – low conveyor speed	▪ Visual check and leak test: _____ packs
Low temperature – optimum conveyor speed	▪ Visual check and leak test: _____ packs
Low temperature – high conveyor speed	▪ Visual check and leak test: _____ packs
Optimum temperature – low conveyor speed	▪ Visual check and leak test: _____ packs
Optimum temperature – optimum conveyor speed	▪ Visual check and leak test: _____ packs
Optimum temperature – high conveyor speed	▪ Visual check and leak test: _____ packs
High temperature – low conveyor speed	▪ Visual check and leak test: _____ packs
High temperature – optimum conveyor speed	▪ Visual check and leak test: _____ packs
High temperature – high conveyor speed	▪ Visual check and leak test: _____ packs
▪ **Guidance: samples shall be withdrawn at the start, middle and end of the packaging process.** ▪ **Visual checks shall be performed based on relevant SOPs.**	

Annexure 7

Blend uniformity and content uniformity sampling and testing plan as per ASTM guidelines

Stage: process performance qualification

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Final blend	Blend uniformity sample shall be collected at final blending stage for initial PPQ batches Three-unit dose samples each shall be withdrawn from 10 different sampling locations/ points of the blender comprising of upper, middle and lower layers and bottom of the blender after mixing for specified time. (Refer to Sampling Location Diagram for sampling points)	More than 3 'Unit' dose quantities from each sampling point in triplicate may be taken, if scientifically justified More than three-unit dose samples may be taken based on the process, if scientifically justified		
	Out of these, one-unit dose sample from each of the 10 locations shall be tested for assay	10-unit doses	Blend uniformity	**Tier I:** SD should not be more than 3.0 %. Mean value of test results should not be less than 95.0% and not more than 105.0% of the labeled amount. (Covering 10 locations at the rate of 1 sample from each location, a total of 10 samples shall be drawn)
	In case of failure to meet acceptance criteria of Tier I, the remaining 20 samples shall be analyzed	20-unit doses	Blend uniformity	**Tier II:** SD should not be more than 5.0 % Mean value of test results should not be less than 95.0% and not more than 105.0% of the labeled amount. (Covering 10 locations at the rate of 3 samples from each location, a total 30 samples shall be drawn. At Tier I testing, 10 samples, and at Tier II testing, 20 samples, shall be used.)
	In case of failure to meet acceptance criteria, investigation shall be carried out. In case samples are required for hypothesis testing and probable cause is established for initial failure, 1 set of samples, from the 10 locations from same container, shall be withdraw for evaluation. Unloaded bin: In case the blend is unloaded to IPC (Intermediate Product Containers/Bins) before further processing, sampling and evaluation shall be done from each container as per the above sampling plan			

Stage: post-process performance qualification of formulation containing active ingredient less than 25% of fill weight or less than 25mg

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Final blend (Contd.)	Blend uniformity sample shall be collected at final blending stage for subsequent number of batches that is decided based on PPQ study, or the number of batches needed to justify test results statistically Three-unit dose samples each shall be withdrawn from 10 different locations of the blender comprising of upper, middle and bottom layers and bottom of the blender after mixing for specified time. (Refer to Sampling Location Diagram for sampling points)	More than 3 'Unit' dose quantities from each sampling point in triplicate may be taken, if scientifically justified More than 3 unit dose samples may be taken based on the process, if scientifically justified	Blend uniformity	
	Out of these, one-unit dose sample from each of the 3 locations shall be tested for assay In case of failure to meet acceptance criteria of Tier I, remaining 20 samples shall be analyzed In case failure to meet acceptance criteria, investigation shall be carried out. In case samples are required for hypothesis testing and probable cause is established for initial failure, 1 set of samples, from the 10 locations from same container, shall be withdraw for evaluation.	10-unit doses 20-unit doses	Blend uniformity	**Tier I:** SD should not be more than 3.0 %. Mean value of test results should not be less than 95.0% and not more than 105.0% of the labeled amount. (Covering 10 locations at the rate of 1 sample from each location, a total of 10 samples shall be drawn) **Tier II:** SD should not be more than 5.0 % Mean value of test results should not be less than 95.0% and not more than 105.0% of the labeled amount. (Covering 10 locations at the rate of 3 samples from each location, a total 30 samples shall be drawn. At Tier I testing, 10 samples, and at Tier II testing, 20 samples, shall be used.)

Stage: process performance qualification of tablets formulation products

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Compression	Samples shall be collected at tablet compression stage for initial PPQ batches If Blend Uniformity test results are SD ≤ 3% at final blend stage, then six units each shall be collected from 40 locations spread across entire batch and samples from each location to be kept in individual sample pouches and numbered as 1, 2, 3….40 Note: In case of double rotary compression machines, equal number of locations shall be selected from both sides of press, i.e. 20 locations from right and 20 locations from the left Set 1 shall comprise of 6 tablets each from 20 locations (start, middle, end and covering the entire run). Sample pouches shall be numbered as indicated: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 Set 2 shall comprise of 6 tablets each from remaining 20 locations. Sample pouches shall be numbered as indicated: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40 Note: events and periodic samples shall be predefined in the sampling plan	240 tablets Sample quantity can be increased based on scientific justification		
	Three units each from 20 locations of set 1 shall be tested For double rotary machines, 3 units each of 10 locations selected from left and 10 locations from right side (covering start, middle, and end) of compression machine shall be tested In case failure to meet acceptance criteria, investigation shall be carried out. Remaining quantity from set 1 (i.e., 3 units each from 20 locations) shall be used for analysis and conclusion of investigation and/or hypothesis testing as required In case sample from set 1 are used for hypothesis testing and probable cause is established for initial failure, samples from remaining 20 locations (set 2) may be used for Tier – II evaluation	60 tablets Sample quantity can be increased based on scientific justification	Uniformity of dosage unit by Content Uniformity	**Tier - I, n=60 units** All individual values should be within 75% to 125 % of label claim and compliant with statistical tests to provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810) **Tier - II, n=120 units** All individual values should be within 75% to 125 % of label claim and compliant with statistical test to provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810)

Stage: process performance qualification of tablets formulation products

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Compression (Contd.)	If Blend Uniformity test results are SD 3.1% to 5.0% at final blend stage and/or compression results are not meet to Tier-I criteria, then 3 units each from 40 locations shall be tested Note: in case of double rotary compression machines, equal number of locations shall be selected from both sides of press, i.e. 20 locations from the right and 20 locations from the left	360 tablets	Uniformity of dosage unit by Content Uniformity	
	3 units each from 40 locations shall be tested For double rotary machines, 3 units each of 20 locations selected from left and 20 locations from right side In case failure to meet acceptance criteria, investigation shall be carried out Remaining quantity from set 1 (i.e., 3 units each from 20/40 locations) shall be used for analysis and conclusion of investigation and/or hypothesis testing as required In case samples are used for hypothesis testing and probable cause is established for initial failure, 3 units from the remaining quantity of samples at each of 40 locations shall be used for Tier - II evaluation	120 tablets Sample quantity can be increased based on scientific justification	Uniformity of dosage unit by Content Uniformity	**Tier - I, n=120 units** All individual values should be within 75% to 125 % of label claim and compliant with statistical testto provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810) **Tier - II, n=240 units** All individual values should be within 75% to 125 % of label claim and compliant with statistical testto provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810)
Compression (Contd.)	24 units each shall be collected from start, middle and end of compression run	72 tablets (24 tablets each from start, middle and end) Sample quantity can be increased based on justification	Dissolution on 6 tablets each from start, middle and end. Remaining tablets may be used for further stages of dissolution, if necessary	Test results shall meet the product specification
Speed Challenge: compression at maximum, optimum and minimum speeds	Samples shall be collected after setting the machine at maximum, minimum and optimum speeds. (Machine shall be run at optimum speed after sampling)	150 tablets at each speed (i.e., minimum, optimum and maximum) Sample quantity can be increased based on scientific justification	Weight variation; thickness; hardness; friability; disintegration time (DT); dissolution	Weight variation, thickness, hardness, friability, and DT test results shall comply with the limits specified in BMR Dissolution test results should meet the product specification

Stage: process performance qualification of tablets formulation products

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Speed Challenge: compression at maximum, optimum and minimum speeds (Contd.)	For content uniformity test, 30 tablets each shall be collected for three different machine speeds, i.e., minimum, optimum and maximum, and these shall be tested for content uniformity	30 Tablets at each speed		
	Out of these, 10 tablets sample from each speed setting shall be tested	10 Tablets out of 30 tablets sampled	Uniformity of dosage unit by Content Uniformity	Individual assay values shall be within 75%-125% and AV value shall be ≤ 15.0 as per USP<905>
	In case of failure to meet acceptance criteria, investigation shall be carried out. Remaining quantity shall be used for analysis and conclusion of investigation and/or hypothesis testing as required In case samples are used for hypothesis testing and probable cause is established for initial failure, 10 units from the remaining quantity of samples from each speed setting shall be used for evaluation Note: if the machine speed challenge study was not performed during pre-exhibit/ exhibit/ revalidation batches, then this study shall be performed on the first batch of process performance qualification			

Stage: post process performance qualification of tablets formulation containing active ingredient less than 25% of fill weight or less than 25mg

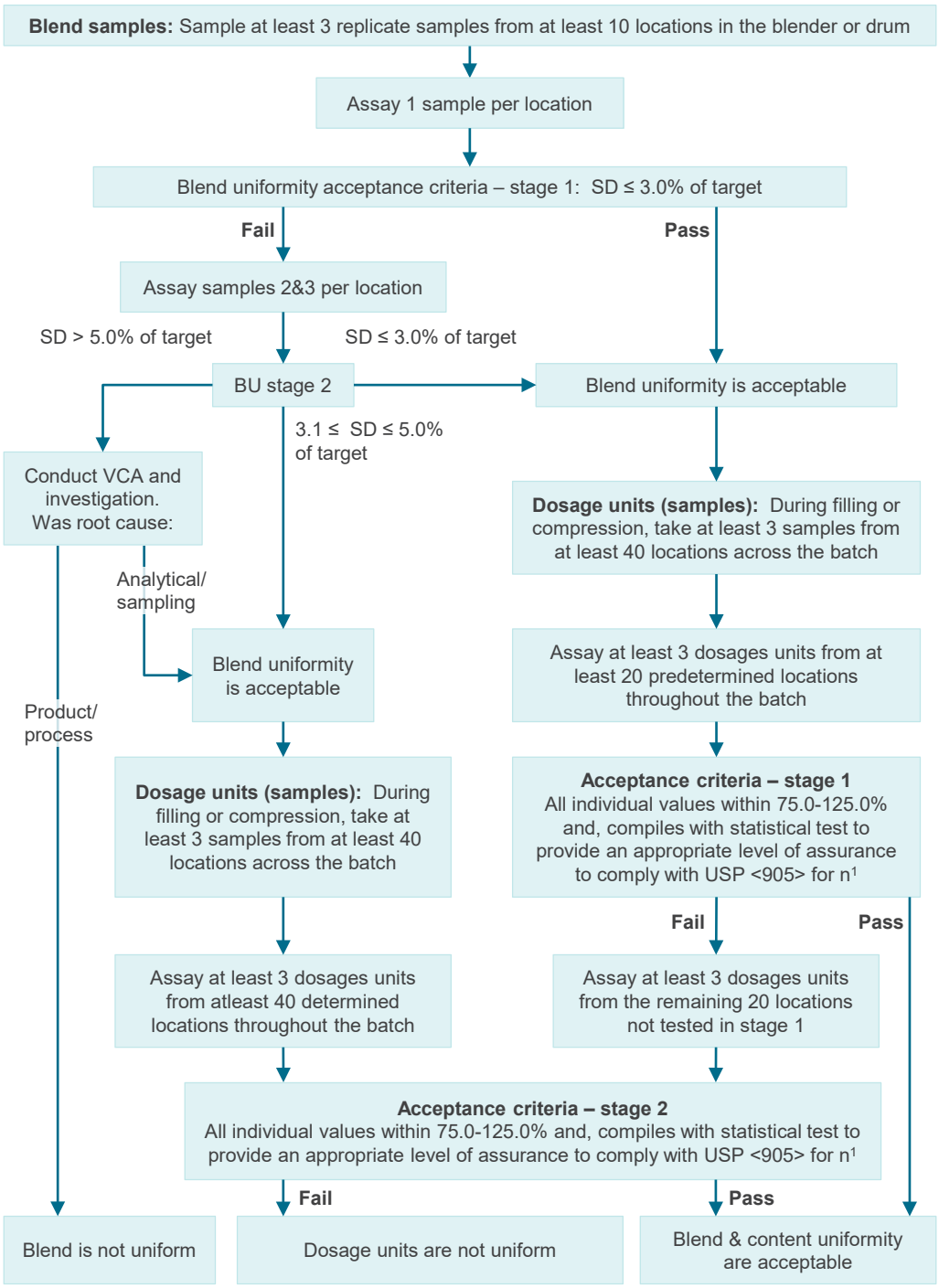
Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Compression	Content uniformity samples shall be collected at tablet compression stage for subsequent 10 batches, or the number of batches needed to justify test results statistically Three units each shall be collected from 30 locations spread across the entire batch and samples from each location shall be kept in individual sample pouches numbered as 1, 2, 3…...30 Note: in case of double rotary compression machines, equal number of locations shall be selected from both sides of press	180 tablets (6 units each from 30 locations)		
	1 unit each from 10 locations shall be tested, (*) i.e. samples numbered as 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 In case Tier I test results do not comply with acceptance criteria, then one tablet from each of the remaining 20 locations shall be tested The sampling plan and acceptance criteria of initial PPQ batches can be extended to a larger numbers of batches based on prior product knowledge, criticality and statistical and/or scientific justification	10 tablets 20 tablets	Uniformity of dosage unit by Content Uniformity	**Tier I** **N=10** All individual values should be within 75% to 125 % of label claim and compliant with statistical test to provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810) **Tier II** **N=30 units** All individual value should be within 75% to 125 % of label claim and compliant with statistical test to provide an appropriate level of assurance to comply with USP <905> for n. (This can be based on ASTM 2709 and/or 2810)
	In case of failure to meet acceptance criteria, investigation shall be carried. Remaining quantity of samples shall be used for analysis and conclusion of investigation and/or hypothesis testing as required In case samples are used for hypothesis testing and probable cause is established for initial failure, 1 unit from the remaining quantity of samples at each location shall be used for evaluation			

Stage: post process performance qualification of tablets formulation containing active ingredient ≥ 25% of fill weight or ≥ 25mg

Process stage	Sampling procedure	Sample quantity	Test	Acceptance criteria
Compression	Weight variation results obtained from batch manufacturing records of approx. 10 subsequent batches covering start, middle and end of compression run.	Weight of 30 tablets (10 each from start, middle and end of compression run)		
		NA	Uniformity of dosage unit by Weight Variation	Individual assay values shall be within 75% -125% and are compliant with ASTM E2810 acceptance limit table for sampling plan 1 with 90% confidence/95% coverage to pass USP <905>

Process flow diagram for assessment of blend and content uniformity for process qualification batches

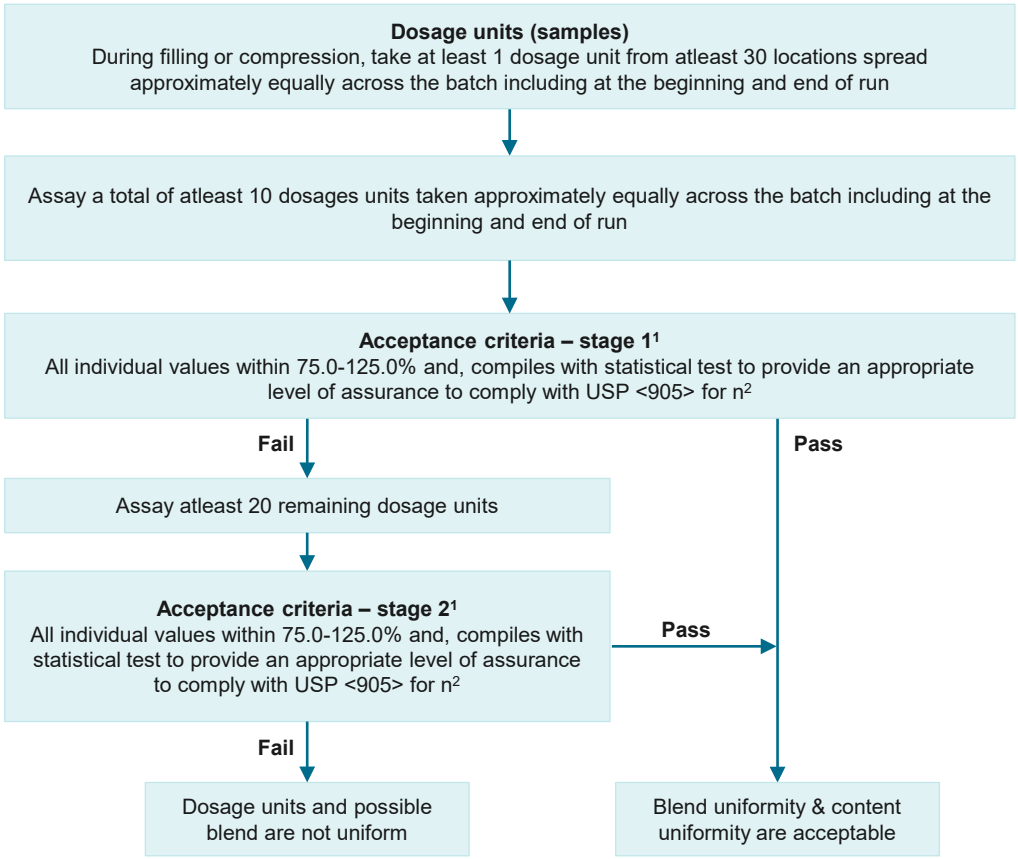
Published in: *J Pharm Innov,* 2014 (DOI) 10.1007/s12247-014-9207-0



1 n is the total number of assay results.

Process flow diagram for assessment of blend and content uniformity for continued process verification (stage 3B) batches

Published in: *J Pharm Innov,* 2014 (DOI) 10.1007/s12247-014-9207-0



1 Acceptance criteria for stage 3 continued process verification may have reduced assurance to comply with USP <905> compared to that used for stage 2 process qualification.
2 n is the total number of assay results.

Annexure 8

Signing of this protocol indicates agreement with the Process Performance Qualification approach of **[PRODUCT NAME]**. If any changes in this protocol are required, this protocol shall be revised and duly approved.

1.0 Protocol pre-approval

Responsibility	Department	Name	Signature and Date
PREPARED BY	TT/Production		
REVIEWED BY	QA (Plant)		
	Production		
	Quality Control		
	Quality (R&D)		
APPROVED BY	Quality Assurance		

PROTOCOL EFFECTIVE DATE	

2.0 Objectives

The objectives of this Process Performance Qualification Protocol are:

- To collect sufficient data to establish that the manufacturing process of **[PRODUCT NAME]** consistently produces a product that meets its predetermined quality parameters based on three consecutive production batches.
- To leverage process understanding and process knowledge gained from product development study, exhibit batch and pre-validation batch in the commercial batches.
- To provide the procedure for collection of Process Performance Qualification samples.
- To generate Process Performance Qualification report to establish documented evidence that the process is capable of manufacturing reproducible commercial batches and consistently deliver quality product and provide recommendations for continued process verification.

3.0 Purpose

This protocol is applicable for the process validation of **[PRODUCT NAME]** as an alternate batch size, under which manufacturing stages shall be validated. Based on the validation data and report, feasibility of the process will be evaluated.

4.0 Responsibility

Production

- To prepare batch manufacturing record for validation.
- To prepare and review the process performance qualification protocol and reports.
- To carry out the validation activity as per approved protocol.
- To review the validation data for consistency.
- To investigate any deviations and failures and to recommend changes (if required).
- To conduct training on protocol for process validation prior to start of the activity.

Quality control

- To perform analyses of samples received as per Process Performance Qualification Protocol.
- To review the Process Performance Qualification Protocol and reports.
- To perform analyses of samples as per stability protocol and compilation of reports.

Regulatory affairs

- To review the Process Performance Qualification Protocol and reports from the regulatory perspective.

Quality assurance

- To approve the Process Performance Qualification Protocol and reports.
- To draw samples as per the Process Performance Qualification Protocol and to send such samples for analyses to Quality Control Department.
- To review the stability data with respect to Process Performance Qualification reports.
- To ensure that training on protocol of Process Performance Qualification has been imparted prior to start of the activity.

5.0 Reference documents

Sr. No.	Document	Reference Number[1]
i	Master Formula Card	
ii	Active Raw Material Specification	
iii	In-process Specification	
iv	In-process Standard Test Procedure	
v	Finished Product Release Specification	
vi	Finished Product Standard Test Procedure	
vii	Batch Manufacturing Record	

1 At any point in time, only the current version should be followed.

6.0 Product details

a. Product name :

b. Generic name :

c. SFG code :

d. Product description :

e. Dosage form :

f. Strength :

g. Label claim :

h. Theoretical tablet weight : Core tablet :

Coated tablet :

i. Punch tooling details : Punch size and shape :

Upper punch :

Lower punch :

j. Category :

7.0 Composition (manufacturing formula)

Sr. No.	Material Code	Ingredients	Specification	Quantity per tablet (mg)	Quantity per batch (kg)
CORE TABLET					
MIXING					
1					
2					
3					
4					
5					
BINDING					
6					
7					
LUBRICATION					
8					
9					
FILM-COATED TABLET					
10					
11					
12					
13					
14					
15					

8.0 Brief description of the process (template#)

1. Material Requisition Note (MRN) is raised as per the BMR and materials are issued from RM store.

2. The materials are sifted, issued for dry mixing, blending and lubrication (separately), using vibratory sifter.

3. The materials are loaded in the RMG and mixed as per the BMR.

4. The binding agent is prepared and added to the RMG containing dry mixed materials. The material is mixed till the required consistency of wet mass is obtained.

5. The wet mass is discharged from the RMG into the clean FBD bowl, and dried in the FBD till the required LOD is obtained.

6. The dried granules are sifted through_____ sieve on vibratory sifter and the granules that pass through the sieve are collected into a clean dry bunker.

7. The oversized granules are milled through a comminuting mill fitted with _____mm SS screen and the milled granules are collected into the bunker.

8. Lubricants are added into the bunker containing the milled granules, and the granules are lubricated by operating the Conta blender as per the BMR.

9. The lubricated granules are compressed using rotary tablet compression machine as per parameters specified in the BMR.

10. The compressed tablets are transferred to the WIP store as per SOP No._____.

11. The compressed tablets are transferred from the WIP store to Coating area.

12. The film coating suspension is prepared, and the coating process is followed as per the BMR.

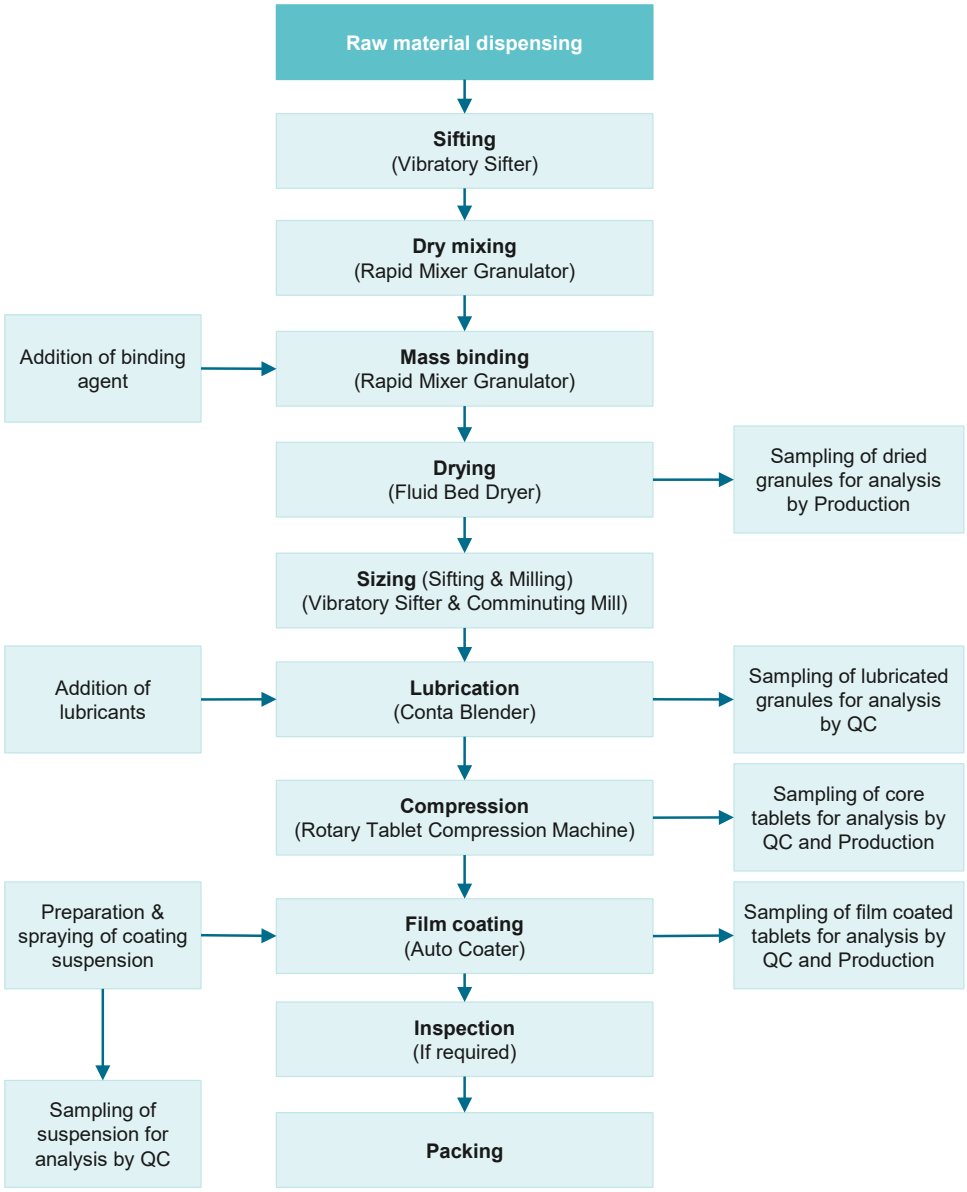
13. The coated tablets are transferred to the WIP store as per SOP No._____.

14. The coated tablets are transferred from the WIP store to the inspection area, if required.

15. After inspection, the tablets that are passed are transferred to the respective storage area for packing.

This document is a template and the blanks are to be filled in with relevant information by the concerned user.

9.0 Process flow-chart



10.0 Process performance qualification methodology

Based on process understanding and process knowledge gained from Product Development studies, Exhibit Batch studies and Process Evaluation studies in the commercial batches, it is recommended that three consecutive batches be considered for Process Performance Qualification study. Based on this PPQ study, the requirement for extensive sampling (if any) in additional batches shall be evaluated and recommended in the PPQ report.

10.1 Process timeframe

The process performance qualification studies for three batches shall be completed within 60 days from the initiation of the first batch.

10.2 Verification of design of the facility and qualification of utilities and equipment

Prior to initiation of batch manufacturing, verification of design and verification of qualification status of facility, utilities and equipment shall be ensured and documented.

10.2.1 Facility design and qualification

The areas where manufacturing of the product is proposed shall be evaluated for its fitness and qualification status in order to manufacture this product.

10.2.2 Utilities qualification

The utilities involved in the manufacturing shall be evaluated for its qualification status.

10.2.3 Equipment qualification

The major equipment involved in the manufacturing this product shall be evaluated for their qualification status.

10.3 Operational controls

10.3.1 Dispensing

All the raw materials shall be dispensed in the dispensing area of the warehouse at stations which are under contamination control, as mentioned in Production Order – Raw Material.

The dispensed raw material shall be transferred to the production facility.

10.3.2 Raw material quantity verification

The quantity of dispensed raw material shall be verified by Production personnel and shall be cross-verified by QA before starting the manufacturing activity.

10.3.3 Personnel performing the activity

Trained personnel shall perform each activity during the manufacturing process.

10.3.4 Production equipment

Sr. No.	Equipment Name	ID No.		Reference SOP No.			
				Cleaning		Operation	
1	Vibratory Sifter						
2	Rapid Mixer Granulator						
3	Stirrer						
4	Fluid Bed Dryer						
5	Comminuting Mill						
6	Conta Blender						
7	Bunker						
8	Rotary Tablet Compression Machine and Metal Detectors	Compression Machine	Metal Detector	Compression Machine	Metal Detector	Compression Machine	Metal Detector
9	Deburring Unit						
10	Colloid Mill						
11	Auto Coater						
12	Stirrer						

10.3.5 Testing instruments

The testing instruments shall be verified for their calibration status and fitness for use.

11.0 Control strategy

Based on process understanding and process knowledge gained from Product Development studies, Exhibit Batch studies and Process Evaluation studies in the commercial batches, the summary of CPP's and CQA's are mentioned below.

11.1 Summary of CPPs and CQAs

After a complete review of the development phase, the lab-scale batch, the exhibit batch, and the commercial-scale trial batches (if any), the process is found to be reproducible.

The following chart indicates the final identified critical process parameters from the point of view of reproducibility and control strategy for the execution of commercial validation batches.

Unit Operation	Process Variable and/or Parameters	CPP (Yes/No)	CQA's	Recommended for Process Validation Batch		Scale Dependent	Remarks
				Range	Target		

Note: The identified CPP and recommendations for the commercial batches should be highlighted in the Batch Record.

11.2 Summary of parameters other than CPPs

Unit Operation	Process Parameters (Other than CPPs)	Recommended for Process Validation		Scale Dependent	Remarks
		Range	Target		

12.0 Study plan template

Whenever a new product is introduced for manufacturing on commercial scale batches, or any major change is introduced either in process or equipment train, it will be subjected to Process Validation with predetermined parameters. Three such batches will be validated. On completion of validation batches, a validation report will be prepared stating the feasibility of the process and achievement of the acceptance criteria. Before Process Validation, the process area and all the equipment should have been qualified and all the necessary Technology Transfer documents should be available.

a	Type of validation	:	Prospective validation
b	Number of batches	:	Three consecutive batches
c	Batch size	:	__Tablets#

This document is a template. The concerned user should fill in the blank with the relevant data.

13.0 Sampling plan template

Manufacturing Stage	Process Variables	Test Parameter	Sample Quantity	Sampling Interval	Sampling Points	Sample Container	Acceptance Criteria
SIFTING	▪ Sieve Size	% Yield [1]	---	---	---	---	NLT %[2]
DRY MIXING	▪ Main Impeller/ Chopper Impeller Speed ▪ Mixing Time	---	---	---	---	---	---
MASS BINDING	▪ Binder Addition Time ▪ Main Impeller/ Chopper Impeller Speed ▪ Wet Mixing Time ▪ Kneading Time ▪ Ampere Load ▪ Torque	----	----	----	----	----	----
DRYING	▪ Inlet Air Temperature ▪ Outlet Air Temperature ▪ Drying Time ▪ Inlet air Dew point ▪ Inlet air Abs Humidity	LOD [1]	Approximate (gm.)	After drying	S1 to S 6 Composite sample (As per figure I)	Glass vials, rubber closures and aluminum seal or LDPE bag	% w/w
		% Yield [1]	---	---	---	---	NLT %[2]
SIZING (Sifting and Milling)	▪ Screen Size ▪ Sieve Size ▪ Space between impeller and screen ▪ Speed of Quadro mill ▪ Oscillation of OG	% Yield [1]	---	---	---	---	NLT %[2]

Remarks:

1 Indicates tests should be performed as part of in-process testing.

2 Will be finalized based on validation batches.

Manufacturing Stage	Process Variables	Test Parameter	Sample Quantity	Sampling Interval	Sampling Points	Sample Container	Acceptance Criteria
LUBRICATION	▪ Lubrication Time	Blend uniformity analysis [2]	Approximate _mg to _mg (1 to 3 unit dose in triplicate, from each location)[4]	After lubrication	S1 to S10 (As per figure II)	Glass vials, rubber closures and aluminum seal or LDPE bag	
		Composite Sample Assay [2]	Approximate 10.00 gm.		Composite sample from top, middle and bottom layer (As per figure II)		
		Description [2]					White to off-white granular powder
		LOD [2]					For reference only
		%Yield [1]	--				NLT % [3]

Remarks:

1 Indicates tests should be performed as part of in-process testing.

2 Indicates tests should be performed by Quality Control Department.

3 Will be finalized based on validation batches.

4 Sampling quantity can be up to 10 dosage unit based on scientific justification/rationale.

Note: Blend uniformity study should be done as per ISPE recommendations.

Manufacturing Stage	Process Variables	Test Parameter	Sample Quantity	Sampling Interval	Sampling Points	Sample Container	Acceptance Criteria
COMPRESSION	▪ Hardness ▪ Machine Speed	Description [1]	Tablets ≅ to number of stations of the machine.	For each test parameter, samples should be collected at lower, normal and higher machine speeds separately.	From chute	LDPE bag	
		Average weight [1]					
		Weight of 10 tablets [1]					
		Uniformity of weight[1]					
		Hardness [1]					
		Thickness [1]					
		Friability [1]	_____Tablets				
		Dissolution [2]	_____Tablets	At lower and higher speeds, and end of compression at normal speed.			
		Content uniformity[2] (by stratified sampling method)	_____Tablets	At lower and higher speeds.			
			_____Tablets	At Normal speed			
		Description [2]	_____Tablets	After completion of compression at normal speed.	From tablets container		
		Assay [2]					
		%Yield [1]	--				NLT %[3]

Remarks:

1 Indicates tests should be performed as part of in-process testing.

2 Indicates tests should be performed by Quality Control Department.

3 Will be finalized based on validation batches.

Note: Content uniformity study should be done as per ISPE recommendations.

Manufacturing Stage	Process Variables	Test Parameter	Sample Quantity	Sampling Interval	Sampling Points	Sample Container	Acceptance Criteria
COATING SUSPENSION PREPARATION	----	Viscosity of coating suspension[2]	Minimum 300 ml	After solution preparation	Solution preparation tank	Glass bottle	For reference only
FILM COATING	▪ Atomization air pressure ▪ Pan speed ▪ Spray Rate ▪ Outlet air temp. ▪ Inlet air temp. ▪ Inlet air flow ▪ Tablet bed temp.	**Core tablets** Water content by KF [2] LOD [2]	Tablets equivalent to 2 gm for each test	Composite core tablets before coating	From tablets container	LDPE bag	For reference only
		Coated tablets Description [1]	100 tablets	After coating	From Coating Pan (As per figure III)	LDPE bag	
		Average weight[1]					
		Weight gain [1]					
		Thickness [1]					
		Water content by KF [2,3]	Tablets equivalent to 2 gm for each test				
		LOD [2]					
		Assay [3]	Not applicable	--	--	--	
		Dissolution [3]					
		Uniformity of dosage units [3] (by content uniformity)					
		Residual solvent [3] — Isopropyl alcohol					
		Residual solvent [3] — Methylene chloride					
		Yield [1]	--				NLT %*
INSPECTION	------	Batch yield [1]	--				NLT %*

Remarks:

14.0 Methodology for sampling template

The following methodology should be adopted during the process validation of **[PRODUCT NAME]**.

Sr. No.	Stage	Functional Department	Process
1	Sifting	Production	▪ The material should be sifted through vibratory sifter as per the BMR. ▪ The observations and yield data should be recorded in test data slip and in the BMR.
2	Dry Mixing	Production	▪ The ingredients should be loaded in the RMG bowl after sifting. ▪ The RMG should be operated as per instructions given in the BMR. ▪ The contents should be mixed for _____ sec. at the impeller and chopper speeds as indicated in the BMR. ▪ The yield should be recorded in test data slip and in the BMR.
3	Mass Binding	Production	▪ The binding agent should be prepared as mentioned in the BMR. ▪ The binding agent should be added through the RMG window, and the RMG should be operated with the impeller and the chopper running at speeds specified mentioned in the BMR. ▪ After addition of the binding agent, the RMG should be operated with the impeller and the chopper running at the speeds specified in the BMR. ▪ Extra vehicle (if required) should be added to get the required consistency of the wet mass. This should be recorded in BMR. ▪ The ampere load, the wet mixing time and the kneading time should all be recorded in the test data slip and in the BMR.
4	Drying	Production	▪ The wet mass from RMG should be unloaded to the cleaned FBD bowl. ▪ The FBD should be operated as per instructions given in BMR, and the wet mass should be dried at the inlet temperature specified in the BMR. ▪ The inlet temperature, the outlet temperature and the drying time of FBD should be noted in the test data slip and in the BMR. ▪ The samples from the FBD bowl should be withdrawn as per the sampling point indicated in Figure I, described later in this Annexure. ▪ A composite sample should be prepared and the LOD should be checked using a halogen moisture analyzer as per instructions given in the BMR. ▪ Drying should be continued till the required LOD is achieved. ▪ The observations and the yield data should be recorded in the test data slip and in the BMR.
5	Sizing (Sifting and Milling)	Production	▪ The dried granules should be sifted through _____# sieve on a vibratory sifter and the granules that are passed through should be collected in a clean dry bunker. ▪ The oversized granules should be milled in the comminuting mill fitted with a _____mm SS screen and the milled granules should be collected in the bunker. ▪ The observations and the yield data should be recorded in the test data slip and in the BMR.
6	Lubrication	Production	▪ The lubricants should be added to the milled granules, and the granules should be lubricated for _____minutes by operating the Conta blender as per instructions given in BMR. ▪ The observations and the yield data should be recorded in the test data slip and in the BMR. ▪ Samples should be drawn after lubrication, using samplers from top, middle and bottom layers as per the sampling point (Figure II, described later in this Annexure). A composite sample should also be drawn. ▪ The samples should be sent to QC for analyses along with test data slip.

<table>
<tr><th>Sr. No.</th><th>Stage</th><th>Functional Department</th><th>Process</th></tr>
<tr><td rowspan="5">7</td><td rowspan="5">Compression</td><td>Production</td><td>▪ The compression machine should be operated as per instructions given in the BMR.
▪ The lubricated granules should be compressed as specified in the BMR.
▪ The machine should be set at a lower speed (RPM[1])
▪ The initial control on product parameters should be achieved.
▪ The samples should be withdrawn after 10 minutes of running at the above set speed, tested for the following parameters and the test data should be recorded in the test data slip.<table><tr><td>▪ Description</td><td>▪ Thickness</td></tr><tr><td>▪ Average Weight</td><td>▪ Friability</td></tr><tr><td>▪ Weight of 10 tablets</td><td>▪ Hardness</td></tr><tr><td>▪ Uniformity of weight</td><td></td></tr></table></td></tr>
<tr><td>QA</td><td>▪ Samples should be collected (by stratified sampling method) for content uniformity testing from locations of the specific events mentioned in the test data slip, and for dissolution after 10 minutes of running at the above set speed.
▪ Samples should be sent to QC for analyses along with test data slip.</td></tr>
<tr><td>Production</td><td>▪ The machine should be set at a higher speed (RPM[1]).
▪ The initial controls on product parameters should be achieved.
▪ The samples should be withdrawn after 10 minutes of running at the above set speed, tested for the following parameters and the test data should be recorded in the test data slip.<table><tr><td>▪ Description</td><td>▪ Thickness</td></tr><tr><td>▪ Average Weight</td><td>▪ Friability</td></tr><tr><td>▪ Weight of 10 tablets</td><td>▪ Hardness</td></tr><tr><td>▪ Uniformity of weight</td><td></td></tr></table></td></tr>
<tr><td>QA</td><td>▪ Samples should be collected (by stratified sampling method) for content uniformity testing from locations of the specific events mentioned in the test data slip, and for dissolution after 10 minutes of running at the above set speed.
▪ Samples should be sent to QC for analyses along with test data slip.</td></tr>
<tr><td>Production</td><td>▪ The machine should be set to run at the normal speed (RPM[1])
▪ The initial controls on product parame ters should be achieved.
▪ The whole batch should be run at the normal speed.
▪ The following in-process control parameters should be checked at the intervals given in the BMR and the data should be recorded in the BMR.<table><tr><td>▪ Description</td><td>▪ Thickness</td></tr><tr><td>▪ Average Weight</td><td>▪ Friability</td></tr><tr><td>▪ Weight of 10 tablets</td><td>▪ Hardness</td></tr><tr><td>▪ Uniformity of weight</td><td></td></tr></table>▪ The testing for the in-process parameters should be carried out throughout the batch, and the compiled data should be recorded in the test data slip.
▪ The yield data should be recorded in the test data slip and in the BMR.</td></tr>
<tr><td>QA</td><td>▪ Samples for content uniformity testing should be collected (by stratified sampling method) from twenty locations and examined for significant events at the periodic intervals specified in the test data slip at normal speed.
▪ Composite sample should also be collected for assay, description and dissolution testing, after completion of the batch at normal speed.
▪ Samples should be sent to QC for analyses along with test data slip.</td></tr>
</table>

<table>
<tr><th>Sr. No.</th><th>Stage</th><th>Functional Department</th><th>Process</th></tr>
<tr><td>8</td><td>Film Coating</td><td>Production</td><td>▪ The film coating suspension should be prepared as per the procedure given in the BMR.
▪ The compressed tablets should be loaded in the coating pan and the coating process should be carried out as per the instructions given in the BMR.
▪ The variable parameters should be recorded in the test data slip and in the BMR.
▪ Testing for the following parameters should be carried out and recorded in the test data slip.<table><tr><td>▪ Description</td><td>▪ Thickness</td></tr><tr><td>▪ Average Weight</td><td>▪ Weight Gain</td></tr></table>▪ The observation and the yield data should be recorded in the test data slip and in the BMR.</td></tr>
<tr><td></td><td></td><td>QA</td><td>▪ The samples should be withdrawn as per Figure III (described later in this Annexure) and tested for the following parameters:
– Core tablets for water by KF and % LOD.
– Seal coating suspension for viscosity.
– Seal coated tablets for water by KF and % LOD.
▪ Samples should be sent to QC for analyses along with test data slip.</td></tr>
<tr><td>9</td><td>Inspection</td><td>Production</td><td>▪ The film coated should be visually inspected using the inspection belt.
▪ The yield data should be recorded in the test data slip and in the BMR.</td></tr>
</table>

1 To be established.

15.0 Stability study

For stability study, a separate protocol should be generated. The stability study should be conducted for accelerated and long-term durations as per the protocol.

16.0 Process performance qualification report

Data generated during the Process Performance Qualification studies, test results, etc., shall be presented in a comprehensive Process Performance Qualification Report. The Process Performance Report shall include the process or product parameters to be captured on continued process verification. The Process Performance Qualification Report shall be certified by Head–R&D/FTT, Head-Production, Head-Regulatory Affairs, Head-QC and Head–QA or their authorized designees.

17.0 Continued process verification

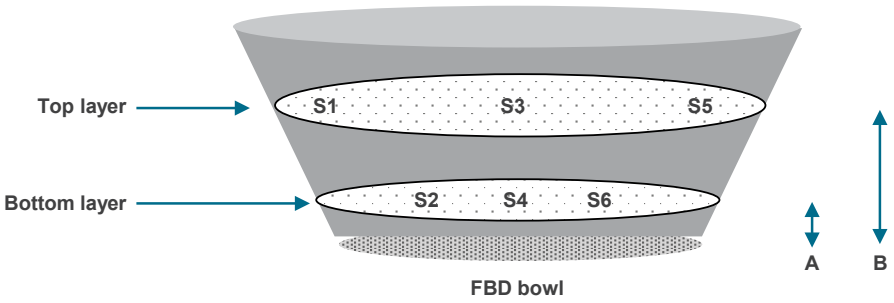
Based on the recommendations in the Process Performance Qualification Report, the relevant process and product parameters shall be monitored. The trends for the identified process and product parameters shall be monitored on an ongoing basis. The Continued Process Verification Report shall be prepared and reviewed by all relevant stakeholders.

18.0 Abbreviations

Abbreviations	Full form
BMR	Batch Manufacturing Record
BP	British Pharmacopoeia
FBD	Fluid Bed Dryer
Gm.	Gram
ID No.	Identification Number
IH	In-house
IP	Indian Pharmacopoeia
Kg.	Kilogram
LOD	Loss on Drying
Mg.	Milligram
mm.	Millimeter
NLT/NMT	Not less than/Not more than
OG	Oscillating Granulator
Ph. Eur.	European Pharmacopoeia
PV	Process validation
QA	Quality Assurance
QC	Quality Control
Qty.	Quantity
RM	Raw Material
Ref. No.	Reference Number
RMG	Rapid Mixer Granulator
RPM	Revolutions Per Minute
RSD	Relative Standard Deviation
SOP	Standard Operating Procedure
Sr. No.	Serial Number
USP	United States Pharmacopoeia
WIP	Work in Progress
w/w	Weight/Weight
COA	Certificate of Analysis
LDPE	Low Density Poly Ethylene

19.0 Sampling points (Diagramatic)

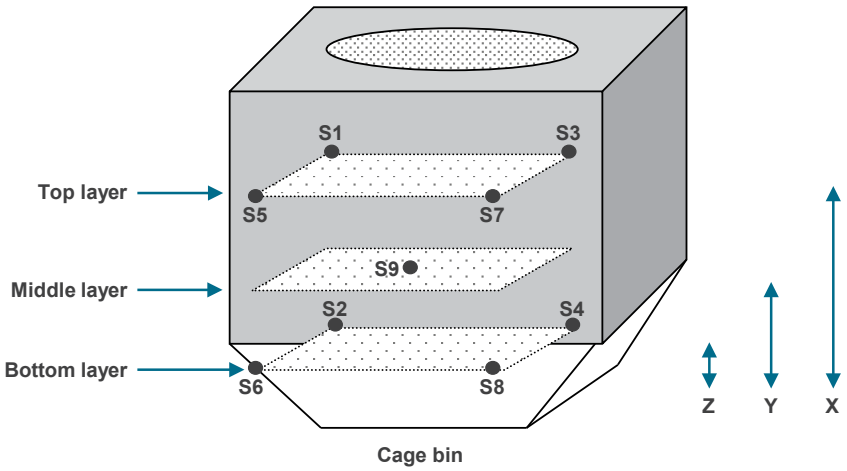
Figure I (Drying stage)



A – 1/3 of the material height from bottom. B – 2/3 of the material height from bottom.

S1 – Top left
S2 – Bottom left
S3 – Top middle
S4 – Bottom middle
S5 – Top right
S6 – Bottom right

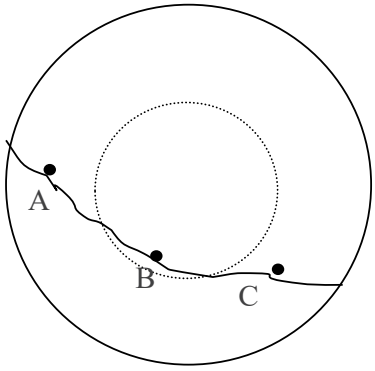
Figure II (Blending and lubrication stage)



X – 2/3 of material height from bottom. Y – 1/2 of the material height from bottom. Z – 1/3 of the material height from bottom.

S1 – Top left back corner
S2 – Bottom left back corner
S3 – Top right back corner
S4 – Bottom right back corner
S5 – Top left front corner
S6 – Bottom left front corner
S7 – Top right front corner
S8 – Bottom Right front corner
S9 – Middle center
S10 – Bottom near lid

Figure III (Coating stage)



20.0 Risk assessment

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Sifting	Sieve size	▪ Any variation in size may affect the particle size of the material leading to variation in the process parameters.	▪ Checking of sieve integrity is done before and after use, and the information is documented in the BMR, together with the ID of the sieve used.	2	1	1	2	▪ The procedure mentioned in the BMR should be followed.
		▪ Improper size could lead to non-removal of foreign particles that may be present in the material.	▪ The size of sieves to be used is mentioned in the batch manufacturing record.	3	1	1	3	▪ The procedure mentioned in the BMR should be followed.
	Torn sieve	▪ Metal contamination. ▪ Improper particle size distribution. ▪ Non-removal of foreign matter.	▪ Process should be monitored manually. ▪ Visual checking should be done before and after use, and the information recorded in the BMR. ▪ Every unit is passed through the metal detector before final batch release.	2	2	1	4	▪ Procedural controls are in place.
	Wrong sieve usage	▪ The material may not pass. ▪ The sifter may pass improper size of material.	▪ Sifter sieve size is documented in the BMR and the validation data sheet.	2	1	3	6	▪ The proper process must be followed thoroughly.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Dry Mixing	Impeller/ Chopper speed and duration	▪ If the speed is not controlled as specified in the BMR, the mixing will be inadequate leading to blend uniformity problems.	▪ The instructions are provided in the BMR including speed and duration of mixing.	3	1	1	3	▪ The procedure mentioned in the BMR should be followed. The results should be documented in the test data sheet of the validation report.
		▪ Inadequate duration and speed of mixing may result in variation in the bulk density of the material. This may impact the BUA of the product.	▪ No specific test for bulk density is carried out at this stage.	3	1	1	3	▪ The BUA is carried out only in the exhibit batches and bulk density testing is not carried even for the exhibit batches.
	Inadequate mixing	▪ Content uniformity problems. ▪ Bulk density not achieved.	▪ Operation is PLC controlled and well established.	3	1	1	3	▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Mass Binding	Binder addition time	▪ If the binder addition time is less, the distribution of the binding agent may not be proper leading to variation in compression parameters.	▪ The details of the addition are documented in the BMR and the activity is monitored by two personnel.	3	1	1	3	▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.
		▪ If the binder addition time is more, excess mixing of granules takes place leading to hard granules, which may affect the compression parameters, and affect the dissolution of the tablet.	▪ The details of the addition are documented in the BMR and the activity is monitored by two personnel.	3	1	1	3	▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.
	Impeller/ Chopper speed	▪ If the speed is not maintained as per the BMR, it will affect the granulometry of the product, which in turn may affect the product parameters.	▪ The instructions are provided in the BMR with respect to speed and are monitored by two personnel.	3	1	1	3	▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.

Item / Function / Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Mass Binding	Kneading	▪ If the mixing time is high, it may lead to over-wetting, resulting in hard granules, which may affect the product parameters.	▪ The limits and the conditions of impeller and chopper are specified in the BMR. ▪ The details are recorded in the BMR and the activity is monitored by two personnel.	3	1	1	3	▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.
		▪ If the mixing time is low, it may lead to under-wetting resulting in soft granules with high quantity of fines, which may affect the product parameters.	▪ The limits and the conditions of impeller and chopper are specified in the BMR. ▪ The details are recorded in the BMR and the activity is monitored by two personnel.					▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Mass Binding	Ampere load	▪ If the ampere load is not maintained as per the limits specified in the BMR, it may affect granulometry of the product, which in turn may affect the product parameters.	▪ The limits are specified in the BMR. The details are recorded in the BMR and the activity is monitored by two personnel. ▪ All timings and operation are PLC-controlled. ▪ The established amperage end-point granulation is PLC-controlled	3	1	1	3	▪ The procedure mentioned in the BMR must be followed. ▪ The results should be documented in the test data sheet of the validation report.
	Over-wetting/ under-wetting	▪ Inadequate or excessive hardness of tablets. ▪ Dissolution and/or D.T. failure. ▪ Problems in compression like flow problem, physical parameters not achieved. ▪ Larger percentage of fines generation.	▪ All timings and operation are PLC-controlled. ▪ The established amperage end-point granulation is PLC-controlled.	3	1	1	3	▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Drying	Inlet air temperature	▪ If the inlet air temperature is above the specified limit, it may affect the product quality. For instance, in the case of thermolabile products, it may lead to degradation. In other products, it may result in over- drying of the materials. This in turn may result in reduction in LOD and affect the compaction of the material. ▪ If the inlet air temperature is less than the specified limit, it will lead to inadequate drying resulting to sticking, lump formation, and increased LOD.	▪ All operational parameters are PLC-controlled. ▪ LOD verification is necessary. ▪ The equipment has a temperature controller to set, monitor and control the temperature. ▪ Further, the inlet temperature is recorded as per the frequency mentioned in the BMR.	3	1	1	3	▪ The instructions mentioned in the BMR must be followed.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Drying	Outlet air temperature	▪ If the outlet air temperature is above the specified limit, it may affect product quality, since, due to over-drying, the LOD may fall below the acceptable limit. This may lead to capping or compaction problems. ▪ If the outlet air temperature is less than the specified limit, it will lead to inadequate drying resulting in sticking, lump formation, and increased LOD.	▪ LOD verification is a necessity. ▪ The equipment has a temperature controller to set, monitor and control the temperature. ▪ Further, the outlet temperature is recorded as per the frequency mentioned in the BMR.	3	1	1	3	▪ The instructions mentioned in the BMR must be followed.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Drying	Drying time	▪ Increase in drying time leads to over- drying, which may affect product quality, since the LOD may fall below the acceptable limit. This may lead to capping and/or compaction problems. ▪ Decrease in the drying time may lead to insufficient drying resulting to sticking, lump formation, and increased LOD.	▪ LOD verification is a must. ▪ The equipment has a controller to set, monitor and control the duration. ▪ Further, the inlet temperature is recorded as per the frequency mentioned in the BMR.	3	1	1	3	▪ The instructions mentioned in the BMR must be followed.
	Inlet air RH Inlet air dew point	▪ Increase in RH leads to decrease moisture removing capacity of inlet Air which may affect drying efficiency.	▪ Equipment should have dehumidification system in place. ▪ Equipment PLC shows Inlet RH/Dew point in PLC.	1	1	3	3	▪ Limit mentioned in BMR must be followed.
	Under-drying/ Over-drying.	▪ Sticking on tablets. ▪ Friability failure. ▪ Specification failure for residual solvent.	▪ All operational parameters are PLC-controlled. ▪ LOD verification is a must.	3	1	1	3	▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Sizing	Screen size	▪ Any variation in size may affect the particle size of the material leading to variation in the process parameters.	▪ Checking of sieve integrity is done before and after use, and the information is documented in the BMR, together with the ID of the sieve used.	2	1	1	2	▪ The procedure mentioned in the BMR must be followed.
		▪ Improper size could lead to non-removal of foreign particles that may be present in the material.	▪ The size of sieves to be used is mentioned in the batch manufacturing record.	3	1	1	3	▪ The procedure mentioned in the BMR must be followed.
	Torn sieve	▪ Particle size distribution not as desired. ▪ Metal contamination. ▪ Mass variation problem during compression.	▪ Process should be monitored manually. ▪ Visual checking should be done before and after use, and the information recorded in the BMR. ▪ Every unit is passed through the metal detector before final batch release.	3	2	1	6	▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Lubrication	Lubrication time	▪ If the lubrication time is less than the specified limit, it may result in improper flow of the material leading to weight variation, and CU problems. ▪ If the lubrication time is more than the specified limit, it may result in BUA test failures due to particle segregation problems. It may even affect the dissolution of the drug.	▪ The time for lubrication is controlled by PLC. ▪ The lubrication time is recorded in the batch record. ▪ BUA is carried out after the activity. ▪ The quality attributes such as assay, description, LOD and yields are monitored.	3	1	1	3	▪ The instructions mentioned in the BMR must be followed.
	Inadequate or over lubrication of granules	▪ Flow problem during compression. ▪ Dissolution failure. ▪ Mass variation problem.	▪ Mixing time is controlled by PLC program.	3	1	1	3	▪ Verification is done from PLC printout. ▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Compression	Hardness	▪ If the hardness of the tablet is higher than the specified limit, it may impact on the thickness, disintegration and dissolution of the tablet. ▪ If the tablet hardness is lower than the specified limit, it may affect the friability of the tablet, appearance, and coating of the tablet.	▪ During initial setting the hardness is verified at the time of machine setting. Also at defined frequency, the relevant parameter is monitored and recorded. ▪ In addition, quality attributes such as description, average weight, weight of 20 tablets, weight variation, hardness, thickness, DT, dissolution, content uniformity, assay and the yield are monitored.	3	1	1	3	▪ The instructions mentioned in the BMR must be followed.
	Defective tooling	▪ Sift and defective tablets. ▪ Capped and chipped tablets. ▪ Collar formation on tablets.	▪ Periodic inspection of tooling should be carried out. ▪ Proper storage of tooling should be done.	3	2	1	6	▪ Procedural controls are in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Compression	Machine speed	▪ If the machine speed is too high, it may impact the flow of granules in the die cavity resulting in weight variation. It may also affect the hardness of the tablet due to less dwell time. ▪ If the machine speed is too low, it may lead to high hardness tablets due to more dwell time; this may in turn affect the DT, dissolution and other parameters.	▪ The machine speed is recorded in the batch record. Further, as per the frequency specified in the BMR, the relevant parameters are also recorded. ▪ In addition, quality attributes such as description, average weight, weight of 20 tablets, weight variation, hardness, thickness, DT, dissolution, content uniformity, assay and the yield are monitored.	3	1	1	3	▪ Based on the validation, the machine speed should be optimized. ▪ The instructions mentioned in the BMR must be followed.
	In-process parameters are outside limits.	▪ Failure to meet batch release specifications. ▪ Packing machinability problems.	▪ Manual setting and monitoring of in-process parameters should be done at specified intervals.	1	1	1	1	▪ Procedural controls are in place. ▪ Control on granulometry must be in place.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Atomization air pressure	▪ If atomization air pressure is too high, it may lead to a narrow spray pattern, resulting in non-uniform coating affecting the description of the tablet, shade variation and release of drug.	▪ The coating equipment is PLC-controlled. ▪ Further, the spraying does not take place if the air pressure is outside the specified limits. ▪ The atomization pressure is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
		▪ If atomization pressure is too low, the coating spray pattern may be broad, resulting in shade variation and improper coverage of the coating. It may also choke the nozzle of the gun, and, further, lead to a rough surface of the tablet.	▪ The coating equipment is PLC-controlled. ▪ Further, the spraying does not take place if the air pressure is outside the specified limits. ▪ The atomization pressure is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Pan speed	▪ If speed of the pan is too high, it may lead to improper coverage of the coating affecting the appearance and the release of the drug. Edge erosion of the tablets may also take place.	▪ The coating equipment is PLC-controlled. ▪ The pan speed is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
		▪ If speed of the pan is too low, it may lead to excess spray on the tablets leading to clumping of the tablets. This may, in turn, lead to improper drying of the tablets.	▪ The coating equipment is PLC-controlled. ▪ The pan speed is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Spray rate	▪ If the spray rate is too high, it may lead to excess coating solution on the tablets, resulting in inadequate drying, thus leading to clumping of the tablets.	▪ The coating equipment is PLC-controlled. ▪ The spray rate is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
		▪ If the spray rate is too low, it may lead to inadequate coating solution on the tablets, resulting in inadequate covering of the coating affecting the appearance and the release of the drug.	▪ The coating equipment is PLC-controlled. ▪ The spray rate is recorded in the batch record at regular intervals as specified in the BMR.					

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Outlet air temperature	▪ If the outlet air temperature is too high, it may result in excess loss of the solvent leading to improper coating and rough surface of the tablet.	▪ The coating equipment is PLC-controlled. ▪ The pan speed is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
		▪ If the outlet air temperature is too low, it may result in improper drying of the tablets resulting in clumping. This may affect the quantity of the solvent in the tablet.	▪ The coating equipment is PLC-controlled. ▪ The outlet air temperature is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Inlet air temperature	▪ If the inlet air temperature is above the specified limit, it may affect the product quality. In case of thermolabile products, it may lead to degradation. In the case of other products, it may result in over-drying of the tablets, affecting the appearance and may lead to a rough surface.	▪ The coating equipment is PLC-controlled. ▪ The inlet air temperature is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
		▪ If the inlet air temperature is less than the specified limit, it will lead to inadequate drying resulting in clumping of tablets.	▪ The coating equipment is PLC-controlled. ▪ The inlet air temperature is recorded in the batch record at regular intervals as specified in the BMR.					

Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Inlet air flow	▪ If the inlet air flow is too high, it may result in excessive loss of solvent leading to non-uniform coating. ▪ If the inlet air is too low, inadequate drying may result leading to clumping of the tablets.	▪ The coating equipment is PLC-controlled. ▪ The inlet air flow is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
	Tablet bed temperature	▪ If the tablet bed temperature is too low, drying of tablets will not take place properly, thus leading to clumping of tablets and improper coverage of the coating.	▪ The coating equipment is PLC-controlled. ▪ The tablet bed temperature is recorded in the batch record at regular intervals as specified in the BMR.	2	1	1	2	▪ The instructions mentioned in the BMR must be followed.
	Improper coating	▪ Edge erosion. ▪ Peeling off. ▪ Shade variation.	▪ The coating pan is loaded to 40% to 70% of its capacity. ▪ Periodical preventive maintenance is undertaken. ▪ Tablets are inspected to remove or minimize such physical defects.	3	2	1	6	▪ Procedural controls are in place.

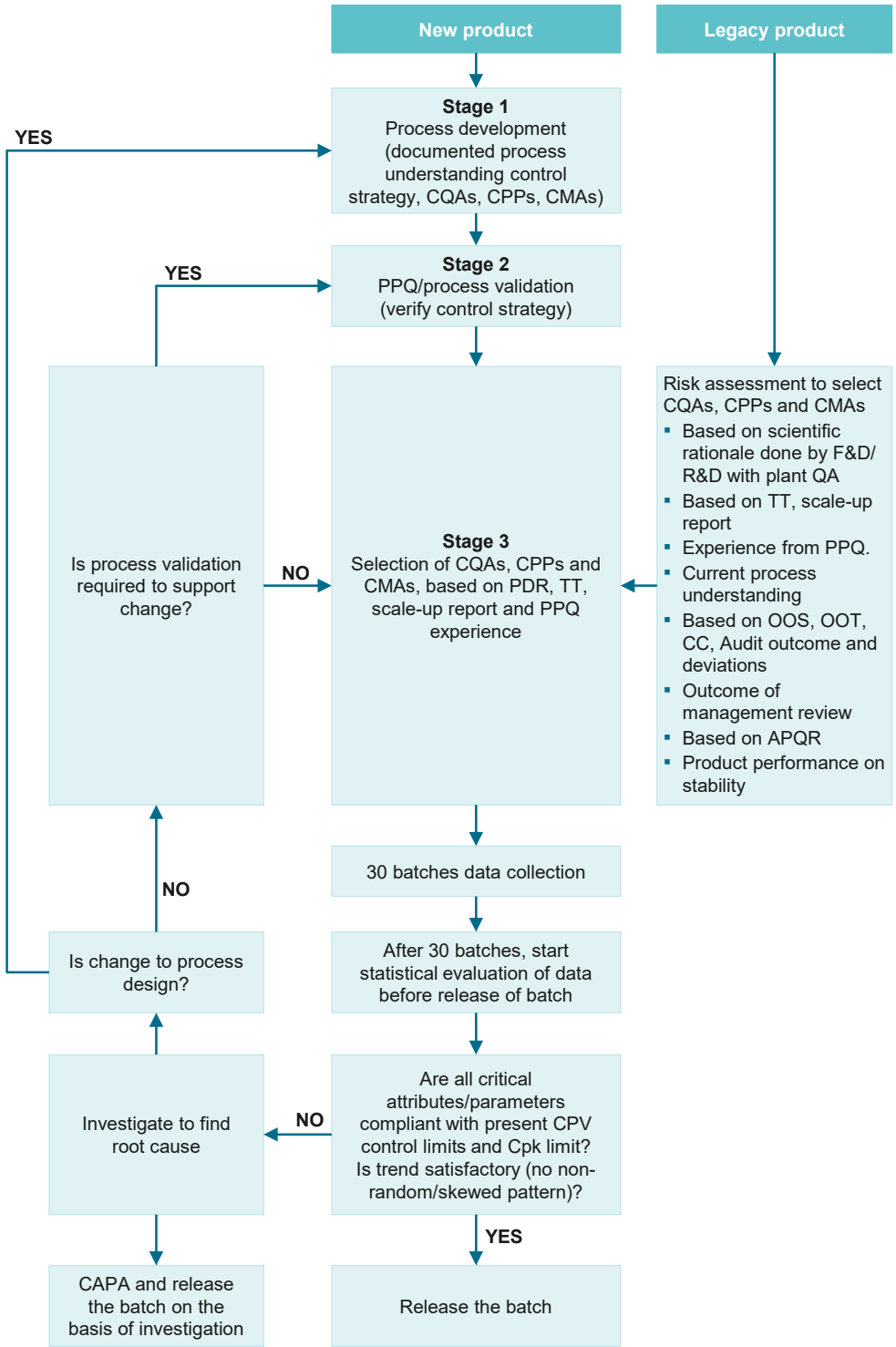
Item/ Function/ Stage	Risk	Potential Consequences	Current Controls	Consequences (3 – High, 2 – Medium, 1 – Low) (A)	Likelihood (3 – High, 2 – Medium, 1 – Low) (B)	Chances of Detection (1 – High, 2 – Medium, 3 – Low) (C)	Risk Score (A x B x C) out 27	Recommended Action (x)
Coating	Inadequate weight gain	▪ Loss of desired functional performance, e.g. film coating or enteric coating, will be affected. ▪ Sustained release function may not be achieved.	▪ All operational parameters are PLC controlled.	3	2	1	6	▪ Procedural controls are in place.
Inspection	Inconsistent removal of physical defects and/or tablet imperfections.	▪ Problems may be due packing machinability. ▪ This may, in turn, lead to market complaints.	▪ Verification of the bulk material is undertaken during sampling. Decision on the extent and severity of physical defects is probabilistic. ▪ Sorting process is manual.	3	2	1	6	▪ Manpower is changed at specific intervals so as to reduce impact of eye fatigue. ▪ Only skilled manpower is used for such functions.

21.0 Enclosures

Sr. No.	Topic	Pages
01	Personal training	
02	Test data slip: In-process parameters	
03	Test data slip: Analytical parameters	

Annexure 9

CPV workflow for new and legacy products



Annexure 10

CPV strategy for new and legacy products

1.0 Stage 3: continued process verification

- This stage is applicable for all new and existing commercial drug products and substances.
- The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacturing.
- The collection and evaluation of information and data about the performance of the process will allow detection of undesired process variability.
- This stage will help in evaluating the performance of the process, identifying problems and determining whether action should be taken to correct, anticipate, and prevent problems so that the process remains under control.
- The data collected should include relevant process trends, quality of incoming critical material attributes, in-process material and finished products.
- In this stage, only the variable numerical data should be considered.
- In Continued Process Verification monitoring, the following parameters shall be monitored.
  - Critical Material Attributes (CMA) analysis.
  - In-process analysis tests (CQA) (QC test).
  - In-process analysis tests, performed by production during manufacturing of the batch for CQA.
  - Finished Product analysis tests (CQA).
  - Critical Process Parameters during manufacturing of the batch.
  - Yield trend (theoretical yield and accountable yield).
  - Addition tests for monitoring of addition parameters or intensive sampling as per requirement.
- Stage 3, Continued Process Verification shall be performed in two separate ways:
  - For new/QbD products.
  - For legacy products.

1.1 For new/QBD products

As new products are developed according to QbD principles, the CQA, CPP, CMA and control strategy identified during development (Stage 1, process design) are based on process understanding and quality risk management provided by the F&D/R&D for CPV monitoring.

1.1.1 Preparation of protocol

- All new products become part of the CPV program after their stage 2 validation.
- The CPV protocol should be prepared as per product code, and the protocol shall define the concept, the criteria and the scope of trending and reporting.
- The protocol should be revised whenever one or more changes in process are made to establish new CPV limits.
- The protocol shall be prepared similar to PPQ protocol.

1.1.2 Selection of CQAs, CPPs and CMAs for monitoring

- The specific CQAs, CPPs and CMAs are given by F&D/R&D Department based on risk assessment in product development report (PDR) and experience from PPQ.
- The critical process parameters and critical quality attributes included in the enhanced sampling and testing in Stage 2 should be considered initially for continued monitoring in Stage 3.
- With the appropriate risk-based analysis and documented justification (scientifically and statistically justified), certain Stage 2 parameters may be eliminated or the level of sampling testing could be reduced in the Stage 3 plan.

1.1.3 Number of batches for defining CPV limit

- Data from a minimum of 30 batches after PPQ will be required.

1.1.3.1 Evaluation and establishment of CPV limit

- When evaluating the performance of a process, it is often useful to set limits to provide an indication about when the variability of a parameter or attribute may be changing, and therefore, needs further attention.
- QA personnel shall enter the values of CPPs from executed BMR and QC personnel shall enter the values of CMAs and CQAs in worksheet form in analytical reports.
- The data should be statistically trended and reviewed by trained personnel (with adequate training in statistical process control techniques).
- While collecting the data of a minimum of 30 batches, if any change is made in manufacturing process through change management and such a change has an impact on critical attributes, then the process of data collection has to be restarted after the change is made effective and with proper justification, in order to establish CPV limits. The new set of data must cover a minimum of 30 batches.
- Where special causes for variations are identified, these values should be removed from calculations for the establishment of CPV limits.
- The moving real-time control (±3 sigma) shall be considered as limit before releasing of any batch. This control evaluation shall be started after production of 30 batches in order to collect sufficient data.
- Any outlying data shall be investigated. While it is possible that past data may fall as an outlier, this must be investigated and documented.

1.1.3.2 Report for freezing the CPV limit

- This should define the CPV limit of each attribute being monitored.
- This should evaluate the process capability index of each attribute.
- This report might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics.
- When the root cause(s) has been determined for results which are out of CPV limits, then, for purposes of improvement of process, QA personnel together with subject matter expert/s shall take necessary corrective and/or preventive action(s) for such improvement.
- The report should assess the action plan for improvement of process, i.e. to check if the change(s) in process design require:
  - Redevelopment of process.
  - Re-process validation (verify control strategy).
  - Reestablish process and sampling plan.

1.2 Existing/legacy products

Existing/legacy products developed traditionally may not have critical attributes or parameters defined in their submissions.

1.2.1 Preparation of protocol

- The CPV protocol should be prepared as per product code, and the protocol shall define the concept, the criteria and the scope of trending and reporting.
- The protocol should be revised whenever a change in process is made to establish new CPV limits.
- The protocol shall be prepared in a manner similar to PPQ protocol.

1.2.1.1 Selection of CQAs, CPPs and CMAs for monitoring

- If a drug product/substance, having defined CQAs, CPPs, and CMAs with PDR and PPQ reports, is adjudged to have a level of risk, the risk assessment shall be referred to PDR and PPQ reports. The specified the CQAs, CPPs, and CMAs shall be considered for monitoring in CPV.
- If drug product/substance, not having defined CQAs, CPPs, and CMAs with PDR and PPQ reports, is adjudged to have a level of risk, the risk assessment shall be performed by a cross-functional team in order to identify CQAs, CPPs, and CMAs for monitoring in CPV. The assessment will be based on TT, engineering batch report, PPQ report, OOS, OOT, CC, audit outcome and deviations, product performance on stability, outcome of management review, based on APQR, and current process understanding.
- As data is collected and analyzed, additional aspects that require evaluation may be identified.

1.2.1.2 Number of batches for defining CPV limit

- Data from a minimum of 30 batches from the last manufacturing run is required for defining CPV limit.
- If during such manufacture, any change has been made in the manufacturing process through change management which may impact on critical attributes, then the data collection has to be restarted after the change has been made effective and with proper justification to establish CPV limits. The data collection exercise must cover minimum 30 batches from the new manufacturing process.
- Batches in which the special cause of variations is identified shall not be considered in the above requirement of a minimum of 30 batches.

1.2.1.3 Evaluation and establishment of CPV limit

- Refer to point no. 1.1.3.1 above.

1.2.1.4 Report for freezing the CPV limit

- Refer to point no. 1.1.3.2 above.

2.0 Batch release procedure:

- Until the establishment of control limits, the batches shall be released based on specification.
- Once the CPV limits are established for CMAs, CPPs and CQAs, the desired state is that potential issues have been identified as soon as data is entered into the process analysis tool by responsible person(s).
- QA personnel are responsible for checking that all attributes values have been met in the CPV limit before the final release of batch.
- Deviations from the CPV limits shall be reviewed and investigated as per investigation procedure and necessary action shall be taken by QA in consultation with concerned departments.
- This check point should be part of BMR's batch release check list.

3.0 Annual product quality review

- During preparation for APQR, data from all the batches manufactured throughout the year shall be re-evaluated to ensure that the manufacturing process is operating in a repeatable, reliable fashion and in a state of control.
- During preparation for APQR, appropriateness of the current approved control strategy will be confirmed so as to highlight any trends and identify the need for product and/or process improvements where such need exists.
- Data gathered during this stage may be used to improve and/or optimize the process by altering some aspect of the process or product.
- Based on trend of data, CPV limits can be revised with scientific rationale through a change management system.
- Summary report shall be prepared and made part of APQR.

4.0 Conclusion

- In routine CPV monitoring if any attribute does not comply the CPV limit then the following action should be taken:
  - If it is an undesired variation with a special cause(s), then root cause should be identified and action should be taken to eliminate or enhance control of the specific special cause(s).
  - If it is a variation due to a common cause (as may be the case for investigation of low capability processes), a more fundamental approach is required to understand the sources of variation and identify ways of reducing that variation.
- From these, a minimum of 30 batches will be taken out in order to establish CPV limits, and calculate the process capability (Cpk value).
- CPV limits should be reviewed where intentional changes are introduced to the system (e.g., additional equipment or process trains, process improvements to reduce variation) in order to ensure that the established CPV limits are appropriate for the new scenario.
- Note: CPV limits can be redefined in case of major changes in process or equipment. Such need shall be identified in change control form.

5.0 Continued process verification tools

Continued Process Verification can be done using many tools and methodologies. Some of them are listed below:

- Graphical charts; for example, Run Chart, Control charts (I-MR chart, XBar-R Chart, XBar-S Chart), etc. Line charts can also be used as tools to determine whether a manufacturing process is in a state of statistical control.
- Statistical tools as explained below:
  - Calculation of control limits

    The UCL and LCL shall be calculated as below:

    UCL (Upper Control Limit) = Xbar + 3σ

    LCL (Lower Control Limit) = Xbar - 3σ

    where Xbar stands for mean and σ stands for standard deviation.

    For CPP and CQA with a single-side specification, the UCL and LCL shall be considered as below:

    Products having Upper Specification Limit, only UCL shall be considered

    Products having Lower Specification Limit, only LCL shall be considered

    If the calculated UCL and LCL are different from the specification limits, then specification limits shall be consider as UCL and LCL
  - Statistical process control indices which should be used are Cp (Process Capability), Cpk (Process Capability Index), Pp (Process Performance) and Ppk (Process Performance Index).

    Cp is a capability tracking mechanism, which compares the width of a product with variation with the process. This metric uses estimated standard deviation.

Cp rate of capability is calculated using the formula below:

$$C_p = \frac{USL - LSL}{6 \times \hat{\sigma}}$$

where σ^ represents the standard deviation for a population taken from, $\hat{\sigma} = \frac{\bar{S}}{C_4}$ with *^s-bar^* representing the mean of deviation for each rational subgroup and *c4^* representing a statistical coefficient of correction.

USL stands for Upper Specification Limit.

LSL stands for Lower Specification Limit.

Cpk uses estimated standard deviation to determine how well a system can meet the specification limits. It also takes the target value into account.

*Cpk^* capability rate is calculated using the formula below:

$$C_{pk} = \min\left(\frac{USL - \mu}{3 \times \hat{\sigma}}, \frac{\mu - LSL}{3 \times \hat{\sigma}}\right)$$

where μ is the mean.

Pp shows process performance. It indicates well a system performs when it comes to upper and lower specification limits. However, it does not focus on the average and instead concentrates on the spread.

$$P_p = \frac{USL - LSL}{6 \times S}$$

where *s* is the standard deviation of the overall data.

Ppk uses actual standard deviation to determine process variation.

The capability rate for Ppk is calculated using the formula below:

$$P_{pk} = \min\left(\frac{USL - \mu}{3 \times \hat{\sigma}}, \frac{\mu - LSL}{3 \times \hat{\sigma}}\right)$$

where σ^ is the standard deviation of the overall data.

The reader should use Annexure V as guidance for interpreting issues of process stability.

6.0 Training

- QA shall conduct training of all concerned persons on CPV plan.
- Persons who are involved in statistical calculations shall be trained on software used for such calculations.
- The training of all concerned personnel, if required, should be conducted after approval of protocol and before execution of validation activity.

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