Product Robustness and Lifecycle Management

Best Practices Document

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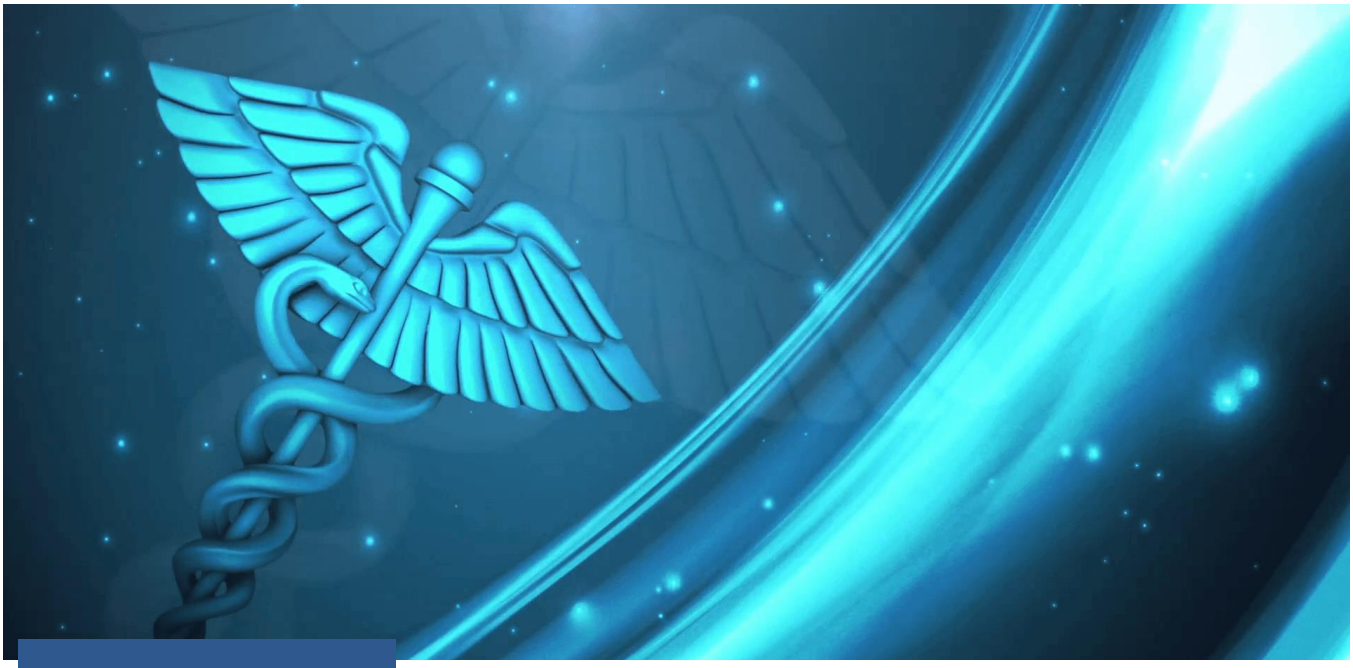


PREFACE

In April 2015, The IPA launched its Quality Forum (QF) 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.

The QF focused on several priority areas in the last four years, namely, Data Reliability, Best Practices & Metrics, Culture & Capability, Investigations, etc. It took upon itself the challenge of developing a comprehensive set of Best Practices Documents for several of these topics. In this document, we focus on best practices for Product Robustness and Lifecycle Management. We had released a comprehensive set of Data Reliability Guideline in February 2017, Process Validation Guideline and Good Documentation Practice Guideline in February 2018, Investigation of non-conformities in February 2019 and Handling Market Complaints Best Practices in February 2020.

The six participating companies in the QF nominated senior managers to study the best practices and frame the guidelines. They are: Gouri Prasad Nanda (Cadila Healthcare); Sanjeev Asgekar (Cipla); Narendira Kumar (Dr Reddy's); Sanjay Sharma (Lupin); Ashish Parekh (Sun); and Rakesh Sheth (Torrent). The IPA wishes to acknowledge their concerted effort over the last 12 months. They shared current practices, benchmarked these with the existing regulatory guidance 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.

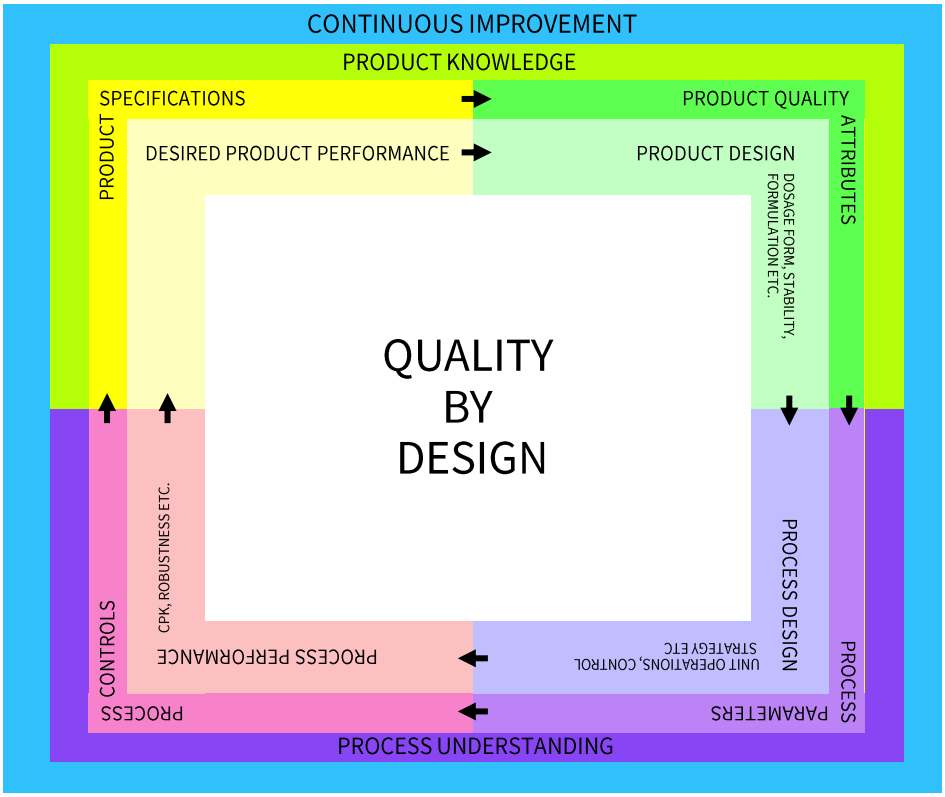
The IPA also wishes to acknowledge the CEOs of six member-companies who have committed their personal time, human resources and provided funding for this initiative.

This document, to be released at the IPA's Advanced GMP Workshop 2020, will be hosted on the IPA website www.ipa-india.org to make it accessible to all manufacturers in India and abroad.

Mumbai
October 2020

1 Abstract

This report outlines the approach proposed by IPA in addressing the FDA and EMA guidance related to product robustness through the entire lifecycle of the product - from development to commercialization.



PRODUCT ROBUSTNESS AND LIFECYCLE MANAGEMENT (LCM)

Best Practices Document

2 Background

- This guidance aligns process development, validation and commercialization activities of a product with a product lifecycle concept. It is very important to assess the ability of a manufacturing process to endure the anticipated or unanticipated variability of input raw materials (API and excipient), processing conditions (equipment, and environment), and human factors to consistently produce a product with desired preset specifications. Process validation is defined as the collection and evaluation of data from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering the desired quality product.
- The lifecycle concept links product and process development, qualification of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.'
- USFDA Guidance on Process Validation 2011
- Process validation should not be viewed as a one-off event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production'
- EMA Guidance on Process Validation 2014
- The above guidance from two of the major health authorities indicates a strong emphasis on lifecycle approach as opposed to an event based one. Though there may be differences in terminologies used across the guidance, the overarching principle of lifecycle management and the use of knowledge gained as part of the product journey as a basis for process improvement and innovation forms the central theme of both the guidance.
- The FDA guidance is more detailed in its recommendations and forms the background of the present report. The guidance highlights three distinct stages as part of the product journey and has associated objectives and elements which must be considered.

2 Vision and aspiration of the best practices document

- To define a process for assessing and improving the product robustness throughout the Product lifecycle, to consistently deliver high quality product.

Proposed Methodology:

- Define 'Product Robustness'
- Identify the assessment techniques to measure process robustness
- Define pre-requisites for technology transfer – protocols, checklists, etc.
- Define stage gates for GO-GO with improvisation - NO-GO
- Risk assessment throughout product lifecycle

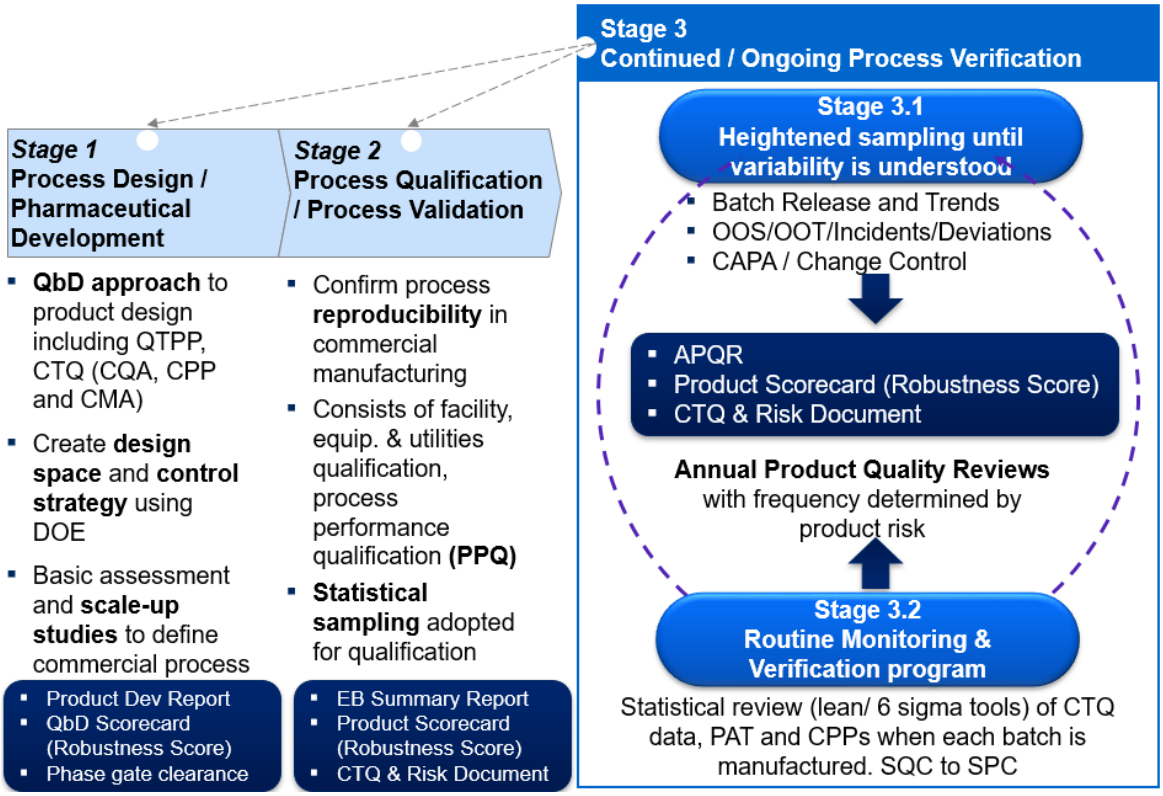
Each of the above is discussed in detail in this Best Practices Document

Product Robustness:

- The objective of an effective process lifecycle management assures that the drug product produced is fit for its intended use and it incorporates the following conditions:
  - Quality, safety, and efficacy are designed or built into the product.
  - Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.

- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes, including specifications.

Exhibit 1: Stages of mechanism to check Product Lifecycle and Robustness



The **assurance for the process should be obtained from objective information, knowledge and data from laboratory, pilot and/or commercial-scale studies**. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes. This Best Practices Document states that the manufacturer should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

Some salient considerations in this Best Practices Document are as follows:

- It recommends an integrated team approach to process validation/qualification that includes expertise from a variety of disciplines e.g., Research and Development, Analytical Development, Process Development, Statistics, Manufacturing and Quality Assurance

- Various studies can be initiated throughout the product lifecycle in order to discover, observe, correlate, or confirm information about the product and the process

- It suggests **a risk-based approach for categorizing attributes and parameters as critical** - a higher degree of control is appropriate for attributes or parameters that pose a higher risk

- **Homogeneity within a batch and consistency between batches** are goals of process validation activities

This Best Practices Document suggests use of Design of Experiment (DOE) studies in conjunction with risk analysis tools to develop process knowledge by revealing relationships and multivariate interactions between the variable inputs and the resulting outputs. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.

Based on the above, strategies for process control can be designed to reduce input variation and adjust for input variation during manufacturing in order to reduce its impact on the output. The controls should include both examination of material quality and equipment monitoring.

For legacy products, knowledge gained from the original process development and qualification work as well as manufacturing experience should be utilized to continually improve their processes and would primarily involve activities in Stage 3.

4 Approach

- It is proposed to implement key recommendations of this Best Practices Document document by revisiting some of the existing processes and documents and bringing it in line with the requirements, while at the same time bringing together new concepts from statistics and technology to make the approach more robust. Each of the three stages is discussed in detail below.

5 Product lifecycle stages

5.1 Stage 1: Process Design

The approach revolves around these key documents and processes:

- Critical to Quality (CTQ) document and Risk Management
- Stage Gate Mechanism
- Product QbD Scorecard (Formulation, Process and Analytical)
- Analytical Robustness check through implementation of Gauge R & R
- Gap Analysis post submission of dossier
- Scale up best practices

a. CTQ Document & Risk Management:

- The CTQ document outlines the critical quality attributes (CQAs) and details the interdependencies between Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs) of input materials which impact the final product quality. This is proposed to be a live document which captures the product journey from development to commercialization. As additional knowledge and information is available, the CTQ document would be updated to capture the most up-to-date information of the product and process. The CTQ document is designed to be a one-stop document for all process related knowledge and history.

- For all under development molecules, the criticalities and interdependencies between CQAs, CPPs and CMAs and the control strategies would be investigated and documented as part of the product development process by R&D. This would be based on QbD principles which have been adopted for all the under-development molecules. For all legacy molecules, the information and knowledge available within the development and commercial manufacturing organization would be leveraged to arrive at the criticalities and control strategies.

Exhibit 2: Flow for the CTQ template

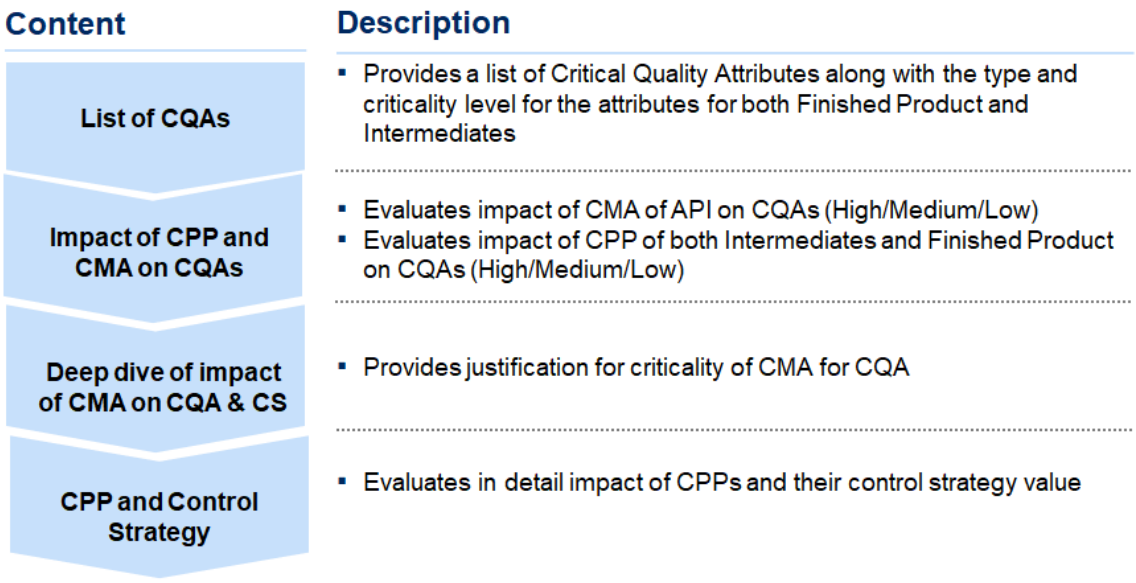


Table 1: List of CQAs (illustration)

Level 1A: Critical Quality Attributes - Finished Product (Coated Tablet)			
Sr.No.	Attribute	Type of attribute: Safety/Quality/Efficacy	Criticality level of the attribute
1	Description	Quality	Medium
2	Odor	Quality	Low
3	Identification	Quality	Medium
4	Assay (%w/w)	Efficacy	High
5	Content uniformity by UOD	Efficacy	High
6	Dissolution profile (%)	Efficacy	High
7	Related substances limit (%w/w)	Safety	High
8	Antioxidant potency (%w/w)	Quality	Medium

Table 2: Impact of CMA on CQAs (illustration)

Sr.No.	**CQA ↓ / CMA →**	**Assay (%w/w)**	**Related Substance (%w/w)**	**Content Uniformity by UOD**	**Dissolution (%)**	**Water Content (%w/w)**
1	API	Low	Medium	Low	Low	High
2	Copovidone	Low	Medium	Low	Low	Low
3	Hypromellose	Low	Low	Low	High	Low
4	Polyethylene Glycol	Low	Low	Low	Low	Low
5	Magnesium Stearate	Low	Low	Low	Low	Low

Table 3: Impact of CPP on CQAs (illustration)

Sr.No.	CQA ↓ / CPP →	Assay (%w/w)	Related Substance (%w/w)	Content Uniformity by UOD	Dissolution (%)	Water Content (%w/w)
1	Fluid Bed Granulation	Low	Low	Low	High	Low
2	Blending	Low	Low	Low	Low	Low
3	Compression	Low	Low	Medium	High	Low
4	Film Coating	Low	Low	Low	Low	Low

Table 4: Detailed impact of CMA on CQA & Control Strategy (CS) (illustration)

Sr.No.	CQA ↓ / CMA →	Specification	Related Substance (%w/w)	Content Uniformity by UOD	Dissolution (%)
1	Water Content (API)	NMT 4.0% w/w	Medium	Low	Low
2	Peroxides (Copovidone)	NMT 0.40% w/w	Medium	Low	Low
3	Viscosity (Hypromellose)	80-100	Low	Low	High

Table 5: CPP and Control Strategy (illustration)

Sr.No.	Unit Operation	Parameter	Value	UOM
1	Fluid Bed Granulation	Spray Rate	36 (15-60)	g/min
		Air Flow	100 (80-140)	CFM
		% Inlet RH	5 -55	%
		Atomization Pressure	1 (0.8-1.2)	bar
2	Compression	Precompression Force	10% of MCF	kN
		Main compression Force (MCF)	20-Oct	kN
		Turret Speed	20-40	RPM

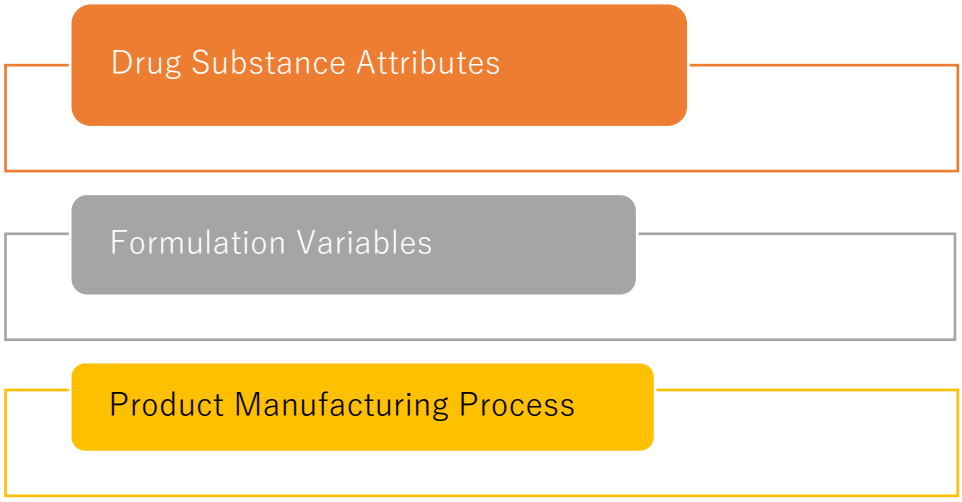
a.1 Quality Risk Assessment during Drug Product Development and Scale-Up

- The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies.
- An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises.
- Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.
- Quality risk management activities are usually done by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas in addition to individuals who are knowledgeable about the quality risk management process.

a.2 Risk Assessment during Drug Product Development

- Quality risk management approach at all stages of the product development will provide both proactive and reactive means to identify and control potential quality issues.
- Risk assessment is supposed to be used throughout product development to identify potentially high-risk formulation and process variables and to determine which studies are necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment should be updated after development to capture the reduced level of risk, based on improved product and process understanding.
- Two primary principles should be considered when implementing quality risk management:
- The evaluation of the risk to quality should be based on scientific knowledge and should ultimately be linked to the protection of the patient; and
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.
- Considering that limited knowledge may be available during drug product development, "Qualitative Risk Assessment" shall be used.

Exhibit 3: Risk assessment shall be done for following



a.3 Risk Assessment of Drug Substance Attributes:

- A risk assessment of the drug substance attributes should be performed to evaluate the impact that each attribute could have on the drug product CQAs.
- The outcome of the assessment and the accompanying justification shall be provided as a summary in the pharmaceutical development report.
- The relative risk that each attribute presents shall be ranked as high, medium or low.

The high-risk attributes warrant further investigation whereas the low risk attributes may require no further investigation.

Medium risk may be considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The same relative risk ranking system should be used throughout pharmaceutical development and is summarized below. For each risk assessment performed, the rationale for the risk assessment tool selection and the details of the risk identification, analysis, and evaluation should be documented.

Overview of Relative Risk Ranking System	
Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

Table 6: Initial Risk Assessment of the Drug Substance Attributes

Drug Product CQAs	Drug Substance Attributes							
	Particle Size Distribution (PSD)	Hygroscopicity	Solubility	Moisture Content	Residual Solvents	Process Impurities	Chemical Stability	Flow Properties
Assay								
Content Uniformity								
Dissolution								
Degradation Products								

Justification for initial risk assessment should be documented.

a.4 Risk Assessment of the Formulation Variables

- During initial risk assessment for formulation development, the detailed manufacturing process may not be established. Thus, risks should be rated assuming that for each formulation attribute that changed, an optimized manufacturing process would be established.

Table 7: Initial Risk Assessment of the Formulation Variables

Drug Product CQAs	Formulation Variables						
	Drug substance PSD	Level of Excipient 1	Level of Excipient 2	Level of Excipient 3	Level of Excipient 4	Level of Excipient 5	Ratio of excipient (a) and (b)
Assay							
Content Uniformity							
Dissolution							
Degradation Products							

Justification for the initial risk assessment of the formulation variables should be documented.

Formulation development studies should be conducted based on the high-risk formulation variables identified during initial risk assessment. Based on various studies conducted, formulation should be finalized.

Table 8: Updated Risk Assessment of the Formulation Variables

Drug Product CQAs	Formulation Variables						
	Drug substance PSD	Level of Excipient 1	Level of Excipient 2	Level of Excipient 3	Level of Excipient 4	Level of Excipient 5	Ratio of excipient (a) and (b)
Assay							
Content Uniformity							
Dissolution							
Degradation Products							

a.5 Initial Risk Assessment of the Drug Product Manufacturing Process

- A risk assessment of the overall drug product manufacturing process should be performed to identify the high-risk steps that may affect the CQAs of the final drug product.

- Subsequently, the intermediate CQAs of the output material from each process step that impact the final drug product CQAs should be identified.

- For each process step, a risk assessment should be conducted to identify potentially high risk process variables which could impact the identified intermediate CQAs and, ultimately, the drug product CQAs. These variables should be investigated in order to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch.

Table 9: Initial Risk Assessment of the Manufacturing Process

Drug Product CQAs	Process steps				
	Pre-mixing	Hot Melt Extrusion	Milling	Final blending	Compression
Assay					
Content Uniformity					
Dissolution					
Degradation Products					

Justification for initial risk assessment should be documented.

Further risk assessment should be performed subsequently on each high-risk process step to identify which process variables may potentially affect the intermediate CQAs. Evaluation of all possible process variables that could potentially affect the quality attributes of the output material of any given process step may not be feasible; therefore, identified variables should be set constant based on current understanding.

a.6 Updated Risk Assessment of the Drug Product Manufacturing Process:

- During process development, the identified high risks for each process step should be addressed. Experimental studies should be defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment should be updated with the current process understanding.

Table 10: Updated Risk Assessment of the Manufacturing Process

Drug Product CQAs	Process steps				
	Pre-mixing	Hot Melt Extrusion	Milling	Final blending	Compression
Assay					
Content Uniformity					
Dissolution					
Degradation Products					

During scale-up at manufacturing site, similar risk assessment should be done on process variables and manufacturing process. In addition, equipment design and facility requirements must be taken into consideration.

a.7 Control Strategy:

- The control strategy for the product should be built upon the outcome of extensive product and process understanding studies. These studies should investigate the material attributes and process parameters that were deemed high risk to the CQAs of the drug product during the initial risk assessment.

- In some cases, variables considered medium risk should also be investigated. Through these systematic studies, the CMAs and CPPs should be identified and the acceptable operating ranges should be established.

- All variables ranked as high risk in the initial risk assessment should be included in the control strategy, because the conclusion of the experiments was dependent on the range(s) studied and the complex multivariate relationship between variables. Thus, the control strategy is an integrated overview of how quality is assured, based on current process and product knowledge.

- The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product.

a.8 Case Study:

- Risk assessment done at process qualifications stage for one of the solid dosage forms (e.g., capsules) product is annexed with this guide **as "Annexure 1"**

b. Stage Gate Mechanism:

- It is proposed to have four stages of review during the product development and approval lifecycle

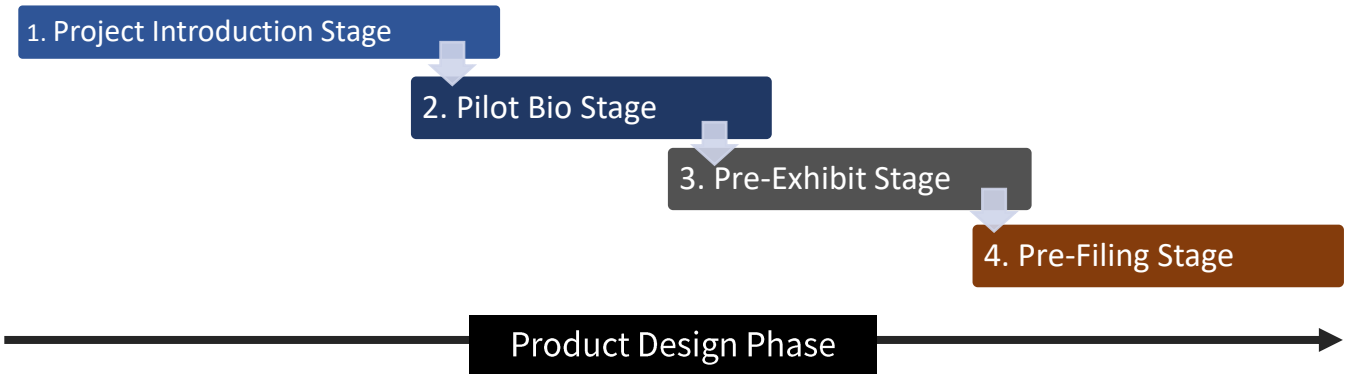
b.1 Objective:

- To enable a systematic review of development data at every stage/milestone
- Provide a detailed overview of the project status with the defined targets, risks identified and mitigation plans.
- Align the requirements of the development across different teams and synergize CFTs.
- To interface with the manufacturing teams (PDL/Production/QA) and enable technology transfer.

b.2 Process:

- **Systematic Review Process (SRP)** should be initiated in the four stages identified by a Cross Functional Team (CFT) including SME/QA/RA/PDL/Site teams (as necessary).

Exhibit 4



SRP requirements at different stages:

- SRP requirements have been detailed at every stage for the dosage forms (i.e. specific dosage forms may have specific requirements which have to be evaluated).

1. Project Introduction Stage:

a. Proposed formulation strategy

b. IP clearance for proposed formulation strategy

c. Innovator lot availability

d. Process selection

e. QbD elements required:

   i. QTPP

   ii. Initial risk assessment

f. IIG clearance for RA, any CC required

g. Feasibility of the analytical methods

h. Availability of all impurities/standards/columns/special reagents

i. Any outside lab required for testing

j. Evaluation of any unique excipients

k. Trade dress approval

l. Clearance of API vendor/alternate vendors

m. BENOC requirement/application/Form 25/29 application

2. **Pre-Pilot Bio Stage:**
    a. Scalable process selection/finalization
    b. QbD elements required:
        i. Finalized QTPP
        ii. CQA/CPP/CMA identification
        iii. Risk assessment
        iv. DOE (for formulation & process as applicable)
    c. Dissolution profile vs comparison with RLD
    d. Method development report for all analytical methods
    e. Bio batch COA
    f. Lab scale batch stability:
        i. 1 M for same formulation
        ii. 3 M for similar formulation
    g. Specification finalization
    h. Final clearance of IP and RA on formulation process/strategy

3. **DOE report. Pre-Pilot Bio Stage:**
    a. Scalable process selection/finalization
    b. QbD elements required:
        i. DOE report.
        ii. Scale dependent factors studied.
        iii. Control strategy.
        iv. Risk assessment.
    c. AMV report for all methods
    d. Final specifications/STP
    e. Lab scale batch stability:
        i. 3 M for same formulation
        ii. 6 M for similar formulation
    f. Development report
    g. MBR final

4. Pre-Filing Stage:

a. Executed MBR

b. 6 M stability data

c. Pivotal BE data

d. Development summary/history

e. Intended batch record

f. Specifications for filing

g. E/L data (if applicable)

At each stage a MOM is prepared for all open action items and is reviewed before the next Phase gate.
A copy of checklist to be followed during course of Product transfer is provided as Annexure 2.

c. Product QbD Scorecard (Formulation, Process and Analytical)

QbD scoring should be done at various stages of development by CFT to ensure that appropriate knowledge is utilized for each stage (Formulation, Process, Analytical, IPA, DQA, RA, etc.)

A score should be allotted by different groups at each stage of development (there will be a number of activities for each stage of development)

Scores should be assessed during phase gate review to ensure development quality, and so that action can be taken immediately before proceeding to the next stage. For example: for quality of literature, knowledge implemented in the product at initial design phase should be scored by all group like F&D, Process Team, QbD, AR&D, DQA etc.

Similarly, repeatability and reproducibility of analytical methodology should be scored by all groups. Process robustness during a particular stage of development should be scored by all groups.

Weaker areas could be fixed in real time by referring to this score. Cross-functional knowledge can be utilized effectively.

c.1 Evaluation Criteria:

Evaluation of the QbD process and approach followed should be done as follows:

- Evaluation should be done at two stages: pre-pilot bio and pre-exhibit stages
- Every point carries equal weightage of 20 and the cumulative score is 100
- Based on the effectiveness of the QbD, the score should be assigned as
    - 20 points: meeting requirement
    - 10 points: needs further improvement
    - 5 points: to be redeveloped

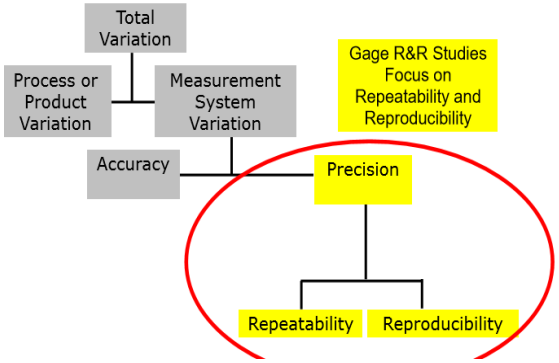
Scoring must be justified during phase gate by CFTs

d. Analytical Robustness Check through Gage R & R

Analytical methods must be able to produce consistent and reliable results to effectively support product development.

It is required to establish an ongoing program to collect and analyze product and process data to monitor process performance and adjust as per CPV expectation.

Exhibit 5



Success of the continued process verification program hinges upon having robust analytical methods. At the same time, these must be capable of generating meaningful data to truly reflect the variation of the process and the definite quality of the product.

All factors that potentially affect method robustness should be carefully considered and systematically studied through a QbD approach and using appropriate tools, such as:

- DoE
- Gage R&R study (Repeatability & Reproducibility)
- Based on statistical confidence level

d.1 Measurement Component Analysis in Gauge R & R

We can estimate of common cause variation with the following equation:

$$\sigma_m^2 = \sigma_p^2 + \sigma_o^2 + \sigma_e^2$$

σ_m^2 = Variation of actual product measurement

σ_p^2 = Variation of true product characteristic

σ_o^2 = Variation due to analyst (reproducibility)

σ_e^2 = Variation due to error (repeatability

d.3 Layout of a typical Gage R & R

Exhibit 6

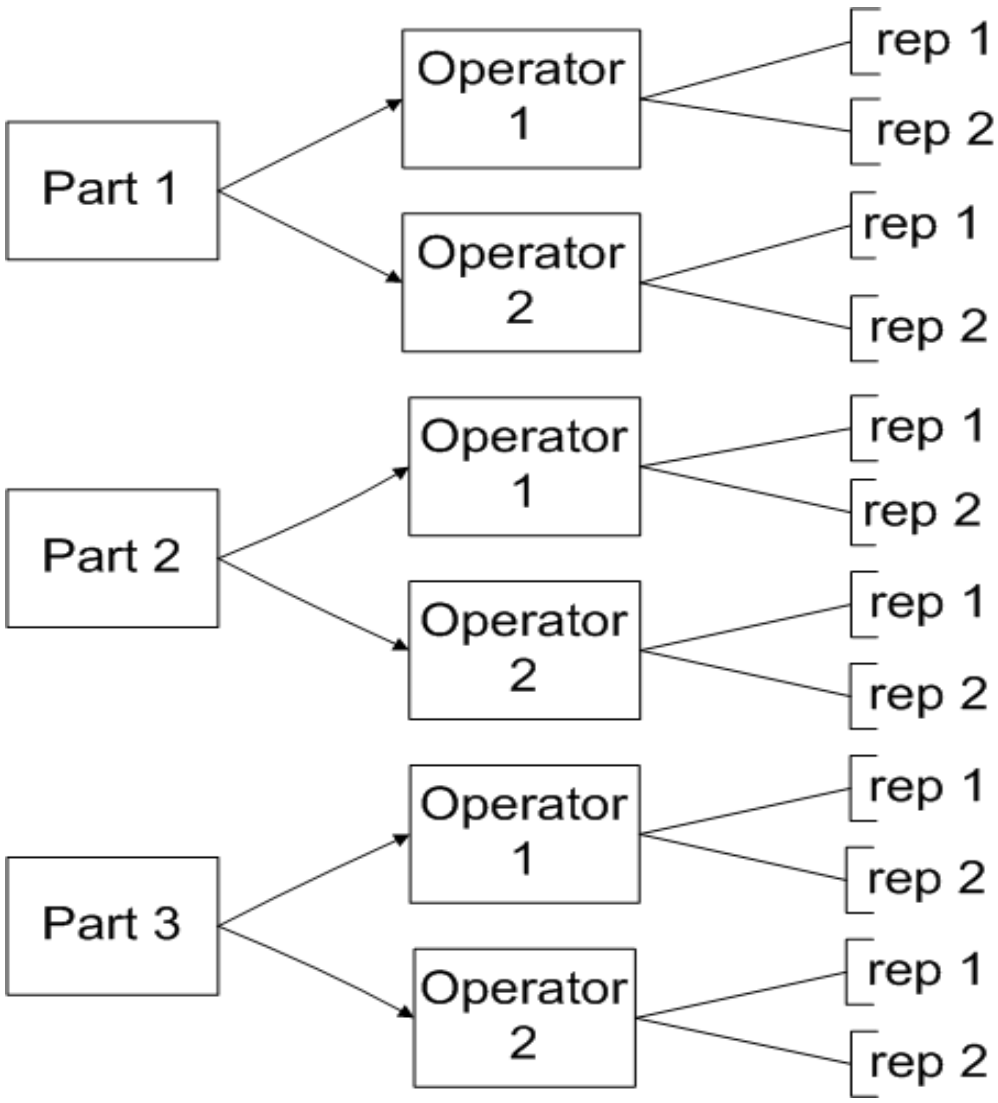


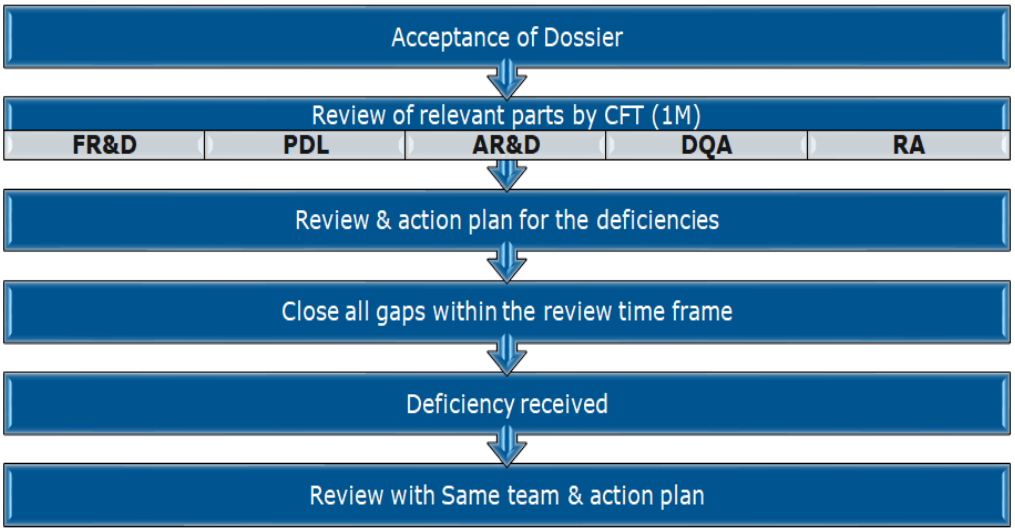
Exhibit 7: Example of Analysis of Variance (ANOVA) can also be used to analyze Gage R&R studies

I. Data set A										
Operator	A	A	WR(A)	B	B	WR(B)	C	C	WR(C)	Part average
Trial	1	2		1	2		1	2		
Part one	67	62	5	55	57	2	52	55	3	58.0
Part two	110	113	3	106	99	7	106	103	3	106.2
Part three	87	83	4	82	79	3	80	81	1	82.0
Part four	89	96	7	84	78	6	80	82	2	84.8
Part five	56	47	9	43	42	1	46	54	8	48.0
Within range average ($\overline{WR}$)			5.6			3.8			3.4	
Appraiser average	81.0				72.5			73.9		
Overall within range average ($\overline{\overline{WR}}$)			4.267							
Range of part average (R_p)			58.167							
Range of appraiser average, $\overline{X}_{diff}$ (R_0)			8.5							

e. Gap Analysis post-submission of Dossier

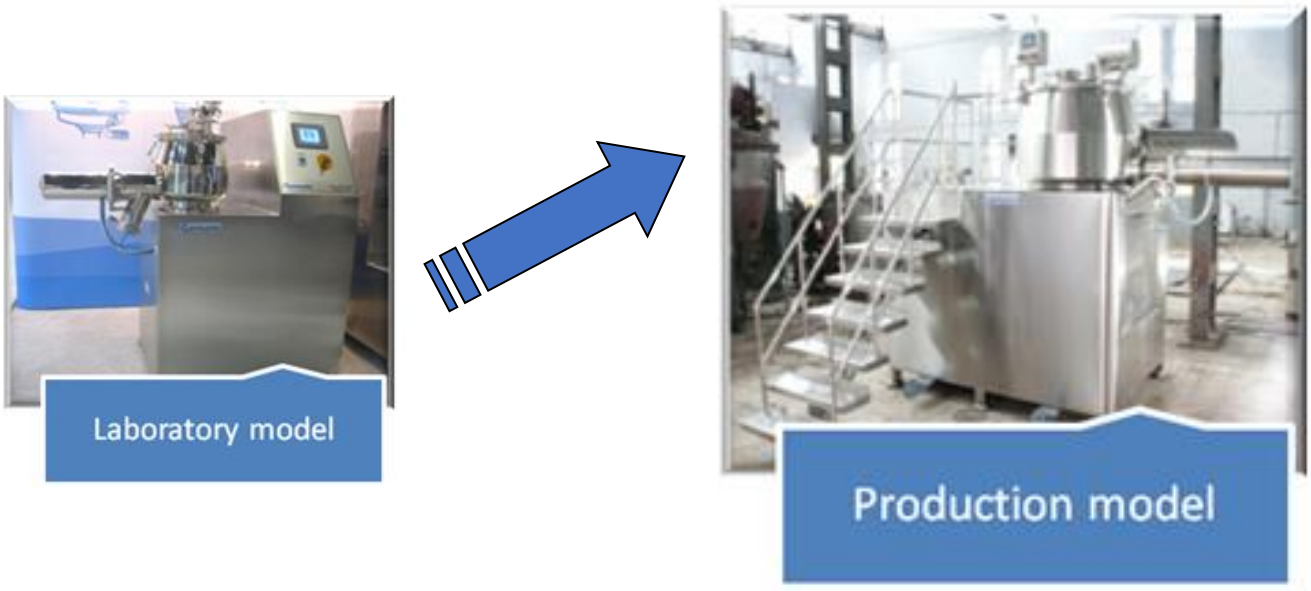
- A detail review of the dossier is necessary after submission to Regulatory by CFTs like FR&D, Process Team, AR&D, RA, QbD, etc., to find all possible gaps and close them before receiving deficiency reports.
- This will help to respond to deficiencies more quickly.
- The actual deficiencies should be compared with the internal findings. This will help the team to predict any deficiency during ongoing development and lead to a superior process review to capture all possible deficiencies.

Exhibit 8



f. Scale-Up Best Practices

- **These are based on scientific scale-up calculations by unit operation and by technology.**



The approach revolves around the following key documents and processes:

- Geometrical similarity
- Kinematic similarity
- Dynamic similarity

If the above three criteria are satisfied, the scaling up of parameters should be linear. However, this is normally the case.

In the pharmaceutical industry ***"Scale-up"*** refers to the processes that are needed for successful transitions from drug discovery to product development to clinical trials to full-scale commercialization. Scale-up is an inevitable part of the product life cycle of every successful drug, and each time it is required, a meticulous process must be followed to ensure that the end result is identical to the product formulation as originally devised.

Scale-up of any pharmaceutical manufacturing process entails a skillful combination of art, experience, science and engineering. Application of statistical methods is constantly increasing to help with design of experiments and development of empirical relationships between process parameters, material attributes and quality attributes.

The scale-up approach has been used in physical sciences, viz. fluid dynamics and chemical engineering, for quite a long time. This approach is based on process similarities between different scales and employs dimensional analysis that was developed a century ago and has gained applications in many industries, especially in chemical engineering.

Dimensional analysis is a method for producing dimensionless numbers that completely characterize the process parameters. The analysis can be applied even when the equations governing the process are not known. According to the theory of models, two processes may be considered completely similar if they take place in

Similar geometrical space and if all the dimensionless numbers necessary to describe the process have the same numerical value. The scale-up procedure is simple if scale up executed in similar geometrical and dimensional environment.

Dimensionless numbers, such as Reynolds and Froude numbers, are frequently used to describe mixing processes. Chemical engineers are routinely concerned with problems of water-air or fluid mixing in vessels equipped with turbine stirrers in which scale-up factors can be up to 1:70. However, scale-up challenges arise when similarity is not possible for geometrical and dimensional parameters.

One way to eliminate potential scale-up challenges is to develop formulations that are very robust with respect to processing conditions. A comprehensive database of excipients detailing their material properties may be indispensable for this purpose. However, in practical terms, this cannot be achieved without some means of testing in a production environment, and, since the initial drug substance is usually available only in small quantities, some form of simulation is required on a small scale. In a very complex manufacturing process scale up, it may need minor modifications in existing process flow, addition or deletion of extra processing steps, minor changes in composition, changes in equipment principles, etc.

Any change in a process of making a pharmaceutical dosage form is a regulatory concern. Scale-Up and Post Approval Changes (SUPAC) are of special interest to the FDA, as is evidenced by a growing number of regulatory documents released in the past several years by the Center for Drug Evaluation and Research (CDER), including Immediate Release Solid Oral Dosage Forms (SUPAC-IR), Modified Release Solid Oral Dosage Forms (SUPAC-MR), and Semisolid Dosage Forms (SUPAC-SS). Additional SUPAC guidance documents that are being developed include Transdermal Delivery Systems (SUPAC-TDS), Bulk Actives (BACPAC)and Sterile Aqueous Solutions (PAC-SAS). Collaborations between the FDA, the pharmaceutical industry, and academia in this and other areas have recently been launched under the framework of the Product Quality Research Institute (PQRI). Scale-up problems may require post-approval changes that affect formulation composition, site, and manufacturing process or equipment (from the regulatory standpoint, scale-up and scale-down are treated with the same degree of scrutiny).

In a typical drug development cycle, once a set of clinical studies has been completed or a NDA/ANDA has been approved, it becomes very difficult to change the product or the process to accommodate specific production needs. Such needs may include changes in batch size and manufacturing equipment or process. Post-approval changes in the size of a batch from the pilot scale to larger or smaller production scales call for submission of additional information in the application, with a specific requirement that the new batches are to be produced using similar test equipment and in full compliance with CGMPs and the existing SOPs. Manufacturing changes may require new stability, dissolution, and in vivo bioequivalence testing. This is especially true for Level 2 equipment changes (change in equipment to a different design and different operating principles) and the process changes of Level 2 (e.g., in mixing times and operating speeds within application/validation ranges) and Level 3 (change in the type of process used in the manufacture of the product, such as from wet granulation to direct compression of dry powder).

Scale-up should be done after getting all information from R&D. It involves transfer of technology as well as transfer of knowledge.

Based on various regulatory agency requirement in the pharma industry, the ideal scale up can be up to 10 times of pilot scale; however, based on suitable supplement, scale-up beyond 10 times of pilot scale may be approved by regulatory authorities.

In an ideal scenario based on the targeted market, the final maximum commercial volume in units can be finalized at the initial stage of product selection for development. This helps the organization to finalize the finale commercial batch size and hence subsequent pilot batch size. An early stage decision on the scale of the product preparation will help to finalize development strategy and effective utilization of available commercial resources.

During development of any product, if the primary scale-up feasibility is taken care of, the subsequent challenges during actual execution of scale-up can be reduced. However, scale-up is not always fully predictable, hence it is necessary to go through a systematic approach in this regard.

The development of robust formulation and process using Design of Experiments (DoE) as well as a good understanding the critical v/s non-critical parameters for each unit operation are major determining factors for success v/s failure on scale-up.

A successful drug product may go through a scaling process several times during its lifecycle. The laboratory scale batches that expand to pilot-scale and finally to commercial scale production may be just a single iteration in a product's evolution. Popular products may also expand production to other manufacturing facilities or even other countries. Conversely, when demand inevitably begins to shrink, a similar process will be used in scaling down production to appropriate levels.
Before starting scale-up, it is necessary to take into account different parameters that are considered to be optimum for successful scale-up. These are:

- Flexibility
- Cost
- Dependability
- Innovation and product quality

It is equally important to realize that good communication is critical for formulation and process transfer to be successful.

f.1 Definition

- "Scale-up is generally defined as a process of increasing batch size and procedure by applying the same process to different output volumes, the migration of a process from the lab scale to the pilot plant scale or commercial scale."

f.2 Stages of Product life cycle:

1. Development batches (lab development/formulation design)
2. Process screening: (QbD/DOE example of wet granulation)
3. Pilot scale/exhibit batches (scale-up 1- lab to pilot scale)
4. Validation/Commercial scale batches (scale-up 2- pilot scale to commercial scale)

1. **Development Batches (Lab Development/Formulation Design)**

- Development batches for prototype formula and process finalization batches at lab scale may be used to support formulation and packaging development, early clinical and/or preclinical stages. Laboratory-scale batches can also be analyzed to assist in the evaluation and definition of critical quality attributes (CQAs). 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. CQAs are generally associated with the drug substance, excipients, intermediates, and drug product.

- After the prototype of formula finalization, formula optimization should be carried out using Quality by design (QbD) approach/OFAT trials and CMAs range should be defined. CMA is a physical, chemical, biological or microbiological property or characteristic of an input material (excipients or API) that should be controlled within an appropriate limit, range, or distribution in a material specification, in order to ensure the desired quality of final product. Further process optimization should be carried out using QbD approaches.

2. Different steps involved in process optimization:

Initial risk assessment for process variables:

- A risk assessment of the overall drug product manufacturing process should be performed to identify the high-risk steps that may affect the CQAs of the final drug product. Considering literature data, physicochemical properties of ingredients and understanding of the manufacturing process, a risk assessment of potential impact of manufacturing unit operations on critical quality attributes of the drug product should be constructed.

Justification for initial risk assessment of the drug product manufacturing process:

- Proper justification should be produced for each process parameter which impacted the drug product CQA considering the physicochemical properties of ingredients.

- Further risk assessment should be performed subsequently on each high/medium risk process step in order to identify the process variables that may potentially impact the CQAs. Evaluation of all possible process variables that could potentially impact the quality attributes of the output material of any given process step may not be feasible; therefore, some of the variables may be kept constant (based on previous learning and current understanding) and the effect of other variables may be measured in DoE.

Process parameter optimization plan:

- Based on QbD approach, DoE, and applicable statistical tools, the process parameter can be optimized and final design space can be identified.

- Based on statistical evaluation and interaction effect, the critical process parameters that could potentially affect on CQA parameters can be finalized. However, the parameters which have minor impact may also considered as and when required using a control strategy with defined risk assessment during scale-up.

3. Pilot scale/exhibit batches (Scale-up 1 – lab to pilot scale)

- These batches may be used to support preclinical and mid to later stage clinical evaluation and to support formal stability studies. If supporting formal registration, a pilot batch size should correspond to at least 10% of the production scale batch. For oral solid-dosage forms, this size should generally be 10% of production scale or 100,000 units, whichever is greater. The choice of pilot scale is often difficult for the project team as members must balance parameters such as anticipated product volumes, anticipated site of production, equipment constraints at that site, and regulatory expectations. With the increasing trend toward developing orphan drugs, the authors believe that the regulatory expectation of pilot-scale batches of 100,000 units is not always valid and should be discussed with the relevant regulatory authority.

- During scaling to pilot scale, each unit operation parameter should be identified as scale dependent or scale independent parameters.

- Scale independent parameters are those which do not change across the scale.

- Scale dependent parameters are those which change with change in scale. Scale dependent parameters can be evaluated through different scientific calculation like Froude number, tip speed, etc.

- Equipment used at lab and commercial scale is usually similar; however in case of unavailability of similar equipment, the complexity and risk is high during scale-up. To reduce risk, understanding of the difference in both sets of scale equipment is necessary. In most of cases, the pilot and commercial scale equipment has better control options than lab scale equipment.

- The person responsible for scale-up should identify the differences in both sets of scale equipment and should evaluate the risk associated with such differences. For ease of evaluation, the differences between equipment can be documented for all the equipment matrix and this document can be made accessible across the cross-functional team. An example of such a document covering high-speed Rapid Mixture Granulator (RMG) and Auto Coating Machine is enclosed in Annexure 3A and 3B.

- The scale-up team should understand the applicable scale-up factors and considerations, described in the following pages of this document.

- Based on the development and equipment and after understanding risk assessment, a control strategy should be defined for individual CPP. Based on the risk assessment, the firm can decide whether any engineering or scale-up batch is required or not before final execution of pilot scale batches.

An example of lab scale challenge study, risk assessment, execution and control strategy is given in Annexure 4.

4. Commercial scale batches (Scale-up 2 – pilot scale to commercial scale)

- Based on the regulatory approval, further scale-up to commercial scale may require. At this scale, experience and the data of pilot scale-up should be considered. The methodology of scale-up will remain the same; however the handling of material at larger scale will play a major role for maintaining of CQA parameters. Even though the process flow of unit operation may remain same, the handing method of material may change; for example, the loading of lubricated blend from bunker/bin to compression machine may change from gravitational to vacuum transfer, and this may lead to segregation of the material and may result in to failure in content uniformity.

- After approval of the dossier/tech pack from the regulatory agency, any changes required will have to be addressed through supplements. Scale-up team should acknowledge such change requirements and be ready to accept changes associated with scale-up to meet final predefine CQAs. Commercial scale-up is crucial as it will have direct impact on end-use health if CQAs are variable from batch to batch even if the batches pass the specification criteria.

f.3 Flow-chart of Scale-up Process

Product Identification

- ❖Commercial volume identification.
- ❖Development and commercial strategy finalization.

Development of Product

- ❖During initial devlopment, commercial scale up strategy should be considered.
- ❖Identify equipment trail, identify the difference in equipment and build this knowledge in development path.

Process Optimization

- ❖Identify the CQA and its correlation with CPP and CMA.
- ❖Design space and control space identification.
- ❖Risk assessment and control strategy.
- ❖PAT evaluation and PAT proposal for pilot scale.

Pilot Scale Planning (Scale-up 1)

- ❖ Identification of gap analysis for equipment.
- ❖ Defining of batch size.
- ❖ Defining scale dependent and scale independent parameters.
- ❖Identifying applicable scale-up factor and establishing theoretical parameters.
- ❖Evaluation of theoretical parameters against equipment qualification and impact on CQA.
- ❖Risk assesment and control strategy.
- ❖Execution of scale-up 1, with applicable PAT (if any) and evaluation of statistical data.
- ❖Re-evluation of risk identification before scale-up and residual risk mitigation plan.

Commercial Scale (Scale-up 2)

- ❖Assess knowledge from experience gained from pilot scale-up.
- ❖Engineering batch/scale-up batch execution and evaluation of data with help of statistical data against pilot scale batches.
- ❖Evaluation of variation filing in case of any variation from submitted dossier.
- ❖Plan for ensuring residual risk mitigation.
- ❖Equipment gap analyis and mitigation plan.

Process Performance Qualification (PPQ)

- ❖Based on sufficient knowledge gained during scale-up activity and residual risk, PPQ protocol should be designed.
- ❖Execution of PPQ batches and evaluation of CQA and proposal for continuous varification plan.

f.4 Methodology for Scale-up of Pharmaceutical Process:

- For scale-up of manufacturing process from one scale to another, factors like prerequisites for scale-up, manufacturing site, equipment finalization, batch size and finalization of scale-up correlation are critical.

f.5 Objectives of scale-up process:

- To meet predefined CQA parameters
- To understand what makes these processes similar, to identify and to eliminate many scale-up problems before investing large sums of money on a production unit
- To maintain efficacy through changes in processes or composition which can help to overcome scale-up issues
- To closely examine the formula in order to determine its ability to withstand large scale and process modifications
- To review a range of relevant processing equipment in order to determine which would be most compatible with the formulation as well as the most economical, simple and reliable in producing the product
- To assess production rates and future market requirements

f.6 Difficulties faced during scale-up

- Equipment geometry may not be similar across scale.
- Equipment make and model may be different.
- Equipment capability to measure some critical parameters may differ across scale.
- Lack of established correlation to scale-up for critical process parameters.
- Interpretation of powder characterization is not extensive.
- Lack of automation may lead to manual errors.
- Lack of process analytical tools to determine endpoint and control process parameters in-line to achieve desired quality attributes.

f.7 Prerequisite of scale-up

Following information is required for successful scale-up of any pharmaceutical product. -

- Targeted manufacturing site and equipment.
- In-depth knowledge of process with a summary of the critical processing steps or critical parameters to be monitored during manufacturing process.
- Process optimization study conclusion (process DoE).
- Physico-chemical characterization of API and excipients.
- Critical quality attributes and finished product specification.
- Details of analytical methods.
- Proposed in process controls with acceptance criteria.
- Sampling plan – where, when and how the samples are taken.
- Details of methods for recording and evaluation of results.
- Proposed timeframe

Equivalency:

Manufacturing site:

- Layout, construction and finishing of buildings and services (HVAC, water, power, compressed air) – impact of such factors on the product, process or method to be transferred during scale-up
- Risks of processes (e. g., reactions, exposure limits, fire and explosion risks) and emergency planning (e. g., in case of gas or dust release, spillage, fire), operator exposure (e. g., atmospheric containment of pharmaceutical dust)
- Waste streams and provisions for re-use, recycling and/or disposal.

Equipment:

- Qualification and validation documentation, i. e., drawings, manuals, maintenance logs, calibration logs and procedures (e. g., regarding equipment set-up, operation, cleaning, maintenance, calibration and storage)

- Qualification status (IQ, OQ, PQ) of all equipment and systems, and preparation of a side-by-side comparison of equipment at the two sites in terms of their functionality, makes, models and qualification status. (e. g., development to commercial, one manufacturing site to another manufacturing site, etc.). Factors to be compared include:
  - Minimum and maximum capacity: as per the capacity of equipment, occupancy to be decided for calculated batch size
  - Material of construction
  - Critical operating parameters
  - Critical equipment components (e. g., filters, screens, and temperature/pressure sensors)
  - Critical quality attributes

- It is important to prepare process flow charts of the manufacturing process including equipment to be used, taking into consideration the flow of personnel and material. The impact of including new products on site, any modification of existing equipment, and other factors need to be documented in the transfer project plan.

- The similarity equipment should be matched across the scale in order to establish correlation to scale-up critical process parameters. The principle of similarity includes the entire subject of dimensional analysis. There are three necessary conditions for complete similarity between a model and a prototype.

- **Geometric similarity:** Two systems are geometrically similar when the ratio of the linear dimensions of the small scale and scaled-up system are constant.

- **Kinematic similarity**: Two systems of different sizes are kinematically similar when, in addition to the systems being geometrically similar, the ratio of velocities between corresponding points in the two systems is equal

Dynamic similarity: Two systems of different size are dynamically similar when in addition to their being geometrically and kinematically similar, the ratio of forces between corresponding points in the two systems are equal

- All forces in the model flow must scale by a constant factor to the corresponding forces in the prototype flow. In other words, the relative importance of different types of forces (e.g., viscous and inertial forces) must be the same for the model and the prototype. This requires that the model and the prototype have the same dimensionless parameters (e.g., the same Reynolds number), although they may (and usually do) have different dimensional variables

However, since it is very difficult to achieve dynamic similarity when more than one dimensionless group is involved in a system, a set of common criteria for scale-up have been developed:

- Constant power/volume
- Constant impeller tip speed (□DN)
- Froude no (Fr.)
- Constant volumetric mass transfer coefficient (kLa)
- Constant impeller Reynolds No
- Constant mixing time (Tmix) or circulation time (Tcirc)
- Common to scale-up in the basis of geometric similarity and at least one of the above
- Torque for power consumption
- Air flow rate
- % Opening area of screen
- Constant droplet size
- Dwell time

Batch size calculation:

Establishing a commercial batch size is a crucial decision in pharmaceutical operations. It is influenced by the type of manufacturing technology being used, regulatory filing commitments, supply chain demands, and operational planning factors. To understand batch size, the differences between “batch,” “continuous,” “semi-batch,” and “semi-continuous” manufacturing must first be defined.

- In batch manufacturing, all materials are charged before the start of processing and discharged at the end of processing. Examples include bin blending and lyophilisation.

- Continuous manufacturing involves materials simultaneously charged and discharged from the process; examples are found in petroleum refining, food processing, and, more recently, in pharmaceutical manufacturing.

- Other manufacturing variations include semi-batch (i.e., fed batch) manufacturing, as found in wet granulation, tablet coating, and fermentation, in which materials are added during processing and discharged at the end of processing.

- In semi-continuous manufacturing, materials are simultaneously charged and discharged, but for a discrete time period. Examples include roller compaction, tablet compression, and encapsulation. For semi-continuous manufacturing processes, the process output is independent of batch size if the material input is set up to produce consistent output as per the controlled process. Therefore, a fixed batch size is not required for semi-continuous manufacturing processes.

Regulatory guidance provide clarity on batch requirements. The FDA Guidance for Industry: Immediate Release Solid Dosage Forms Scale Up and Post Approval Changes outlines the maximum allowable batch size as 10 times the size of the pilot/bio batch. A European Medicines Agency (EMA) draft guideline on the manufacture of finished dosage forms notes that the batch size for a product to be marketed should normally be compatible with qualified equipment. It should be enough to allow process capability to be established. For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided. The equipment capacity and maximum quantity allowed determines the maximum batch size.

Risk assessment and control strategy after process scale-up:

- A systematic process of organizing information to support a risk decision should be made within a risk management process. Risk assessment consists of the identification, analysis, and evaluation of risk.

Table 11: Risk Assessment for Drug Product and Manufacturing Process Parameters

Unit Operation		Risk Involved	Impact	Control Strategy
Sifting		1. Sieve integrity. 2. Improper sieve size. 3. Improper sifting.	1. Foreign matter. 2. Product quality.	1. Intactness of sieve to be checked prior and after sifting. 2. Sieve size to be ensured as per given instruction.
Granulation	RMG	1. High/low spray rate. 2. Binder addition/kneading time. 3. Improper impeller and chopper speed. 4. Wrong volume/occupancy of product.	1.Hardness 2.Friability 3.Dissolution 4. Disintegration yime 5.Granules quality.	1. Spray rate limit to be decided and instructed. 2. Spray rate calibration was done prior to spraying and using Mass flowmeterfor accurate amount of spraying solution. 3. Binder addition and kneading time range to be studied and defined. 4. Study range to be studied of product temperature, atomization air pressure, Inlet air flow. 5. Volume/occupancy to be studied and defined
	FBP/bottom granulation and drying	1. High/low product temperature. 2. High/low spray rate. 3.Wrong atomization air pressure 4. Improper inlet air flow. 5. Wrong volume/occupancy of product.		
Milling		1. Screen integrity. 2. Improper screen size and type. 3. Improper machine speed.	1. Product quality. 2. Particle size distribution. 3. Hardness.	1. Intactness of screen to be checked prior and after sifting. 2. Screen size and type to be ensured as per given instruction. 3. Check screen regularly for chocking. 4. Speed range to be studied.
Blending and Lubrication		1.Loading and mixing pattern 2.RPM and time variation	1. Blend uniformity 2. PSD	1. Blending & lubrication time, RPM, materials loading and mixing pattern, qualification are defined and to be instructed. 2. Using NIR as a PAT tool. The NIR output is used to determine the blending and lubrication endpoint so that, despite the wide range of blend times, product of suitable quality could be produced under all conditions. 3. BUA results variability should be evaluated and control strategy decided upon, like unit dose sample hardness/pressure, quantity (sample size).
Compression		1. Improper selection of tooling. 2. Wrong machine set up. 3. Contamination of drug. 4. Force feeder type. 5. Improper turret/feeder RPM ratio. 6. Wrong pre-compaction and compaction force. 7. Wrong cam size.	1. Product appearance. 2. Hardness. 3. Thickness. 4. Physical appearance. 5. Disintegration time. 6. Capping. 7. Product quality. 8. Content uniformity. 9. Weight variation.	1. Machine set up as per instructed process. 2. Instruction for verification of the process. 3. Match dwell time across the scale. 4. Content uniformity: need to evaluate for intra and inter variability, and conclusion report as part of control strategy.
Coater		1. Pan RPM. 2. High/low spray rate. 3. Coater occupancy. 4. Improper atomization pressure. 5. Wrong nozzle size. 6. Improper gun to bed distance.	1. Product appearance. 2. Dissolution.	1. All parameters studied, and limit instructed. 2. Using mass flowmeterfor accurate amount of Spraying solution. 3. Using Spraytech for droplet size measurement for uniform film across the scale. 4. In case of functional coating impact of coating on dissolution RSD need to establish.
Manufacturing vessel		1. Anchor speed and time. 2. Homogenizer speed and time. 3. Cooling time	1. Product appearance. 2. Viscosity. 3. IVRT.	1. All parameters studied, and limit instructed.

Statistical Analysis of Scale-up Data and Establishing a Range

- All equipment and instruments should be maintained, qualified and calibrated before use. After the process scale-up, batches parameters and results should be evaluated and a range established where the process meets its predetermined specifications. The table below illustrates this point.

Table 12: Data of %LOD at the end of drying

Test Parameter	Sample Point	Observation (in minutes)									Proposed Limit
		Batch-A			Batch-B			Batch-C			
		20	30	40	20	30	40	20	30	40	
Loss on Drying (%)	Top	1.86	1.65	1.50	2.12	1.75	1.51	1.94	1.68	1.56	1.00-3.00%
	Middle	1.95	1.79	1.68	2.06	1.69	1.50	2.25	1.50	1.59	
	Bottom	1.89	1.33	1.52	2.32	1.65	1.54	1.98	1.78	1.54	

After drying, % LOD data was evaluated for all locations in the particular batch and other batches, and based on the data, limits were proposed for future batches.

Table 13: Scale-up model – by unit in operation

Critical Unit Operations		Scale Dependent Parameters	Scale Independent Parameters
Equipment	Operation		
Rapid mix granulator (RMG)/High shear mixer granulator (HSMG)	Wet granulation	• Impeller RPM.	• Occupancy. • Impeller tip speed. • Newton's Power number for torque. • Binder addition/kneading time. • Fill Ratio. -Bed Height/RMG Diameter. -Impeller relative swept volume.
FBD/FBP	Drying/top spray/bottom spray	• Inlet air flow. • Spray rate. • Atomization air pressure of gun.	• Occupancy. • Product temperature. • Inlet air temperature and RH. • Gun nozzle size. • Droplet size.
Roll compactor	Dry granulation /compaction	• Roller speed. • Feeder screw speed.	• Roller gap. • Compaction force/unit area.
Blender	Mixing	• No. of rotations. • Blender speed. • Blending time.	• Froude number. • Tip speed. • Occupancy.
Quadro-co mill	Size reduction	NA	• Tip speed. • Clearance b/w screen and impeller. • % Opening of screen and hole diameter.
Compression	Tableting	• Compression speed	• Blend residence time in feeder. • Compression force. • Dwell time.
Coater	Pan coating	• Inlet air flow. • Spray rate. • Pan speed. • Atomization air pressure of gun.	• Occupancy (pan load(kg)/brim volume). • Product temperature. • Inlet air temperature/RH. • Gun nozzle size. • Droplet size. • Gun to bed distance.
Manufacturing vessel	Semisolid/ liquid manufacturing	• Anchor RPM. • Homogenizer speed.	• Ratio of height of bBulk/diameter of vessel • Ratio of power (W)/volume(m^3) of anchor. • Heating and cooling rate. • Product temperature. • Homogenizer tip speed. • Anchor mixing time. • Homogenizer run time.

Examples of scale-up factor applications:

1. Rapid mix granulator (RMG)/High share mixer granulator(HSMG):

Batch size should be scaled up according to:

- Fill ratio is defined as the ratio of bed height and RMG diameter
- Relative swept volume is defined as the ratio of blade height to bed height
- Impeller RPM should be scaled down or scaled up according to tip speed [2*(∏) *R*N]
- Newton's power number can be used to scale torque [$Ne_P = P/(\rho R^5N^3)$]
  - P = Power consumption by the impeller blade = Torque* (2*∏*N)
  - N = Impeller RPM
  - R = Impeller radius
  - ρ = Wet mass density of granules (method to determine ρ needs to be finalized)
- Newton's power number relates the drag force acting on a unit area of the impeller and the inertial stress.

2. FBD/FBP:

- If fill ratio of the equipment remains the same in all scales, then in any scale the air velocity should remain the same.
- Air velocity (feet/min) = Air flow (cubic feet/min)/Base plate area (square feet)
- Spray rate of Scale 2 batch (gm/min) (Q2) = $\frac{Q1 \times A2}{A1}$

Where

Q1= Spray rate of Scale 1 Batch (gm/min)

A2= Base plate area at Scale 2

A1= Base plate area at Scale 1

Differential pressure across bowl should be maintained.

3. Roll compactor:

- Roller gap needs to be kept constant across the scale. At constant gap, the compaction pressure must be increased slightly for downscaling and to be decreased slightly for upscaling.
- The compaction force should be scaled up according to following formula, where the ratio between the compaction force is equal to the ratio of the roller diameters multiplied by a factor called t_c.

$$SF_2 = \frac{RD_2}{RD_1} * CF_1 * t_c$$

Where

CF_1 = Compaction force (Machine A)

CF_2 = Compaction force (Machine B)

RD_1 = Outer roller diameter (Machine A)

RD_2 = Outer roller diameter (Machine B)

t_c = Correction factor for dwell time

- Correction factor depends on the dwell time of the product in the nip area of the roller and product characteristic; in most of the case t_c equals 1.

4. Blender:

Blending

- Froude number should be kept the same across the scale to achieve uniform mixing/shear; RPM of blender will vary.
- To have same number of rotations, blending time will change.
- Blending time: Froude No. = $\frac{R*\omega^2}{g}$
- R= Rotational length of the blender
- g= Gravitational constant= 9.81m/s^2
- Angular velocity (ω)= $\frac{2*3.14*N}{60}$
- N= Rotational speed of the blender (RPM)

Lubrication

- Considering head space and the Froude number, lubrication time will change across the scale to keep the number of revolutions constant.
- r_1=$\frac{{v_2}^{1/3}}{{v_1}^{1/3}}$ * r_2*$\frac{Head\ space_2}{head\ space_1}$\
- v_1 = Volume of smaller blender
- v_2 = Volume of larger blender

Head Space = 100% Occupancy of blender
r1= Number of revolutions in smaller blender
r2= Number of revolutions in larger blender
No of Revolution = N*Blending (or Lubrication) Time
N= Rotational speed of the blender (RPM)

5. Scale up Factor for Milling (Quadro Co-Mill)

- In Quadro co-mill, as a scale up factor, the tip speed of the impeller should match across the scale.

$$\text{Tip Speed} = \frac{3.14 \times D \times N}{60}$$

Where

D = Diameter of impeller

N = RPM of impeller

6. Compression

- Compression machine speed is determined based on dwell time.

$$DT = \frac{PHF \times 60{,}000}{\prod \times PCD \times N}$$

Where

PHF (Punch Head Flat)= 12.7 mm for B tooling and 18.23 mm for D tooling

N= No. of rotations per minute of turret

$\prod = 3.14$

PCD = Pitch circle diameter of turret (mm)

DT (msec) = Dwell time in milli seconds

7. Pan Coating

- Occupancy (Pan load[kg]/Brim volume) should be keep constant.
- Spray rate: (Spray rate * Pan dia/Batch size) should be kept constant across scale.
- Air flow rate: Drying capacity (CFM/Spray rate) should be kept constant across scale.
- There should be consistency in baffle design across scale.
- Differential air pressure of bowl should be maintained.
- For functional coating, the droplet size needs to be kept constant across the scale to achieve identical film formation. Droplet size measurement can be done by using appropriate droplet size measurement tool.

8. Scale up Factor Calculation for CFM and Spray rate

$$\text{Scale up factor} = \frac{\text{Batch Size in kg (Higher Scale)}}{\text{Batch Size in kg (Lower Scale)}} \times \frac{\text{Coating Pan Size (Lower Scale)}}{\text{Coating Pan Size (Higher Scale)}}$$

Scale up Factor Calculation for Pan RPM

$$\text{Scale up factor} = \sqrt{A/B}$$

Where

A = Coating pan size of higher scale

B = Coating pan size of lower scale

9. Semisolid/Liquid Manufacturing vessel

- Batch size should be finalized on H/D, where ratio of height of bulk/diameter of vessel should be kept constant across scale.
- Anchor speed should be fixed on the basis of P/V ratio. Based on anchor size, the anchor speed will change across the scale by keeping constant the ratio of Power(W)/Volume(m3) of anchor.

$$P/V = \frac{Np*N^3*\rho*D^5}{V}$$

Where
Np =Power Number (W)
N =Anchor RPM (per Sec)
ρ= Density (Kg/m^3)
D=Diameter of Anchor (m)
V=Volume (m^3)

- For homogenizer, speed will change across the scale by keeping tip speed constant.

$$\text{Tip Speed} = \frac{3.14 \times D \times N}{60}$$

Where
D = Diameter of homogenizer rotor-stator
N = RPM of homogenizer.

Note: Geometry of vessel, anchor/stirrer design need to be maintained similar in order to derive better scale-up correlation.

Example of solid oral dosage form given here is for reference as a science-based approach to scale-up; however, it should be noted that challenges are inherent in scaling up. Based on actual execution, the knowledge gained during scale-up should be documented. Risk assessment-based Scale-up can enhance the scale-up process. Other than solid oral dosage form also evaluated based on science, engineering scale up concept and automation.

An example of application and calculation of scale-up factor is presented in Annexure 5.

5.2 Stage 2: Process Performance Qualification (PPQ)

a. Leveraging Stage 1 data for calculating number of validation batches for PPQ

- The intent of leveraging the data from stage 1 batches is to support the existing body of knowledge and demonstrate the control strategy in order to potentially justify the number of PPQ batches to be manufactured in order to establish the validated state of the process.

- For a new product, stage 1 data typically includes scale-up, exhibit batches, and pre-validation building batches.

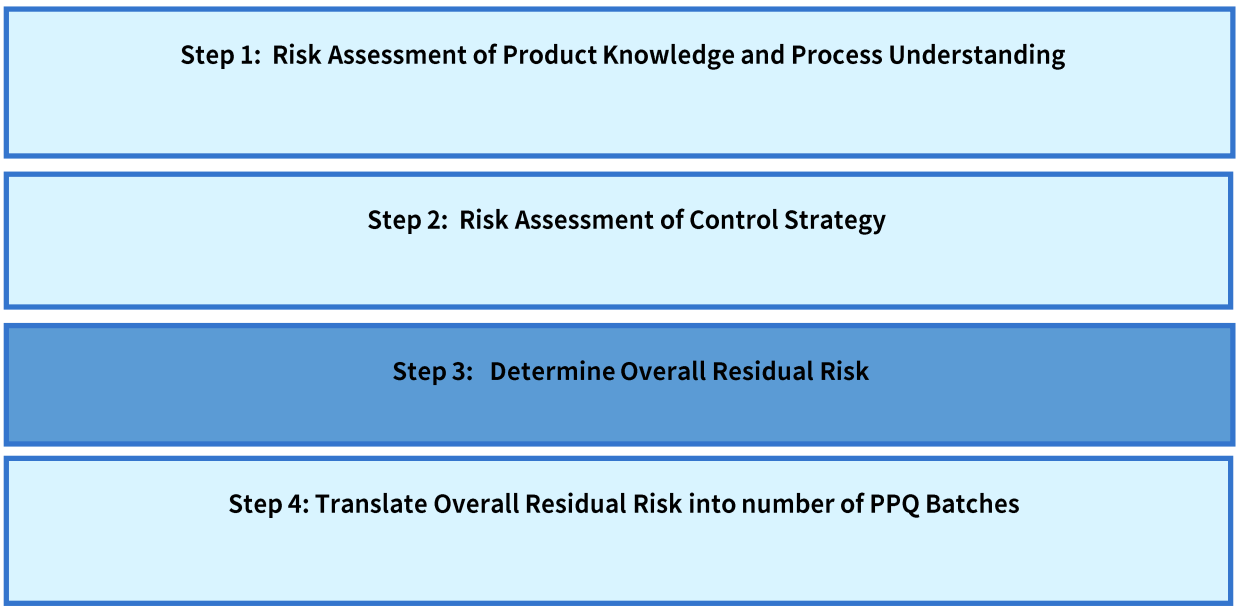
- For existing commercial product, stage 1 data is typically represented by the commercial batches manufactured (prior knowledge batches) at the site and-/-or technology transfer batches manufactured at the receiving site.

b. Approach followed for calculating number of PPQ batches

The number of PPQ batches depends on the residual risk remaining following Stage 1 and the expected inter-batch variability with an understanding of the sources that influence product quality.

- The *Bayesian method* can be used to determine the number of validation batches required for stage 2 PPQ.
- Process performance data from stage 1 are modelled through *Beta error distribution* and combined with expected outcomes of stage 2 PPQ to derive posterior probability for future batches to meet specifications.

Irrespective of the method used, the first step is to determine the overall residual risk levels based on the following table.



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

- The justification for the minimum number of batches (n) should be documented prior to approval of PPQ protocol.
- A copy of the template for performing Process Performance Qualification (PPQ) is provided as Annexure 6.

5.3 Continuous Process Verification

On the basis of the residual risk post the PPQ batches execution, the number of CPV batches should be decided on the basis of a XX% pass rate and YY% confidence interval. On the basis of this, the target Cpk could be decided and made part of the CPV protocol. If due to any reason the pre-decided Cpk is not achieved, CPV can be further extended for additional batches.

A copy of the CPV template is attached in Annexure 7.

a. Product Score Card

- The product score card can be used for quantifying the robustness of a product using statistically valid principles. Some important best practices adopted while designing the scoreboard are as follows:
    - These should be simple to understand and comprehend by the entire organization from the management to shop floor level personnel, and should enable them to take decisions based on the principle of management by exception.
    - These should be composed of independent quality score contribution, based on criticality level of the CQAs, each able to describe the trend by itself which will help explain causality and thus support root cause investigation.
    - These should have the capability of handling both qualitative and quantitative data.
    - These should not be hampered by any assumption of a theoretical distribution (normal or non-normal) for the underlying data or the sample size, so that they can be applied across the portfolio of products.

The methodology of arriving at the product score involves calculating the robustness score on the basis of the Ppk (Process Performance Capability). The Ppk is a weighted average of all the critical quality attributes associated with the product. The weightage is calculated on the basis of relative ranking of the following factors against each of the CQA with a rating scale of 1-5.

Metric
Deviation
Market Complaints
Out of Specifications (OOS)
Out of Trend (OOT)
Product Recall

An illustration of calculating the Product robustness score is provided as Annexure 8.

b. Dynamic APQR

The annual PQR document has traditionally been a year-end activity that highlights the performance of the product quality, incidents, quality issues, etc., which is a retrospective evaluation. This review should be revisited in order to incorporate a risk based approach where a product with higher risk associated with process performance would be reviewed at more regular intervals and hence the frequency of review, viz. monthly, quarterly, half yearly, etc., can be decided The product scorecard would be an important parameter used in deciding the frequency of the review process.

Applications:

- The product scorecard approach in conjunction with the CTQ document and Dynamic APQR document will enable **a timely intervention** as opposed to post facto (end of the year) evaluation and thus also supports the organization's continuous improvement philosophy.

- The product scorecard can be used as a comparator across products and can be used as the criteria for prioritizing various interventions for improving the product robustness.

- It provides a metric to **assess the effectiveness of the process improvement interventions** by its impact on the CQAs and product score.

- The metrics and the supporting document will be a useful resource for the product managers and will also be a very potent tool in **carrying out future investigations.**

Annexures

Annexure 1: Qualitative Risk Assessment

Identified Risk or Reference Document No.	##########
Date of Assessment	DD-MM-YYY

Description: This Risk Assessment evaluates the risk involved in the manufacturing of process performance qualification batches of [**CAPSULES**] which are planned to be manufactured at [**SITE NAME].** The objective is to identify, qualify and to propose mitigation plans for the medium or high risks, if any, for the smooth manufacturing of process performance qualification batches to be executed, which provide a high degree of assurance that the manufacturing process will consistently produce [**CAPSULES**] meeting the predetermined acceptance criteria and quality attributes.

Background information or any facts which forms the basis for this assessment

The product [CAPSULES] is an immediate release dosage form indicated for treatment of a specific disease. The manufacturing of three process performance qualification batches of capsules shall be carried out in [**UNIT**] as per approved batch manufacturing record and approved process performance qualification protocols.

Team Selection :

S. No	Department	Member Name	Role (Team Leader/Member)	Area of Expertise	Signature &Date
1			Team member/Team leader		
2			Team member/Team leader		
3			Team member/Team leader		
4			Team member/Team leader		

Reference SOP no.:

1.0 Initial Risk Assessment of the Manufacturing Process

- Initial risk assessment of manufacturing process of [CAPSULES] is captured from product development report (PDR)

Process Steps					
Quality Attributes	Sifting	Blending of Premix	Roller Compaction	Final Blending	Capsule Filling
Intermediate CQAs					
Blend Assay	Low	Low	Low	Low	NA
Blend Uniformity	Low	Medium	Medium	Medium	NA
Weight variation	NA	NA	NA	NA	Medium
Drug Product CQAs					
Assay	Low	Low	Low	Low	Medium
Uniformity of Dosage Units	Low	Medium	Medium	Medium	Medium
Related Substances	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low

Low	**Broadly acceptable risk. No further investigation is needed.**
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.
NA	Risk is not applicable. Therespective quality attributes are not related to respective unit operations and will not be discussed further.

1.1 Initial risk assessments for process variables:

S.No	Process steps	Process parameters	Intermediate CQAs			Drug Product CQAs				Justification
			Blend Uniformity	Blend Assay	Weight variation	Assay	UOD	Related Substances	Dissolution	
1	Sifting	Screen aperture size	Low	Low	Low	Low	Low	Low	Low	The purpose of sifting is to remove extraneous matter and de-agglomerate lumps in the raw material, if any. Hence it unlikely to have any impact on intermediate and drug product CQA's. Hence risk is low
		Order of sifting	Low	Low	Low	Low	Low	Low	Low	
		Sifting speed	Low	Low	Low	Low	Low	Low	Low	
2	Blending of premix	Occupancy	Medium	Low	NA	Low	Medium	Low	Low	Formulation contains High % (above 70%) API and objective of this unit operation is to mix excipient with drug substance for roller compaction process. This is a closed process and by this process the chance for loss of material is reduced. Therefore the blend assay will not be impacted. Hence, the risk is low and unlikely to impact related substance, dissolution and assay. Improper blending may impact blend uniformity and UOD, hence the risk is medium.
		Total number of revolutions	Medium	Low	NA	Low	Medium	Low	Low	
3	Roller Compaction	Roller speed	Medium	Low	NA	Low	Medium	Low	Low	The objective of this unit operation is to form the granules by roller compaction process. The compaction process has been adopted to avoid segregation and the issue of flowability, hence the process has no impact on related substance, assay and dissolution.Variability in ribbon density during processing can potentially impact the PSD of the milled granules, thus impacting flowability and ultimately, UOD. Therefore, the risk is medium
		Roller gap	Medium	Low	NA	Low	Medium	Low	Low	
		Hydraulic pressure	Medium	Low	NA	Low	Medium	Low	Low	
4	Final Blending	Occupancy	Medium	Low	NA	Low	Medium	Low	Low	The objective of this step is to mix the roll compacted blend and the lubricant. Improper mixing may lead to variation in BU. Hence BU and UOD are likely to be impacted. Hence the risk is medium. The drug belongs to BCS class I, and based on initial studies performed for lower strengths, it was identified that assay, dissolution and related substances would not be impacted by the blending unit operation stage. Hence the risk is low.
		Total number of revolutions	Medium	Low	NA	Low	Medium	Low	Low	
5	Capsule filling	Machine speed	Low	Low	Medium	Medium	Mediu M	Low	Low	Weight variation may get impacted at different machine speeds which will in turn impact assay and weight variation. Hence risk is medium. Related substances and dissolution will not be impacted by capsule filling. Hence the risk is low. In capsule filling, the tamping pin height and dosing disc thickness are fixed based on input material bulk density. Hence the risk is captured as low.

1.2 Justification for updated risk assessments for process variables

S. No	Process steps	Process parameters	Intermediate CQAs			Drug Product CQAs				Justification
			Blend Uniformity	Blend Assay	Weight variation	Assay	UOD	Related Substances	Dissolution	
1	Sifting	Screen aperture size	Low	Low	Low	Low	Low	Low	Low	As detailed in the initial risk assessment.
		Order of sifting	Low	Low	Low	Low	Low	Low	Low	
		Sifting speed	Low	Low	Low	Low	Low	Low	Low	
2	Blending of premix	Occupancy	Low	Low	NA	Low	Low	Low	Low	Impact of blender occupancy on blend uniformity and UOD in capsule filling was evaluated in lab scale trials, pre-submission, submission and pre- validation batches. Based on the blend uniformity and UOD data, criticality has been reduced to low.
		Total number of revolutions	Low	Low	NA	Low	Low	Low	Low	The impact of the total number of revolution has been studied and optimized for XXXX L blender. It was observed that, with established parameters, there was no significant difference in the blend uniformity. Since blend uniformity was within the limits, it is believed that the uniformity of dose will also be within the limits.Hence the criticality has been reduced to low.
3	Roller Compaction	Roller speed	Low	Low	NA	Low	Low	Low	Low	With the established process parameters of roll compaction, the physical parameters like BD, TD and PSD of the granules are similar across various scale batches, and BU data and UOD data after capsule filling are well within the specified limits.Hence the criticality has been reduced to low.
		Roller gap	Low	Low	NA	Low	Low	Low	Low	
		Hydraulic pressure	Low	Low	NA	Low	Low	Low	Low	
4	Final Blending	Occupancy	Low	Low	NA	Low	Low	Low	Low	Impact of blender occupancy on blend uniformity and UOD in capsule filling was evaluated in various scale batches. Based on the blend uniformity and UOD data, criticality has been reduced to low.
		Total number of revolutions	Low	Low	NA	Low	Low	Low	Low	The impact of total number of revolution has been studied and optimized for XXXXL blender. It was observed that, with established parameters, there was no significant difference in the blend uniformity. Since blend uniformity was within the limits, it is believed that the uniformity of dose will also be within the limits.Hence the criticality has been reduced to low.
5	Capsule filling	Machine speed	Low	Low	Low	Low	Low	Low	Low	Variation in machine speed can induce material segregation and is likely to impact assay and UOD. Nevertheless, operating machine speed will be optimized in speed challenge test. The impact of machine speed on mentioned CQAs assay and UOD were thoroughly evaluated and finalized. Within the optimized speed range of capsule filling machine, there will not be any effect on assay and UOD. Hence the risk is captured as low.
		Tampingheight	Low	Low	Low	Low	Low	Low	Low	
		Dosing disc	Low	Low	Low	Low	Low	Low	Low	

1.3 Updated risk assessment for unit operations

S. No	Process Steps	Process Parameters	Intermediate CQAs			Drug Product CQAs			
			Blend Uniformity	Blend Assay	Weight variation	Assay	UOD	Related Substances	Dissolution
1	Sifting	Screen aperture size	Low	Low	Low	Low	Low	Low	Low
		Order of sifting	Low	Low	Low	Low	Low	Low	Low
		Sifting speed	Low	Low	Low	Low	Low	Low	Low
2	Blending of premix	Occupancy	Medium Risk has been mitigated to low by optimization scale-up studies and control strategy. $$$	Low	NA	Low	$$$	Low	Low
		Total number of revolutions	$$$	Low	NA	Low	$$$	Low	Low
3	Roller Compaction	Roller speed	$$$	Low	NA	Low	$$$	Low	Low
		Roller gap	$$$	Low	NA	Low	$$$	Low	Low
		Hydraulic pressure	$$$	Low	NA	Low	$$$	Low	Low
4	Final Blending	Occupancy	$$$	Low	NA	Low	$$$	Low	Low
		Total number of revolutions	$$$	Low	NA	Low	$$$	Low	Low
5	Capsule filling	Machine speed	Low	Low	$$$	$$$	$$$	Low	Low
		Tampingheight	Low	Low	Low	Low	Low	Low	Low
		Dosing disc	Low	Low	Low	Low	Low	Low	Low

1.4 Control Strategy

Control Strategy proposed for Validation Batches

- After a complete review of development phase, submission and pre-validation batches, the following are the final identified critical process parameters from the point of view of reproducibility and control strategy for the execution of validation batches. Control strategy for process parameters were decided for validation batch according to the proven acceptance criteria based on observations made during development, pre-submission, submission and process evaluation [pre-validation] batches.

S. No	Stage	Attribute/CPP	Product CQA	Control strategy for Validation Batch		Scale dependent	Remarks
				Range	Target		
1	Sifting	Screen size	NA	NA		No	
2	Blending of premix	Blender speed	Blend Uniformity & UOD	NA		Yes	
		Blending time (total number of revolutions)		NA		No	
		Blender occupancy		%		No	
3	Roll compaction	Roller gap	Blend Uniformity & UOD	Range in mm		Yes	
		Roller speed		Range in rpm		Yes	
		Hydraulic pressure		Range in bar		Yes	
4	Lubrication	Blender speed	Blend Uniformity & UOD	NA		Yes	
		Blending time (total number of revolutions)		NA		No	
		Blender occupancy		%		No	
5	Capsule filling	Machine speed	Blend Uniformity, UOD, Assay and Dissolution			Yes	

Summary of Parameters Other Than CPPs

Unit Operation	Process Parameters [Other Than CPPs]	Recommended for Validation		Scale Dependent	Remarks
		Range	Target		
Sifting	Sifter RPM			No	Dosing discs were finalized based on the BD of the blend and evaluated in the pre-validation batch. Tamping pin height will be adjusted based on the weight variation during execution.
Capsule filling	Tamping height	To be monitored		No	
	Dosing disc	To be monitored		No	

Annexure 2: Phase Gate Self-Assessment Checklist – OSD

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
1.	Is the exhibit batch size and PPQ batch size same?									
2.	Is the equipment train same or similar in size?									
3.	If batch size is different, is the equipment using same operating principle?									
4.	Are there any changes to STP of RM or p roduct, post regulatory submission?									
5.	Was exhibit batch packed in the commercial format?									
6.	Is the packing equipment and change part same or similar in size?									
7.	Does the product possess cleaning validation challenges, i.e., ❖ Less soluble than matrix? ❖ Lower PDE than matrix?									
8.	Does the exhibit batch show any OOS/OOT or stability failures to current specifications?									
9.	Critical Material Attributes (CMAs) - Active									
a.	Do the actives have CMAs like PSD, BD, and RS limits?									
b.	Are assay limits identified for actives?									
c.	Does the active have polymorphism characteristics?									
d.	Is there evidence of QbD batch taken between Low & High end of specification limit materials to establish affecting key CQA?									
e.	Have special storage conditions (protection from moisture, temperature and light; short expiry) been defined?									
f.	Is the active added in assay compensation mode?									
10.	Critical Material Attributes (CMAs) – Non-Actives									
a.	Is particle size range (PSD) established for key non-actives like MCC?									
b.	Is surfactant procured from branded (original) OR from generic vendor like SLS?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
c.	**Is the viscosity level defined for functional coatings?**									
d.	Is the disintegrant imported OR obtained from a local vendor?									
e.	Has disintegrant level study been done and optimum concentration established?									
f.	Is the level of lubricant (like Mg-St) optimized in PDR/scale-up report?									
11.	Unit Operations - Sifting									
a.	Is it security sifting OR functional sifting?									
b.	Does it involve geometric mixing OR co-sifting in low dose formulation?									
c.	Is rinsing indicated for low dose actives in sifting step?									
d.	Is weighing scale commensurate with weighing quantity in terms of accuracy in low dose quantity weighments?									
e.	Are special environmental conditions (like low temperature/% RH, nitrogen purging) specified for dispensing/sifting?									
f.	Is CPP for sifting like sieve size defined?									
g.	**Are CQAs for sifting (like % yield, particle size) defined?**									
12.	Unit Operations - Milling									
a.	Are the following CPPs for Milling defined? ❖ Mill type ❖ Mill RPM ❖ Screen size ❖ Screen type									
b.	Are the following CQAs defined? ❖ % yield ❖ PSD ❖ BD/TD									
c.	QTPP / Specification Relation to CPP's Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within the equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									
13.	Unit Operations – Wet Granulation									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
a.	**Are the following CPPs for RMG defined?** ❖ **Impeller speed** ❖ **Chopper speed** ❖ **Dry mixing time** ❖ **Wet mixing (granulation) time** ❖ **End point detection (Visual/Amperage/Torque)** ❖ **Binder addition time** ❖ **Binder solution temperature**									
b.	Are the following CQAs defined? ❖ % LOD of wet Mmass ❖ Granule size distribution ❖ BD/TD									
c.	Sampling Plan Adequacy:									
i.	Are sampling locations defined as per granulator geometry?									
ii.	Is Assay/BU testing done?									
d.	QTPP/Specification Relation to CPPs Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
iv.	**What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?**									
v.	Has any CQA's / CPP's in-process listed for same?									
e.	Has hold time for binder solution been established?									
14.	Unit Operations – Dry Granulation									
a.	Are following CPPs for roller compaction defined? ❖ Roller speed ❖ Feeder speed ❖ Roller gap ❖ Compaction force ❖ Roller type ❖ Screen size ❖ Granulator speed ❖ Cooling temperature ❖ Number of cycles (re-compaction)									
b.	Are the following CQAs defined? ❖ BD, TD, ❖ PSD									
c.	Is blend loading mechanism (manual/auto) defined?									
d.	Has segregation potential been verified (applicable for auto loading)?									
e.	Has throughput study been carried out at different roller speeds?									
f.	**QTPP / Specification Relation to CPPs Qualified and Range**									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPP's recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									
15.	Unit Operations - Drying									
a.	Are the following CPPs for drying defined? ❖ Inlet air temperature ❖ Product temperature ❖ Outlet air temperature ❖ CFM ❖ Dew point/Absolute Hhumidity ❖ Drying time									
b.	Are the following CQAs defined? ❖ % LOD									
c.	Sampling Plan Adequacy:									
i.	Are sampling locations defined as per dryer geometry?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
ii.	**Is % LOD Testing done?**									
d.	QTPP / Specification Relation to CPP's Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									
16.	Unit Operations – Blending									
a.	Are the following CPPs for blending defined? ❖ Blender RPM ❖ Blending time ❖ Blender occupancy									
b.	Are the following CQAs defined? ❖ Blend uniformity ❖ Blend assay									
c.	Sampling Plan Adequacy:									
i.	Are sampling locations defined as per blender geometry?									
ii.	**Is Blend uniformity testing (BU) done?**									
iii.	Is 1x – 3x OR 3x – 5x established?									
iv.	Is powder vs compact study done?									
v.	Is BU mean reported as assay?									
vi.	Are specifications of BU and BA overlapping? If yes, are they justified?									
vii.	Are recommendations for sampling rod and die size provided?									
viii.	Are there any gaps w.r.t. quality policy on assessment of blend uniformity for new product?									
d.	QTPP /Specification Relation to CPPs Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPP's recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
e.	**Are BU samples taken from unloaded container (IPC)?**									
f.	Have BD, TD, PSD limits been established based on data?									
g.	Is PSD enumeration at blending stage based on triple sample, each sample of minimum 100gm?									
h.	Has scale-up correlation between blender used for exhibit batches and proposed PPQ batches been done?									
17.	Unit Operations - Compression									
a.	Are the following CPPs for compression defined? ❖ Machine RPM ❖ Main compression force ❖ Feeder RPM									
b.	Are the following CQAs defined? ❖ Description ❖ Individual weight variation ❖ Average weight ❖ Hardness ❖ Thickness ❖ Friability ❖ Disintegration time ❖ Dissolution & dissolution profile ❖ Content uniformity ❖ Assay ❖ Physical attributes like capping, lamination, etc.									
c.	**Sampling Plan Adequacy:**									
i.	Are samples taken from not less than one revolution of machine output at each stage?									
ii.	For each test parameter, are samples collected at lower and higher machine speeds separately?									
iii.	Has hardness challenge study done?									
iv.	Has CU samples been taken from different Containers?									
v.	Is tablet weight compensation based on blend assay? Are BMR fill weight range and API assay range overlapping? If yes, is it justified?									
vi.	Are FP assay and stability assay limits the same? If no, is it justified?									
vii.	Are the FP dissolution and stability dissolution limits the same? If no, is it justified?									
viii.	Have the FP assay and dissolution lower limits been rationally arrived at? If no, is it justified?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
ix.	**Are the FP assay and CU individual results in the specifications overlapping? If yes, is it justified?**									
x.	Are FP and stability specifications overlapping? If yes, are they justified?									
xi.	Are samples collected by stratified sampling method for content uniformity testing?									
xii.	Are there any gaps w.r.t. quality policy on assessment of content uniformity for a new product?									
d.	QTPP/Specification Relation to CPPs Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of Active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	**Has any CQA's / CPP's in-process listed for same?**									
e.	Is tooling the same for exhibit and PPQ batches?									
f.	D well time study done?									
g.	Has blend loading mechanism (manual/auto) been defined?									
h.	Has force vs hardness and force vs thickness profiling been done and range defined for main compression force?									
i.	Is the guidance value for pre-compression force defined for products having known issues like capping, lamination, etc.?									
j.	Is stress study data of high hardness tablets available?									
k.	Is design correlation between assay limit and CU limit adequate?									
l.	Has hopper design comparison for exhibit batches and proposed PPQ batches been done?									
m.	Has feeder design comparison for exhibit batches and proposed PPQ batches been done?									
n.	Has scale-up correlation between compression machine used for exhibit batches and proposed PPQ batches been done?									

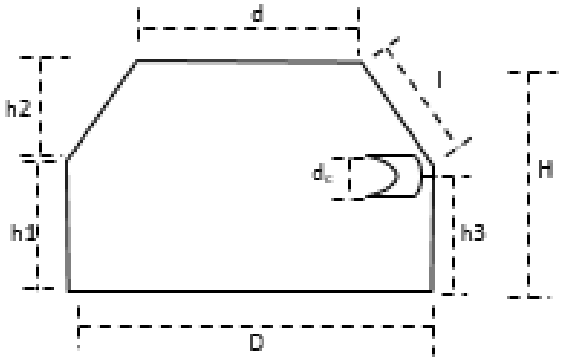
Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
18.	**Unit Operations – Film Coating**									
a.	Are the following CPPs for coating defined? ❖ Pan RPM ❖ Pan load ❖ Inlet temperature ❖ Product temperature ❖ Outlet temperature ❖ Gun to bed distance ❖ Spray rate ❖ Atomization pressure ❖ Inlet air flow ❖ Dew point/Absolute humidity ❖ Pan DP ❖ Viscosity of coating solution ❖ % Solid content									
b.	Are the following CQAs defined? ❖ Description ❖ Weight gain ❖ Average weight ❖ Thickness ❖ Disintegration time ❖ Dissolution & dissolution profile ❖ Content uniformity ❖ Residual solvent ❖ % LOD ❖ Assay ❖ Physical attributes like capping, lamination, mottling tendency, etc.									
c.	**Sampling Plan Adequacy**									
i.	Are % weight gain samples taken from different locations?									
ii.	Are CU samples taken from different locations?									
iii.	Are samples collected by stratified sampling method for content uniformity testing?									
d.	QTPP/Specification Relation to CPP-s Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									
e.	Is coating data available for both low and high hardness tablets?									
f.	Are dissolution results showing central tendency for ER tablets?									

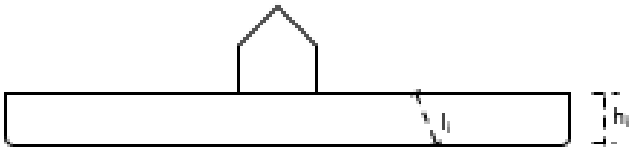
Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
g.	**Is the design correlation between assay limit and CU limit adequate?**									
h.	Has scale-up correlation between compression machine used for exhibit batches and proposed PPQ batches been done?									
19.	Unit Operations –Wurster Coating									
a.	Are the following CPPs for coating defined? ❖ Inlet air temperature ❖ Product temperature ❖ Outlet air temperature ❖ Spray rate ❖ Nozzle diameter ❖ Atomization pressure ❖ Inlet air flow ❖ Dew point/Absolute humidity ❖ Inlet % RH ❖ Mode of shaking ❖ Partition column height ❖ % Occupancy ❖ Base plate type ❖ Filter bag type ❖ Filter bag mesh size ❖ Sifting screen									
b.	Are the following CQAs defined? ❖ % LOD ❖ % Weight gain ❖ Assay ❖ Related substances ❖ Residual solvent									
c.	**Sampling Plan Adequacy**									
i.	Are sampling locations defined as per bowl capacity/geometry?									
ii.	Is % LOD testing done?									
iii.	Is Assay testing done?									
iv.	Is potency adjustment done during Wurster coating process? If yes, verify sampling result values are mean of three or more than three sample values.									
v.	Are specifications of API assay and drug loaded pellet assay and blend assay overlapping? If yes, are they justified?									
d.	QTPP/Specification Relation to CPPs Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									

Sr. No.	Particulars	Observations	Any gaps observed (Yes/No)	Risk management Low (1), Medium (2), High (3); RPN ≤ 8: Low, 9 – 18: Medium; > 18: High						Remarks, if any
				S	P	D	RPN	Overall Risk	Control strategy	
v.	**Has any CQA's / CPP's in-process listed for same?**									
20.	Unit Operations – Capsule Filling									
a.	Are the following CPPs for Capsule filling defined? ❖ Machine RPM ❖ Vacuum pressure ❖ Tooling format/set-up									
b.	Are the following CQAs defined? ❖ Description ❖ Individual weight variation ❖ Average weight ❖ Lock length ❖ Disintegration time ❖ Dissolution & dissolution profile ❖ Content uniformity ❖ Assay ❖ Physical attributes									
c.	Sampling Plan Adequacy									
i.	Are samples taken from not less than one revolution of machine output at each stage?									
ii.	For each test parameter, are samples collected at lower and higher machine speeds separately?									
iii.	**Is fill weight compensated based on blend assay? Are BMR fill weight range and API assay range overlapping? If yes, is it justified?**									
iv.	Are CU samples taken from different containers?									
v.	Are samples collected by stratified sampling method for content uniformity testing?									
vi.	Are there any gaps w.r.t. quality policy on assessment of content uniformity for new product?									
d.	QTPP / Specification Relation to CPP's Qualified and Range									
i.	Is every CQA linked to one or more CPPs?									
ii.	Are the CPPs indicated range supported with data?									
iii.	Are the CPPs recommended within equipment qualified range?									
iv.	What is the degradation pathway/profile of active, and the actions w.r.t. EM controls/CPPs recommended in BMR?									
v.	Has any CQA's / CPP's in-process listed for same?									

Annexure 3A

RMG Equipment Details





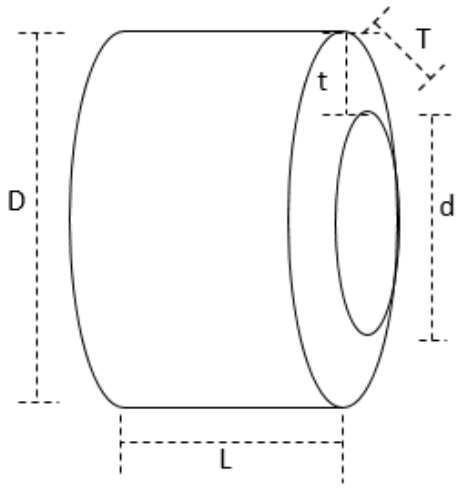
Type 1 - One side tapered
Type 2 – both side tapered

Title: TECHNICAL DETAILS OF RMG										
Sr.No.	Parameter									
1	Manufacturing site									
2	Area									
3	Equipment ID									
4	Make and model									
Capacity and General Dimensions										
5	Volumetric capacity of bottom dish to shell									
6	Volumetric capacity of cone									
7	Designed working volume range									
8	Qualified working volume range									
9	Bottom dia (D)									
10	Top dia (d)									
11	Cylindrical height (h1)									
12	Conical height (h2)									
13	Conical length (l)									
14	Total height (H)									
15	H/D ratio									
Nozzles										
16	Charging hole dia									
17	Vent dia									
18	Discharge dia									
19	Sprinkler/peristaltic pump nozzle dia									
20	Jacket inlet dia									
21	Jacket outlet dia									
22	Thermowell dia									
23	Sight glass dia									
Design Conditions										
24	Design pressure of bowl (kg/m^2)									
25	Design pressure of jacket (kg/m^2)									
26	Design temperature of bowl (°C)									
27	Design temperature of jacket (°C)									
28	Heating media availability									
29	Cooling media availability									
30	Product temperature sensor range (°C)									

Title: TECHNICAL DETAILS OF RMG										
Sr.No.	Parameter									
31	**Impeller type (I/II)**									
32	Direction of rotation									
33	Designed impeller RPM range									
34	Qualified impeller RPM range									
35	Impeller height (h_i)									
36	Impeller slant length (l_i)									
37	Impeller slant angle (°)									
38	Motor make and model									
39	Motor power (hp)									
40	Motor RPM									
41	Gear ratio									
42	Torque monitoring									
Chopper										
43	Chopper diameter (dc)									
44	Shape and number of blades									
45	Designed chopper RPM range									
46	Qualified chopper RPM range									
47	Direction of rotation									
48	Chopper height from bottom (h_3)									
49	Motor make and model									
50	Motor power (hp)									
51	Motor RPM									
Sprinkler/Binder Spray										
52	Availability									
53	Distributor pipe diameter (m)									
Peristaltic Pump										
54	Make and Model									
55	Designed RPM range									
56	Qualified RPM range									
57	Flowrate range (LPM)									
58	Solution tank capacity									
Attached Cone Mill										
59	Availability (Yes/No)									

Annexure 3B

Auto coater equipment details



Title: TECHNICAL DETAILS OF COATER							
Sr. No.	**Parameter**						
1	Manufacturing site						
2	Area						
3	Equipment ID						
4	Make and model						
5	PLC based control						
6	SCADA based control						
Pan Details							
7	Interchangeable pans (Yes/No)						
8	Available pan size (inch)						
9	Brim volume (lit)						
10	Pan dia						
11	Pan opening diameter (d)						
12	Pan cylindrical length (L)						
13	Pan taper length (T)						
14	Pan taper depth (t)						
15	Pan total depth						
16	Pan dia to total depth ratio						
17	Cone angle of pan						
18	Type of baffle						
19	Baffle interchangeable (Yes/No)						
Gun Details							
20	Gun make and model						
21	Number of guns						
22	Types of guns						
23	Nozzle sizes available						
Design and Qualification Parameters							
24	Design pan capacity range (kg)						
25	Qualified pan capacity range (kg)						
26	Design pan RPM						
27	Qualified pan RPM						
28	Design air flow range						
29	Qualified air flow range						
30	Design inlet air temp range (°C)						
31	Qualified inlet air temp range (°C)						

Annexure IB

Title: TECHNICAL DETAILS OF COATER							
Sr. No.	**Parameter**						
32	**Design %RH or abs. humidity range**						
33	Qualified %RH or abs. humidity range						
34	Availability of humidifier						
35	Spray gun pressure qualified range – atomization						
36	Spray gun pressure qualified range - pattern						
37	Spray gun - spray rate qualification range						
Peristaltic Pump							
38	Qualified spray rate range (gm/min)						
39	Spray metering by (mass flow meter/weighing balance)						
40	Peristaltic pump RPM range						
41	Solution tank capacity (lit)						
42	Mass flow meter range (lit/min)						
Sensor Qualification							
43	Inlet temperature sensor range						
44	Exhaust temperature sensor range						
45	Product temperature sensor range						
46	Pan DP range						
47	RH/abs humidity sensor range						
48	Dew point temperature sensor range						
49	CFM sensor range						

Annexure 4

Case Study of Roller Compaction Process from Development to Scale-up

- **Target Product Profile:** The pharmaceutical target profile for any drug product should be a safe efficacious convenient dosage form that should facilitate patient compliance. Here the tablets dosage form is discussed with roller compaction process. The tablet should be of an appropriate size, with a single tablet per dose. The manufacturing process for the tablet should be robust and reproducible, and should result in a product that meets the appropriate drug product critical quality attributes.

- A target product profile mentioned in Table 1 details the Critical Quality Attributes which are used to define the satisfactory quality parameters identified.

Table 1: Target Product Profile

Quality Attribute	Target	Criticality
Dosage form	Tablet, maximum weight 200mg	Not applicable
Potency	30 mg	Not applicable
Pharmacokinetics	Immediate release enabling Tmax in 2 hours or less	Related to dissolution
Appearance	Tablet conforming to description shape and size	Critical
Identity	Positive for drug substance	Critical
Assay	95 – 105%	Critical
Impurities	Impurity A: NMT 0.5%, Other impurities: NMT 0.2%, Total: NMT 1%	Critical
Water	NMT 1%	Not critical – API not sensitive to hydrolysis
Blend Uniformity	10 location SD should NMT 3	Critical
Content Uniformity	Meets ASTM 2810 criteria	Critical
Resistance to Crushing (Hardness)	50-120N	Not critical since related to dissolution
Friability	NMT 1.0%	Not critical
Dissolution	Consistent with immediate release, e.g., NLT 80% (Q) at 30mins	Critical
Disintegration	NMT 15mins	Not critical, a precursor to dissolution
Microbiology	If testing required, meets USP criteria	Critical only if drug product supports microbial growth

This pertains to the development of drug product (DP) with roller compaction process. The Composition Risk concluded from the development of the drug product is mentioned in Table 2.

Table 2: DP Formula Composition Risk identified after Development at Lab Scale

Formulation Composition Attributes							
API Particle Size	API Level	Lactose Level	Disintegrant Level	MCC Particle Size	Glidant Level	Magnesium Stearate Level	
Low	Low	Low	Low	Low	Low	High	
Low	Low	Low	Low	Low	Low	Low	
Low	Low	Low	Low	Low	Low	Low	
Low	Low	Low	Low	Low	Low	Low	
High	High	Low	Low	High	Low	Low	
High	High	Low	Low	High	Low	Low	
High	High	Low	High	Low	Low	High	

Based on development study, the concluded component levels and attributes are listed in Table 3

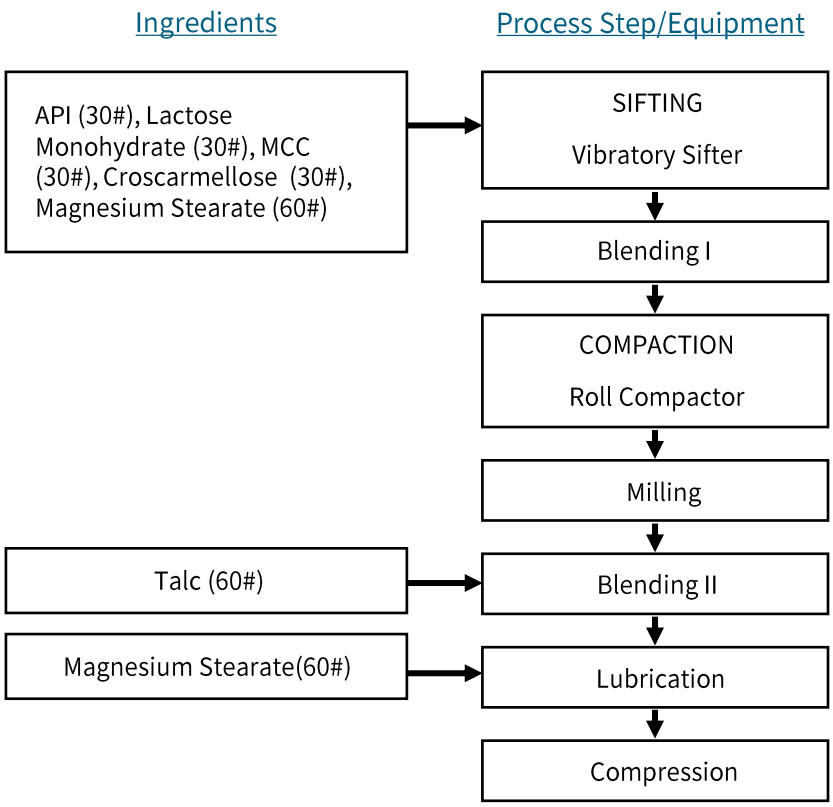
Table 3: Summary of Outcome of Formulation Components Study

Drug substance particle size	**D90 35-45 micron**
API concentration	14.28% w/w
Croscarmellose level (Disintegrant)	3-4 % w/w
Magnesium stearate lLevel	1-2 % w/w (Intragranular) 0.25 % w/w (Extragranular)
Microcrystalline cellulose level	40 % w/w
Lactose monohydrate level	39.00- 40.75%
Talc level (Glidant)	5%

Summary of the Selected Process after Development

- In this case study, based on the physico-chemical properties of the API roller compaction is selected as the most appropriate manufacturing process. The API is sensitive to heat which would preclude wet granulation, due to chemical instability during the drying process. In addition, the API physical properties (flow) precluded direct compression at the concentrations required. Tablet coating was also precluded due to chemical instability during drying.
- A flow diagram of the manufacturing process for the drug product is provided in Figure 1.
- Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium
- stearate are separately weighed and screened and then blended with sifted API. The blend is
- then roller-compacted to produce a ribbon which is milled to give active granules. Extragranular ingredients (magnesium stearate and talc) are separately weighed and screened and then blended with the granules. The blend is then compressed into tablets.

Figure 1: Process Flow Diagram:



Based on scientific understanding and prior knowledge, a risk assessment of the potential impact of the unit operations on the drug product CQAs was identified after development.

Table 4 shows the result of the risk assessment and identifies the unit operations which require further investigation to determine the appropriate control strategy.

Table 4: Risk Assessment to Identify Variables Potentially Impacting Product Quality

DP CQA	Blending I	Roller Compaction	Milling	Blending II	Lubrication	Compression
Appearance	Low	Low	Low	Low	Low	High
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	High
Impurity	Low	Low	Low	Low	Low	Low
Blend Uniformity	High	High	High	High	High	High
Content Uniformity	High	High	High	High	High	High
Dissolution	Low	High	High	Low	High	High

Annexure 5

Example of Scaleup Factor Application and Calculation

Operation	Development Batch		Scale-up Factor/Equivalency	Commercial Scale Batch	
Batch Size	10500 Tablets			160000 Tablets	
Granulation	RMG:	63 L	Tip Speed H/D Ratio	RMG :	900 L
	Occupancy:	49.22%		Occupancy:	52.50%
	Bed High/RMG diameter ratio	0.24		Bed High/RMG diameter ratio	0.23
	RPM:	103		RPM:	41
	Tip speed:	2.97 m/s		Tip speed:	2.97 m/s
Wet Milling	Quadro mill:	U5	Tip Speed	Quadro mill:	Ganson 194
	Impeller RPM:	1750		Impeller RPM:	700
	Tip speed:	6.96 m/s		Tip speed:	6.96 m/s
Drying	FBD:	10.6 L	Base Plate Area Ratio	FBD:	600 L
	CFM:	160		CFM:	2437
	Range	(90-210)		Range	(1370-3200)
Sizing	Quadro mill:	U5	Tip Speed	Quadro mill:	Ganson 194
	Impeller RPM:	1750		Impeller RPM:	700
	Tip speed:	6.96 m/s		Tip speed:	6.96 m/s
Blending & Lubrication	Blender	50 L	Froude Number	Blender	600 L
	Occupancy:	50.17 %		Occupancy:	63.70 %
	RPM:	9		RPM:	7
	Blending time:	14 min		Blending time:	18 min
	Lubrication time:	4 min		Lubrication time:	3 min
Compression	Fette compression (102i) (Turret RPM)	14-40 RPM	Dwell Time Calculation	Fette compression (P3030) (Turret RPM)	6-17 RPM (Qualification range 10-19)
Coating	Coater	18 Inch	Scale-up factor for CFM and Spray rate =12.53 for Pan RPM =0.56	Coater	57 Inch
	0 to 60 min			0 to 60 min	
	Pan RPM:	2-8		Pan RPM:	1-5
	Spray rate:	1-8 gm/min		Spray rate:	13-100 gm/min
	60 min to end			60 min to end	
	Pan RPM:	6-10		Pan RPM:	3-6
	Spray rate:	5-11 gm/min		Spray rate:	63-138 gm/min
	CFM:	100-200		CFM:	1253-2507

Annexure 6

Process Performance Qualification Protocol

Product	
Product Code	
Label Claim	
Change Control No.	
Market	
Batch Size	XX Kg. (XXX Tablets)
Batch No.	
Protocol Issuance:	
Batch No.	
Issuance No.	
Protocol Issued By (Sign & Date)	

PROTOCOL APPROVAL PAGE:

Signing this protocol approval section expresses agreement with the tests, methods, relevant SOPs and documentation defined in this document.

---	NAME	DESIGNATION	SIGN/ DATE
PREPARED BY			
Name of Department			
REVIEWED BY			
Quality Assurance			
Production			
Technology Transfer			
Quality Control			
Regulatory Affairs			
APPROVED BY			
Head - Production			
Head - Quality Assurance			

TRAINING RECORD

Purpose	To train all personnel involved in the execution of the process performance qualification protocol to have an understanding of the process and requirements.
Topics	1. Design and plan 2. Acceptancecriteria 3. Sample collection and labeling 4. Documentation
Training By (Name)	

Name of Participant	Area of Operation	Signature/Date of Participants	Trainer's Signature/ Remark as 'Self reading'

PROTOCOL SIGNATURE LOG:

The names and signatures of individuals who are performing process validation are to be recorded.

NAME	DESIGNATION	SIGNATURE/DATE

OBJECTIVE:

The objective of the Process Validation Protocol is to detail the in-process tests to be performed during the execution of the process validation batch which shall:

- Validate the process for the batch size XXX Kg. within 0X of stability batch.
- Demonstrate that the manufacturing process and process control parameters of the product produce uniform drug product and are reproducible.
- Characterize the process at the completion of significant stages of manufacturing to demonstrate that the physical and analytical parameters are uniform.

The successful completion of process validation study shall provide a high degree of assurance that the process is capable of consistently producing product to meet the established specifications for safety, identity, strength, purity, and quality characteristics.

DESIGN AND SCOPE:

- The process flow diagram, material, equipment, sampling plan and in-process tests to be performed for successful validation batches are defined in this protocol.
- Process validation for batch size of XX **Kg. (XX Tablets)** shall be performed in accordance with MBMR No.: XX prior to the further processing of the batches.
- Hold time study for granulating fluid, wet granules, dry granules and dry milled granules shall be performed
- The sampling for process validation batch shall be performed at the target parameters in accordance with batch manufacturing record specifications.
- Granulation shall be performed utilizing rapid mixer granulator (RMG) XXXL.
- Drying shall be performed utilizing fluid bed dryer (FBD) XXX Kg. Samples shall be collected from top, middle and bottom layers of FBD bowl and checked for loss on drying at drying stage to demonstrate uniform drying of granules.
- Dry milling shall be performed utilizing - XXX Mill.
- Blending shall be performed by utilizing XXX blender with XXX L bunker. Sample shall be collected from different layers of the blender at the blending stage to demonstrate uniformity of blend.

- The composition of the active ingredients per dosage form unit of drug product is XX mg. Samples shall be collected at the blending stage to demonstrate uniformity of blend. Blend samples shall be collected in **triplicate** as per **X – 3X criteria** for blend uniformity analysis.

- The physical characterization test such as particle size distribution and bulk and tapped density for the final blend shall be performed to demonstrate the uniform distribution of granules throughout blending process.

- Compression shall be performed in XXX Station YY rotary compression machine, tooling 'D/B/BB' Type. The validation sample shall be collected at initial, middle and end run of compression to demonstrate that the granulation attributes of the final blend are capable of filling tableting dies and compressing uniform tablets throughout the compression process.

- Samples shall be collected at compression stage and shall be evaluated for physical parameters, dissolution and uniformity of dosage unit which is clubbed with hopper depletion study and shall demonstrate the die fill uniformity.

- The level of blend in the hopper of compression machine is constantly maintained throughout the compression by acceleration due to gravity since the blends are charged from overhead compression cubicle for XX Station XX rotary compression machine. Towards the end of compression, the level of blend in the hoppers is emptied out. Therefore, the end sample at compression stage will represent the impact upon the uniformity in die fill as depleted hopper sample thus demonstrating that there is no potential segregation of blend.

- To prove the uniformity of the blend throughout the batch, stratified samples are to be collected during compression of the batch and to be analyzed for uniformity of dosage unit which proves the uniform distribution of API within specified quantity.

- Samples amounting to 3 tablets shall be collected from the 40 locations- during entire compression run. Initially 3 tablets from 20 odd location shall be analyzed for uniformity of dosage unit for stage 1. Remaining 3 tablets from even 20 locations will be analyzed later if stage 1 criteria are not met.

- Considering the batch size and compression machine speed, stratified samples (3 tablets) shall be collected during compression process. These random sampling points shall cover significant steps of the process, i.e., beginning of the run, filled hopper (full hopper), half-filled hopper, empty hopper, change of blend containers, stoppage of compression machine, restart of compression machine after a stoppage, operator/shift change, machine adjustments, different compression time intervals and at the end of the run.

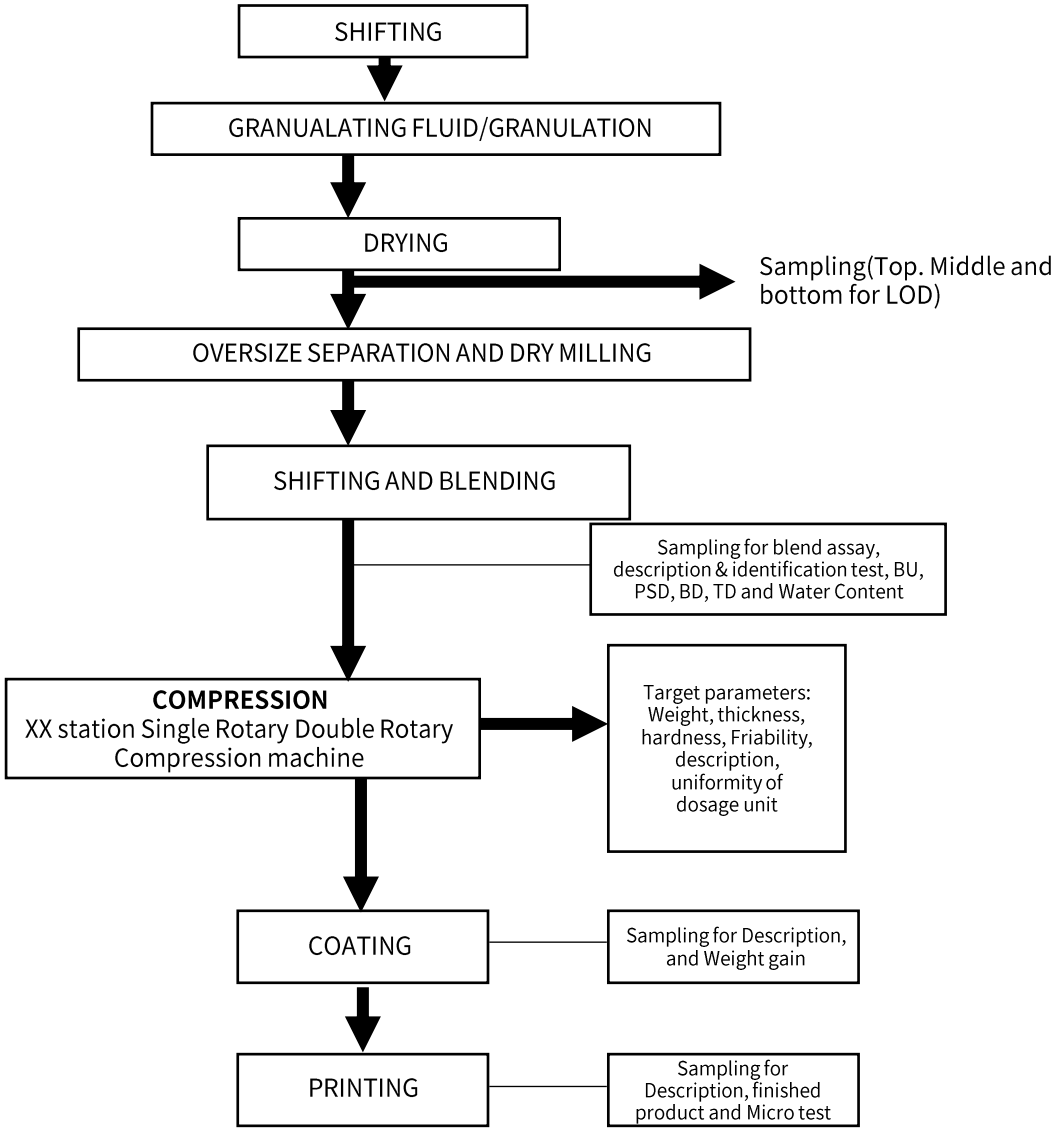
- The coating shall be performed in XXX in one or two lots.

- Samples shall be withdrawn from the coating pan after completion of coating and shall be checked for description, % weight gain, etc.
- Finished product sample, i.e., tablet, printing shall be collected as per BMR and shall be analyzed as per finished product specification.
- The summary of results and evaluation shall be illustrated in the summary report.

Note: QC sample to be collected in xxx container along with silica canister.

PROCESS VALIDATION FLOW DIAGRAM:

Process validation batch shall be manufactured in accordance with flow diagram shown below.



EVALUATION OF FORMULATION INGREDIENTS:

Comparative quantitative formulation of stability batch, process characterization batch, and process validation batch is given below.

Manufacturing Formula			
Raw Materials	Stability Batch Size: xxx Tablets	Process Characterization Batch Size: xxx Tablets	Process Validation Batch Size: xxx Tablets
	mg/tab	mg/tab	mg/tab
DRY-MIXING			
GRANULATING FLUID			
	-------	-------	-------
Purified Water USP	-------	-------	-------
Solvent	-------	-------	-------
ADDITIONAL GRANULATING FLUID (if required)			
Purified Water USP	---	---	---
LUBRICATION			
Compressed tablets weight			
COATING			
Net Weight			
TABLET PRINTING			

Evaluation of Primary Packing Materials

Identical qualitative primary packing materials, which have been utilized in the stability batch, shall be utilized in the commercial batches.

Packing Material	Vendor	
	Stability Batch	Commercial Batch
30/90/100/500 Tablets CRC Pack		
Blister/Strip Pack		

EVALUATION OF MANUFACTURING EQUIPMENT :

The equipment to be utilized in the process validation batch is mentioned below. Comparison between the manufacturing equipment utilized during stability batch, process characterization batch, and process validation batch has been provided in the table below.

Stability Batch (Size: XX Tablets)	Process Characterization Batch (Size: XX Tablets)	Process Validation Batch (Size: XX Tablets)
Equipment		
Vibro Sifter	Vibro Sifter	Vibro Sifter
Rapid mixer granulator (RMG) [Capacity: XXliter]	Rapid mixer granulator (RMG) [Capacity : XX liter]	Rapid mixer granulator (RMG) [Capacity : 600 liter]
Fluid Bed Dryer (FBD) XX kg	Fluid Bed Dryer (FBD) XX kg	Fluid Bed Dryer (FBD) XX kg
XX Mill	XX Mill	XX Mill
Blender, Bunker (Capacity: XX liter)	Blender, Bunker (Capacity: XX liter)	Blender, Bunker (Capacity: XX liter)
XX Station single rotary compression machine	XX Station single rotary compression machine	XX Station single rotary compression machine
Combo metal detector with vertical deduster	Combo metal detector with vertical deduster	Combo metal detector with vertical deduster
Stirrer	Stirrer	Stirrer
Colloid mill	Colloid mill	Colloid mill
Coating pan	Coating pan	Coating pan
Tablet printing machine	Tablet printing machine	Tablet printing machine
Tablet inspection belt	Automatic vision tablet inspection machine	Automatic vision tablet inspection machine

RESPONSIBILITY:

1. Quality Assurance (QA)

1.1 To review the protocol.

1.2 To provide training to concerned personnel.

1.3 To withdraw the samples as per the sampling plan.

1.4 To assemble the processing and analytical data in final form.

1.5 To prepare the summary report and approve the conclusions to provide assurance that protocol acceptance criteria have been met.

1.6 To verify qualification status of equipment in which validation batches are to be manufactured.

2. PRODUCTION

2.1 To ensure implementation of protocol.

2.2 To involve trained personnel in manufacturing activities.

2.3 To ensure that qualified equipment is used.

2.4 To review the protocol and report.

3. QUALITY CONTROL (QC)

3.1 To analyze the validation samples.

3.2 To assemble analytical results in final form.

3.3 To review the protocol and report.

4. TECHNOLOGY TRANSFER GROUP

4.1 To prepare and review the protocol.

4.2 To involve trained personnel in manufacturing activities.

4.3 To assist Quality Assurance department in withdrawal of samples.

4.4 To review in-process data, analytical result and validation report.

5. REGULATORY

5.1 To review the protocol and report.

6. QUALITY ASSURANCE HEAD/PRODUCTION HEAD

6.1 To approve the protocol and report.

DOCUMENTATION:

Process validation activities shall be performed as defined in the approved protocol and Batch Manufacturing Record (BMR).

- All documentation shall be completed concurrently during the execution of the process. However, the protocol does not define the specific order in which the test/documentation is to be completed.
- Recording of information shall be made in permanent black ink.
- Complete information shall be filled in the format provided.
- Mistakes shall be corrected by drawing a single line through the incorrect data, recording the correct information, and then initialing and dating the change.

After completion of the protocol execution, a summary report shall be prepared by Quality Assurance Department stating the following information:

- Processing parameters monitored during the process.
- Discussion of analytical results.
- Any temporary change observed during execution of the protocol/BMR/BPR.
- Investigation before batch release of any incidence that occurred during process validation, and its impact on finished product quality parameter, together with evaluation and justification.
- Conclusions and recommendations, if any.

FACILITY:

The site of manufacturing, packaging, control operations, stability and analysis shall be at,

Company name & Address

QUALIFICATION OF EQUIPMENT:

Verification for the equipment qualification, in which the manufacturing of process validation batch is to be performed, shall be done to provide assurance that the system is installed and operates as per requirements.

Sr. No.	Name of Equipment	Equipment Code No.	Date of Qualification due on	Qualified Range	Checked by/date	
					Prod.	QA
1	Vibro Sifter		NA	NA		
			NA	NA		
2	Rapid mixer granulator (RMG) capacity : XX liter attached with co-mill			Operating Range: kg		
3	Fluid bed dryer (FBD) XX kg			Kg		
5	XX co-mill			Speed: X-Y RPM		
6	XX blender			XX RPM		
7	Bunker capacity: X liter		NA	kg		
8	XX station compression machine			Turret Speed: X-Y RPM Feeder Speed: X-Y RPM		
9	Tablet coating					
10	Tablet printing					

SIFTING, MILLING, GRANULATION AND WET MILLING (3 LOTS)

- The granulation shall be performed in the Rapid Mixer Granulator, XXL as per step mentioned in respective BMR.
- Granulation is performed by mixing of ingredients with binder solution.
- Observation shall be recorded in the table below.

Sr. No.	Parameters	Specification	Observation		
			Lot A	Lot B	Lot C
1	Temperature / RH	NMT X°C			
		NMT Y %			
2	Sift the following material through ASTM 40 #, and collect in duly labelled polyethylene lined container.	ASTM #, XX kg			
3	Granulation process steps to be mentioned.				

DRYING (NUMBER OF LOTS)

- The drying shall be performed in the Fluid Bed Dryer, xx Kg as per step mentioned in BMR.
- The batch load for drying and target temperature shall be uniform.
- The drying shall be performed till the per-determined LOD specification is achieved.
- Observation shall be recorded in the table below.
- The material shall be sampled as per the sampling plan mentioned below.

Sr. No.	Parameters	Specification	Observation		
			Lot A	Lot B	Lot C
1	Process steps to be written				
	Loss on drying (%w/w), at X°C for constant weight.	Target: w/w Limit: NMT % w/w			
Checked by/date:					
Reviewed by/date:					

SAMPLING PLAN:

Step No.	Activity	Performed by/date		
		Lot - A	Lot - B	Lot - C
1.	Perform the drying in accordance with instructions specified in the Batch Manufacturing Record.			
2.	After completion of drying, collect composite from top, middle and bottom.			
3.	Composite: Collect approximately X g composite samples of top, middle and bottom. Mix samples of all layers together in the sample container and perform LOD testing.			
4.	Determine the loss on drying for about X gm of the composite sample, by using the Halogen Moisture Analyzer, at a setting of X °C for constant weight.			
Reviewed by/date:				
Note: Sample to be collected in duly labelled container.				

RESULTS:

LOT				
Instrument ID No.:				
Calibration Valid up to:				
Log Book No.:				
Log Book Entry No.:				
Page No.:				
LOD Results of Dry Granule Sample				

Location	% LOD		
	Lot A	Lot B	Lot B
Composite			
Performed by/date			
Acceptance criteria: Target: X%, Limit: NMT X % w/w at X °C for constant weight.			
Reviewed by/date			

SIFTING & DRY MILLING (3 LOTS):

- The dry milling shall be performed using XX Mill as per step mentioned in BMR.
- Observation will be recorded in the following table.

Sr. No.	Parameters	Specification	Observation		
			Lot A	Lot B	Lot C
1	Sieve size	ASTM #			
2	Intactness of the sieve before and after sifting.	Intact			
3	Weight of oversize granules obtained	To be recorded			
4	Screen pore size	#			
5	Intactness of screen before milling	Intact			
6	Dry milling speed (RPM)	Range: 600 - 800			
7	Intactness of screen after milling	Intact			
8	Intactness of the sieve before & after sifting	Intact			
9	Actual yield of sifted and dry milled granules.	%			
Checked by/date:					
Reviewed by/date:					

SIFTING AND BLENDING:

- The blending shall be performed in XX blender with powder transfer system or, having Bunker capacity X L as per step mentioned in BMR.

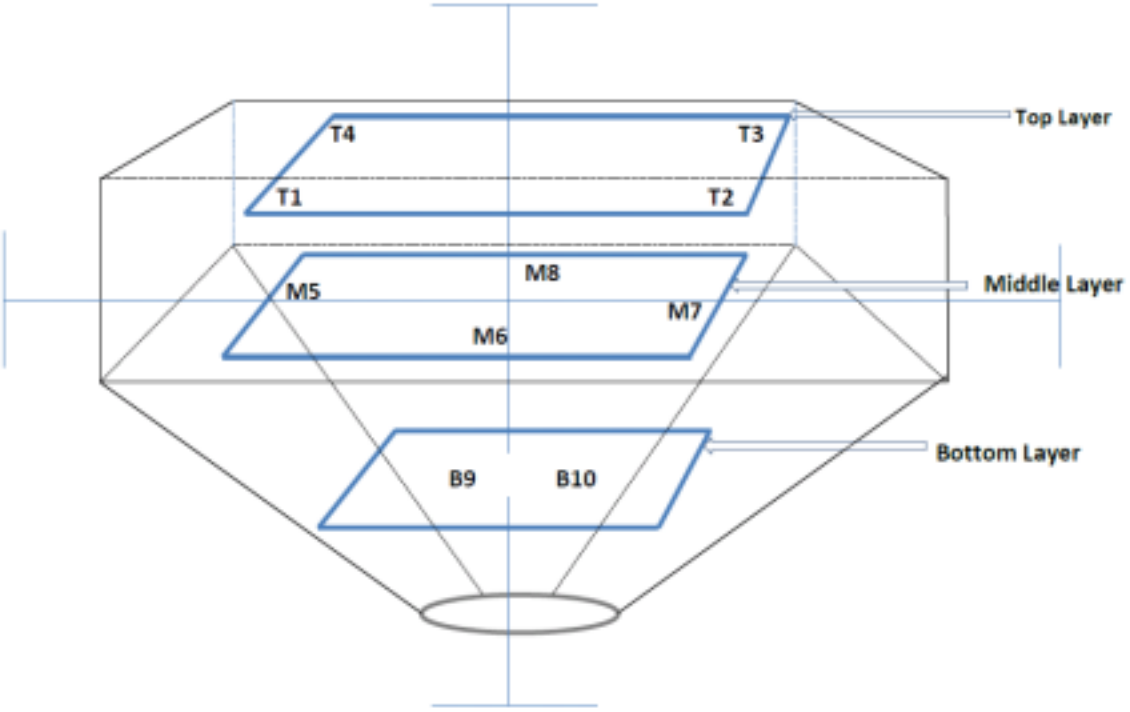
Sr. No.	Parameters	Specifications	Observation
1	Sift the following materials through ASTM 40 # (Intact) XX Kg. o f Y Y	ASTM 40 # Intact	
2	Write down all process steps		

SAMPLING PLAN BLENDING:

- The specified blending time shall provide uniform and consistent blending.
- Samples shall be collected to demonstrate uniformity of blend. Blend Samples shall be collected in triplicate as per X - 3X criteria between X mg – Y mg for blend uniformity analysis.

Step No.	Activity	Performed by/date	Reviewed by/date
1.	After completion of blending, collect 10 samples from the bunker as per the sampling locations defined in Figure 2 each weighing between X mg – Y mg in triplicates using the unit dose sampling rod. Send samples to Quality Control Department for Description, Blend Uniformity, etc.		
2.	Collect 10 gm of one composite sample (from top, middle and bottom) for other tests, for example, water content test.		
3.	Collect one composite blend sample from top, middle and bottom layers to make approximate 200 g as mentioned the sampling diagram of Figure 2 and send samples to Quality Control Department for particle size distribution, bulk density and tapped density. (Retained on ASTM #20, ASTM #40, ASTM #60, ASTM #80, ASTM #100 and Passed through ASTM #100)		

SAMPLING LOCATION: FIGURE 2



REPRESENTS SAMPLING POINTS:

For Blend Uniformity
T1, T2, T3, T4: Top Layer
M1, M2, M3: Middle Layer
B1, B2, B3: Bottom Layer
For composite sample: Composite of Top, Middle & Bottom Layers

COMPRESSION:

- The compression shall be performed using XX Station single rotary compression machine or XX Station double rotary compression machine.
- Record the machine set-up observation in the following table.
- Sample the material as per the sampling plan mentioned below.

Sr. No.	Parameters	Specifications	Observation
XX Station Single/Double Rotary Compression:			
1	Temperature(°C) & Relativehumidity(%)	NMT X °C NMT Y %	
2	Description		
3	Turret(RPM)		
4	Forcefeeder(RPM)		
5	Compactionforce(KN)	Not more than 38.0 KN	
6	Fill depth		
7	Individualweight(mg) For 47 tablets	Target: Control Range: X – Y	Min: Max:
8	Weight of 20 tablets (gm) (For 5 x 20 tablets)	Target: range:X – Y	M i n : M a x :
9	Hardness(Kp)	Target: Range:	Min: Max:
10	Thickness(mm)	Range:	M i n : M a x :
11	Friability (%) (For 10 tablets) (Tab. Wt. ≥ 6.5 gm)	Not more than 1.0 %w/w, Breakages Nil.	
Checked by/date:			
Reviewed by/date:			

SAMPLING PLAN: XX STATION SINGLE/DOUBLE ROTARY COMPRESSION:

Step No.	Activity	Performed by/date	Reviewed by/date
1.	Set the machine at target parameters of hardness X Kp, target weight Y mg and target machine speed Z RPM and perform physical evaluation of X tablets (XX Station of comp machine + 10 additional) at initial stage after obtaining the sample.		
2.	Collect approximate 100 tablets at initial compression run into the appropriately labelled container and send to QC for dissolution.		
3.	Production person shall perform physical evaluation of X tablets at middle run after obtaining the sample.		
4.	Collect approximate 100 tablets at middle compression run into the appropriately labelled container and send to QC for dissolution.		
5.	Production person shall perform physical evaluation of X tablets at end run after obtaining the sample.		
6.	Collect approximate 100 tablets at End compression run into the appropriately labelled container and send to QC for dissolution.		
7.	Perform weight variation, hardness, thickness, friability and description after obtaining the sample from each run and record in data sheet.		

Expected Results		
Physical Parameters	Control Limit	Analytical Parameters
Individual tablet weight (mg)	X mg – Y mg	dissolution for information
Individual tablet h a r d n e s s (Kp)	X - Y kp	
Individual tablet thickness (mm)	X mm - Y mm	
Friability (%) (For 20 tablets) (Wt. of tabs. ≥ 6.50 gm)	Not more than 1.0%; Breakages Nil.	
Description		

FRIABILITY TEST RESULTS (INITIAL, MIDDLE AND END):

Instrument ID No.:	Balance ID No.:
Calibration valid up to:	Calibration valid up to:
Log book no.:	Log book no.:
Log book entry no.:	Log book entry no.:
Log book page no.:	Log book page no.:
Limit: Not more than 1.0%, Breakages Nil.	

STAGE	Observation		Done by/date	Reviewed by/date
Initial				
Middle				
End				

STRATIFIED SAMPLES COLLECTION RECORD (COMPRESSION):

Stratified samples of 3 tablets each shall be collected for 40 sampling locations (approximately every # **minutes** interval) throughout the compression process. Sampling locations shall comprise of significant time points such as beginning of the run, filled hopper (full hopper), half-filled hopper, empty hopper, change of blend containers, stoppage of compression machine, restart of compression machine after a stoppage, machine adjustments, different compression, and end of the run.

Sr. No.	Sampling Location	Remark	Sample collection date/time	Number of tablets collected	Sampled by/date
1.	Beginning of Run (Initial)				
2.	Filled Hopper (Full Hopper)				
3.	Half Filled Hopper				
4.	Empty Hopper (At the sensor level)				
5.	*Change of Blend Container				
6.	Re-start of Machine				
7.	*Machine Adjustments – Change in RPM				
8.	Shift and operator change				
9.	Compression Run				
10.	Compression Run				
11.	Compression Run				
12.	Compression Run				
13.	Compression Run				
14.	Compression Run				
15.	Compression Run				
16.	Compression Run				
17.	Compression Run				
18.	Compression Run				
39.	Compression Run				
40.	End of Run				

The collected sample shall be submitted to quality control lab for uniformity of dosage unit testing. Quality Control Laboratory shall test 3 tablets out of the 7 seven tablets submitted.

COATING DISPERSION PREPARATION

- The enteric coating suspension shall be prepared using SS stirrer in SS Container as per the step mentioned in BMR.
- The observation of enteric coating suspension preparation parameters shall be recorded in table below.

Sr.No.	Parameters	Specifications	Observation
1.	Temperature/RH	NMT 27 °C/NMT 60 %	
2.	Temperature of purified water	NMT 30°C	
3.	Quantity of purified water and/or solvents	XX Kg	
	Coating composition		
.	Stirrer RPM	To be recorded	
	Stirring time	To be recorded	
	Hold time of coating dispersion	To be recorded	
	Quantity of coating suspension used	To be recorded	
Checked by/date:			
Reviewed by/date:			

COATING:

- The coating shall be performed in auto-coater.
- Load the core tablets in coating pan. Initially warm the tablets at inlet temperature of X °C to achieve bed temperature of Y °C to Z °C with intermittent rolling at 1 to 2 RPM.
- The observation of coating set-up parameters from BMR shall be recorded in the following table.

COATING PARAMETERS:

Sr. No.	Parameters	Specifications	Observation	
			Lot A	Lot B
1	Temperature (°C) & Relative humidity (%)	NMT X°C NMT Y %		
2	Coating pan (inch)			
3	Baffle type			
4	No. of spray guns	X		
5	Spray nozzle diameter (mm)			
6	Gun - tablet bed distance (cm)	16 – 24		
7	Gun - gun distance (cm)	Target: 16, Limit: 15 – 17		
8	Inlet air temperature (°C)	X – Y		
9	Outlet air temperature (°C)	To be recorded		
10	Bed temperature (°C)	*Target : , Limit: X – Y		
11	Coating dispersion spray rate (gm/gun/min)	X – Y		
12	Pan RPM	RPM		
13	Compressed air pressure for atomization (kg/cm2)	Limit :		
14	Compressed air pressure for fan width (kg/cm2)	Limit :		
15	Spray cycle	Continuous		
16	Inlet CFM	Limit:		
17	Inlet damper	Limit:		
18	Outlet damper	Limit:		
19	Differential pressure	Limit:		
20	Weight gain (% w/w)	Target: Range:		
Checked by/date:				
Reviewed by/date:				

SAMPLING PLAN – COATING:

Step No.	Activity	Performed by/date	
1	After completion of coating, collect approximately 500 (5 x 100) tablets from five different locations (four corner and centre) for each lot and check for **description and weight gain.**		
2	After completion of coating collect approximately **50 coated** tablets for **dissolution.**		
Reviewed by/date			
Acceptance Criteria			
Description			
Observation			
Dissolution	As per finished product specification		
% Weight Gain: Target: Range: X – Y			

Details (Lot A)	----	----	----	----	----	Performed by/date	Reviewed by/date
Weigh of 100 core tablets (As per BMR)							
----	Corner 1	Corner 2	Corner 3	Corner 4	Center	----	----
Weigh of 100 film coated tablets							
% Weight gain							

TABLET PRINTING:

- The tablet printing shall be performed in tablet printing machine as per MBMR No.
- During the printing operation, sample the printed tablets as specified in following table and check for physical appearance.

SAMPLING PLAN :

Step No.	Activity	Performed by/date	Reviewed by/date
1	Collect approximately 100 tablets at initial run of tablet printing operation and check the physical appearance.		
2	Collect approximately 100 tablets at middle run of tablet printing operation and check the physical appearance.		
3	Collect approximately 100 tablets at end run of tablet printing operation and check the physical appearance.		
Acceptance Criteria			

Description	
Initial Run	
Middle Run	
End Run	

TABLETS VISUAL INSPECTION AND SORTING:

The tablets inspection and sorting shall be performed using Automatic Tablets/Capsules Inspection and Sorting Machine as per step mentioned in BMR.

SAMPLING PLAN :

Step No.	Activity	Performed by/date	Checked by/date
1	After completion of printing, take 100 tablets from good (inspected) container and check for presence of rejection and record in observation table below.		

Sr. No.	Parameters	Observation
1	Vacuum	
2	Speed	
3	Broken Tablets	
4	Missing Printing	
5	Smudging	
6	Color Spot/Particle	
Performed by		
Checked By		

FINISH PRODUCT SAMPLING PLAN:

Step No.	Activity	Performed by/date
1	After completion of printing, collect X gm sample along with finished product sampling and send to QC.	
Reviewed by/date		

Deviation

- **Details of Deviation**
- **Root Cause**
- **Impact Analysis**
- **Corrective Action**
- **Preventive Action**
- **Recommendation**
- **Supporting Documents (if any)**

Reported by

Reviewed by

Reviewed by (Concerned department)

(Production Head or Designee)

QA Head / Designee

Annexure 7: Template of Continued Process Verification Report

Product Name	
Label Claim	
Report No.	
Product Code	
Batch Size	
Country	

Purpose

- To provide a procedure for continued process verification that shall assure that the process is in state of control (the validated state) during commercial manufacturing.

Scope

- Applicable to API and drug products manufactured for commercial purpose.

Responsibility

Production

- Identification and evaluation of Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs).
- Monitoring and evaluation of CQAs, CMAs and CPPs.
- Investigation of any atypical observation/Out of trend (OOT) result along with Unit QA.

Quality Control

- Identification and evaluation of Critical Quality Attributes and Critical Material Attributes.
- Establish trend limits of identified CQAs and CMAs.
- Monitoring and evaluation of CQAs, CMAs and CPPs.
- Investigation of any atypical observation/OOT result along with Unit QA.

Quality Assurance

- Evaluation of Identified Critical Quality Attributes, Critical Material Attributes and Critical Process Parameters.
- Review trend limits of identified CQAs and CMAs.
- Monitoring and evaluation of CQAs, CMAs and CPPs.
- Investigation and notification of any atypical observation/OOT result.
- Statistical evaluation should be done for adequately/low performed CQAs of the product as per the frequency mentioned in the guidance document.

Quality Assurance of Quality Control

- To review Continuous Process Verification protocol for commercialized drug products.
- To assist in investigation in case of out of trend observations in Continuous Process Verification.

Head Unit Quality Assurance

- Approve the trend limits of identified CQAs.
- Review the investigation and recommendation in case of any atypical observation/OOT result.

Unit Head

- Ensure timely completion of investigation of any atypical observation/OOT result.

Definition:

- **Continued Process Verification:**
  - Assuring that during routine production the process is in state of control (the validated state) during commercial manufacturing.
  - Note: As per EMA, Continued Process Verification shall be termed as Continuous Process Verification.

- **Critical Process Parameter (CPP):**
  - A process parameter whose variability has an impact on critical quality attributes and therefore shall be monitored or controlled to ensure that the process consistently produces product of the desired quality.

- **Critical Quality Attribute (CQA):**
  - A physical, chemical, biological or microbiological property or characteristic that shall be within an appropriate limit, range or distribution, in order to ensure the desired product quality and performance.

- **Critical Material Attributes (CMA):**
  - A material attribute which is a quantifiable physical, chemical and biological or microbiological property or characteristic of the material that shall be within an appropriate limit, range or distribution, in order to ensure the desired finished product quality.

- **Atypical Results:**
  - Results observed with a significant drift are considered to be atypical results.

- **Out of Trend (OOT) Test Result:**
  - A test result that does not follow the expected trend, in comparison with either results obtained within the batch, or results of other batches, or atypical observations identified, which are not obvious or as per expectations.

- **Process Capability:**
  - This refers to the normal behaviour of a process when operating in a state of statistical control. It refers to the inherent ability of a process to produce similar results for a sustained period of time under a given set of conditions. It is also defined as the capability of a process to meet its purpose as managed by an organization's management and process definition structure.

- **Mean:**
  - Mean is the simple average of the observations used to determine whether, on average, the process is operating around a desirable target value. AVERAGE in Microsoft Excel© uses the following formula:

$$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i = \frac{1}{n}(x_1 + \cdots + x_n)$$

- **Standard Deviation:**
  - The standard deviation (denoted by σ or sd) measures the variability of the observations around the mean. It is equal to the positive square root of the variance. The higher the sigma value, more dispersed the data is from the norm. STDEV in Microsoft Excel© uses the following formula:

$$\text{sd or } \sigma = \sqrt{\frac{\sum(x-\bar{x})^2}{(n-1)}}$$

- **Specification Limits:**
  - Specification limits are used to determine if the product is consistent with regard to defined quality attributes.

- **State of Control:**
  - This is a condition in which the set of controls consistently provides assurance of continuous process performance and product quality.

- **Control Strategy:**
  - A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include measures related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specification, and the associated methods and frequency of monitoring and control.

- **Health, Safety and Environment:**
  - Not applicable.

- **Procedure:**
  - **The process shall be monitored and evaluated continuously for every batch of the API and finished products manufactured for commercial purpose. Flow of continued process verification is given as Annexure XX.**

❖ **Continuous process verification shall be performed in steps as given below:**

- ❖ Identification of CPP and CQA for continuous process verification.
- ❖ Continuous process verification throughout the lifecycle of the drug product
- ❖ Annual product review/product quality review.

Products are classified in to two groups based on the frequency of manufacturing:

- ❖ Slow moving products: If the number of batches manufactured per year is less than or equal to 20, then those products shall be categorized as Slow Moving Products.
- ❖ Fast moving products: If the number of batches manufactured per year is more than 20, then those products shall be categorized as Fast Moving Products.

Note: If 20 batches are not manufactured in the initial year, then evaluation shall be through APR, provided that all the recommended CPP and CQA are covered in this evaluation.

Identification of CQAs, CPPs, CMAs:

- ❖ For legacy products: CQAs, CMAs and CPPs shall be identified from the process validation data, during the impact assessment of process variables on product quality as per SOP No. XX and based on the knowledge of the product.
- ❖ For new products: CQAs, CMAs and CPPs shall be identified from the respective development documents provided by R&D, process validation data and during the impact assessment of process variables on product quality as per SOP No. XX.

In the continuous process verification protocol, the following types of data shall be monitored:

- ❖ Finished product tests (CQAs measured by QC lab on finished product).
- ❖ In-process control test results (performed by production during manufacturing of the batch).
- ❖ Critical process parameters (CPPs) measured during batch manufacturing.
- ❖ Rejection, yield and accountability trend data at each significant stage of manufacturing.

- **Establishing trend limits for CQAs and CMAs:**

  - Excel sheets or any other automated system like Minitab shall be used to maintain the trend for CQAs and CMAs.

  - If an Excel sheet is used, it shall be used and validated for all formulae as per SOP XX.

  - For CQAs and CMAs, historical data for a minimum of 20/30 consecutive batches shall be collated and trend limits shall be established as per SOP No. XX.

  - The CPPs and CQAs identified in the continuous process verification protocol shall be analyzed and verified on an ongoing basis using a control chart (I-Chart) and Line Plot or both using Minitab software. Control chart shall not be used for parameters that are controlled by the equipment through in-built auto adjustment, and where the equipment is facilitated with engineering controls, e.g., tablet physical parameters like individual tablet weight, thickness, hardness, friability disintegration time, etc.

  - For CPPs, if there is a specified batch record control limit and/or a batch record tolerance limit, the data for the CPP shall be presented on a Line Plot with the control limits and/or tolerance limits displayed. This will provide a visual indication of the ability of the process to meet the particular batch record requirement.

  - The control chart (I-Chart) shall be used for monitoring, if testing of the sample generates a single value, e.g., assay.

  - Control limits (UCL & LCL) shall be established for control chart (I-Chart) after data collection and analysis of 20 commercial batches for slow moving products and after minimum 30 commercial batches for fast moving products; the control limits shall be calculated by Minitab software at the 3 standard deviation level or more than 3 standard deviation, and the data shall be monitored visually for obvious pattern and any point outside the control limit.

- **Guidance given above for number of batches is a general direction. The specific number of batches for both type of products needs to be derived based on statistical risk assessment of the product or any other specific predefined criteria.**

  - In general, the chart contains a centre line that represents the mean value for the process or limit, two horizontal lines, called the upper control limit (UCL) and the lower control limit (LCL).

  - Control limits for all control charts shall be calculated at the 3 standard deviation level. However, if it is demonstrated that:

- Control limits for all control charts shall be calculated at the 3 standard deviation level. However, if it is demonstrated that:
    - The data frequently fall outside the 3 standard deviation control limits, and
    - There are no other obvious cause in the trend data that indicates the presence of special cause of variation, such as clear shifts or upward or downward trends, and
    - The source of the special cause has been investigated and no assignable cause could be determined, and
    - The attribute being monitored is less critical than some other attributes being monitored, and
    - The process is suitably capable (Cpk) and there is low risk of exceeding specifications, then control limits may be calculated using a broader limit, e.g., at the 4 or 5 standard deviation level, as opposed to the 3 standard deviation level.

- Any data points falling outside the control limit for any critical process parameters (CPPs) or any critical quality attribute (CQAs) shall be reviewed and investigated as per SOP XY (Deviation Process). QA shall initiate investigation as per OOT investigation and collaborate with concerned departments like Manufacturing , Quality Control, Engineering, etc., to address the same.

- Failure to meet acceptance criteria for process drifts at the end of the investigation and subsequent changes, if proposed, may also be used to trigger additional process design and process qualification activities, if needed, on a case to case basis.

- After selection of the 20 commercial batches (for slow moving products) and a minimum of 30 commercial batches (for fast moving products) for finalization of control limit, trending of the further upcoming batches shall be performed. After protocol approval and implementation, all the CQAs and CPPs in those further batches shall be evaluated against the finalized control limit, and if any of the CQA and CPP is observed to be out of their respective control limit, then a deviation alert shall be raised and investigation shall be performed.

Monitoring of CQAs, CMAs on continual basis

Monitoring of CQAs and CMAs shall be done as per SOP No. XX during the analysis
Note: During batch release, monitoring of CQAs and CMAs shall be based on trend limits.

Trending of the batch shall be performed in Minitab before batch release. Batch release shall be done after verification that there is no data point outside the control limits or exceeding any other BMR limit for the respective CPP and CQA.

a. Process performance evaluation (PpK) for the identified CQAs shall be done on an annual basis during APQR as per SOP No. XX. For fast moving products, it may not be appropriate to wait for one year for evaluation of PpK, and thus on a case to case basis and on the basis of risks identified, an appropriate frequency will be defined for PpK evaluation; this can be monthly,quarterly, or every 6 months, other than APQR.

a. In case of trend charts, data of current batch shall be compared with data of earlier batches for any shift in trend. In case any significant shift is observed, impact evaluation shall be done.

Monitoring of CPP's on continual basis

- Identified CPPs shall be included and documented as a part of batch manufacturing/packing records and shall be monitored during the manufacturing of each lot

- CPPs shall be within the acceptance criteria specified in the part of batch manufacturing/ packing records.

Identification and investigation of out of trend results

a. Out of trend results observed in products with already established trend limits shall be handled as per SOP No. XX.

a. For products without predefined trend limits, data collected from the results of the tests shall be checked by Quality Assurance, and if any atypical observation is found, the same shall be notified to Head - Unit Quality and shall be investigated by an investigation team comprising Production, Quality Assurance, Quality Control or any other concerned department and shall be notified to Unit Head. The investigation shall be recorded as per SOP No. XXY.

a. All the critical quality attributes data shall be verified by Quality Assurance before batch release. In case atypical results are observed, the same shall be acknowledged and considered during the process capability evaluation.

a. Investigations and data collected from the results of the tests might suggest ways to improve and/or optimise 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.

a. If change is required, same shall be routed through Corrective and Preventive Action (CAPA) as per SOP XX.

Evaluation of Process Performance:

- ❖ QA shall evaluate the process performance annually, at the time of preparation of Annual Product Quality Review as per SOP No. XXY.

Abbreviations

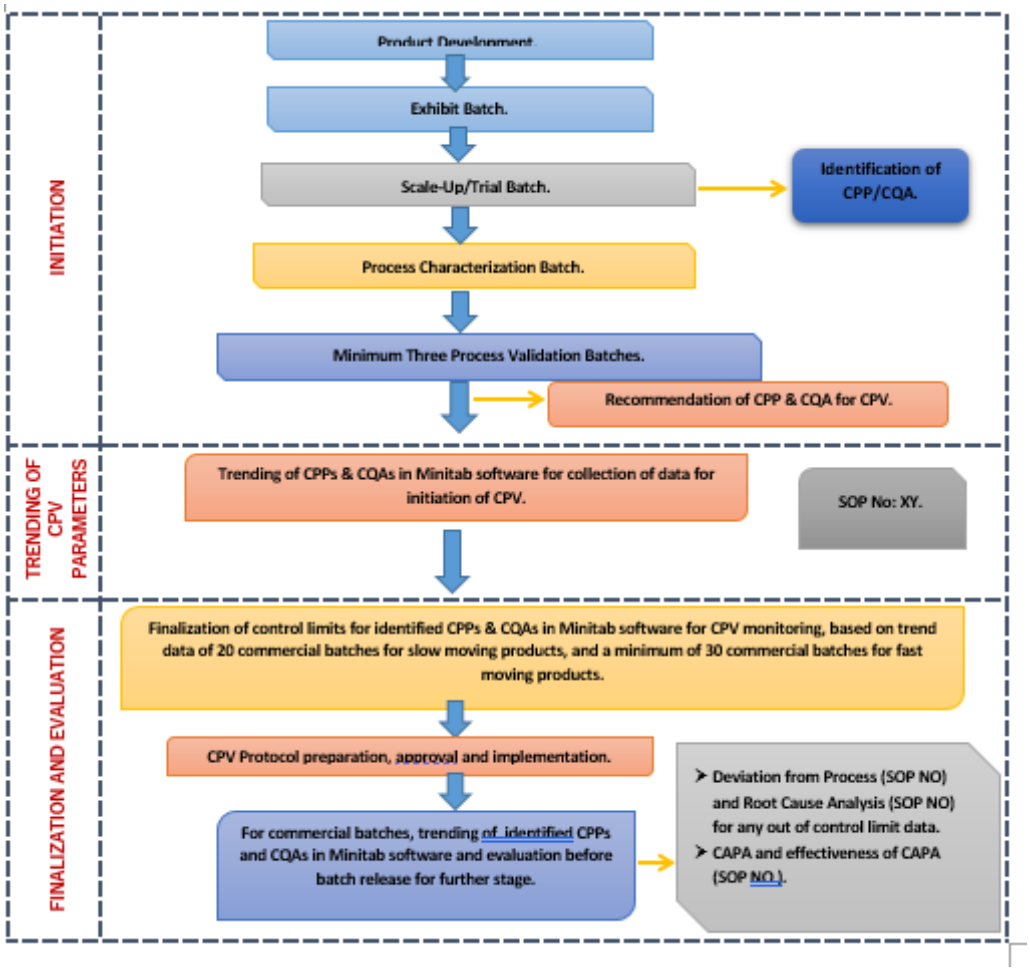
API	:	Active Pharmaceutical Ingredient
APQR	:	Annual Product Quality Review
AR	:	Atypical Results
AR No.	:	Analytical Reference Number
CMA	:	Critical Material Attributes
CPP	:	Critical Process Parameter
CPV	:	Continued Process Verification
CQA	:	Critical Quality Attributes
LCL	:	Lower Control Limit
No .	:	Number
PQR:	:	Product Quality Review.
QA	:	Quality assurance
SOP	:	Standard Operating Procedure
UCL	:	Upper Control Limit

References

- Guidance for Industry: Process Validation; General Principles and Practices (Revision 1); U.S. Department of Human Health and Services.
- Guideline on Process Validation for Finished Products; Information and Data to be provided in Regulatory Submissions; EMA/CHMP/CVMP/QWP/BWP/70278/2012 Revision 1.
- WHO TRS 992 - Annex 3 Guidelines on Good Manufacturing Practices: Validation; Appendix 7: Non-Sterile Process Validation.
- CH Q8: International Conference on Harmonisation.
- 1035-L-0062: Generation of Trend Limit and Monitoring Trend of Quality Attributes.
- 1035-G-0005: Change Request
- 1035-G-0168: Impact Assessment of Process Variables on Product Quality.
- 1035-G-0170: Creation, Updation, Protection and Usage of MS Excel Work Sheet.
- 1035-G-0016: Annual Product Quality Review.
- 1035-G-0015: Investigation and Root Cause Analysis

3.0 ANNEXURES:

Annexure Number	Annexure Name	To be used as
XXY	Flowchart for Continued Process Verification (1035-G-0172/FL1)	For reference



Annexure 8

Product Scores

PRODUCT	BATCH NO	DESCRIPTION	IDENTIFICATION	LOD (1-4%)	UOD/AV (1-15)	DISSO ACID (NMT10%)	DISSO BASE (NLT 90%)	ASSAY (95-105%)	IMPURITY (NMT1%)	RS (NMT 3500PPM)
	B1	COMPLIES	COMPLIES	1.1	3.1	1	92	98	0.08	555
	B2	COMPLIES	COMPLIES	1.2	3.2	2	93	97	0.07	565
	B3	COMPLIES	COMPLIES	1.3	3.1	1	95	98	0.07	545
	B4	COMPLIES	COMPLIES	1.4	3.3	3	93	96	0.07	345
	B5	COMPLIES	COMPLIES	1.1	3.2	1	94	98	0.05	545
	B6	COMPLIES	COMPLIES	1.2	3	2	95	97	0.06	654
	B7	COMPLIES	COMPLIES	1.1	3.4	1	92	98	0.04	456
	B8	COMPLIES	COMPLIES	1.1	3.1	2	93	95	0.08	543
	B9	COMPLIES	COMPLIES	2	3.3	0	96	95	0.07	444
	B10	COMPLIES	COMPLIES	1.2	5.2	1	97	97	0.07	345
MEAN	NA	NA	NA	1.27	3.39	1.4	94	96.9	0.066	499.7
SD	NA	NA	NA	0.28	0.65	0.84	1.70	1.20	0.01	99.99
MEDIAN	NA	NA	NA	1.2	3.2	1	93.5	97	0.07	544
PPK		5	5	0.33	1.23	0.55	0.78	0.53	1.74	1.67
CORRECTION FACTOR (CF)		0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
PPK*CF (Corrected PPK)		0.83	0.83	0.06	0.21	0.09	0.13	0.09	0.29	0.28
PRI. SCORE		4.17	4.17	0.45	9.48	1.26	2.54	1.17	16.67	16.67
WEIGHTAGE		0.19	0.04	0.19	0.04	0.12	0.12	0.04	0.04	0.19
WEIGHTED PPK		0.79	0.17	0.09	0.38	0.15	0.30	0.05	0.67	3.17
FINAL SCORE	5.76	A	Na	A	Na	A	A	Na	A	A

Ppk Range	Score Range
Ppk <= 1	0 – 25
1 < Ppk <= 1.33	26 – 50
1.33 < Ppk <= 1.67	51 – 75
Ppk > 1.67	75 – 100

A	action needed
Na	no action

Product Weightages

PRODUCT	ABCD 400 MG	BATCH NO	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	RANK (1-3-5)	WEIGHTAGE
1	DESCRIPTION	DEVIATION	0	0	0	0	0	0	0	0	0	0	5	0.19
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	1	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
2	IDENTIFICATION	DEVIATION	0	0	0	0	0	0	0	0	0	0	1	0.04
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
3	LOD (1-4%)	DEVIATION	0	0	1	0	0	0	0	0	0	1	5	0.19
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
4	UOD/AV (1-15)	DEVIATION	0	0	0	0	0	0	0	0	0	0	1	0.04
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
5	ACID RELEASE (NMT10%,0-10%)	DEVIATION	0	0	-1	0	0	0	0	0	0	0	3	0.12
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
6	BASE RELEASE (NLT 90%, 90-100%)	DEVIATION	0	0	0	0	0	0	0	0	0	0	3	0.12
		OOS/OOT	0	0	0	0	0	-2	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
7	ASSAY (95-105%)	DEVIATION	0	0	0	0	0	0	0	0	0	0	1	0.04
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
8	IND. IMPURITY (NMT1%)	DEVIATION	0	0	0	0	0	0	0	0	0	0	1	0.04
		OOS/OOT	0	0	-1	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
9	TOT. IMPURITY (NMT2%)	DEVIATION	0	0	0	0	0	0	0	0	0	0	1	0.04
		OOS/OOT	0	0	0	0	0	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
10	RS (NMT 3500PPM)	DEVIATION	0	0	0	0	0	0	0	0	0	0	5	0.19
		OOS/OOT	0	0	0	0	1	0	0	0	0	0		
		RECALL	0	0	0	0	0	0	0	0	0	0		
		MARKET COMPLAINT	0	0	0	0	0	0	0	0	0	0		
TOTAL													26	1.00

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