Process Validation

PRACTICAL TRAINING

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References to be used

- PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME , annex 15, process validation.
- EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1 Guideline on process validation for finished products - information and data to be provided in regulatory submissions.
- World Health Organization, Appendix 7, Non-sterile process validation update already published as Annex 3, WHO Technical Report Series, No. 992, 2015,

What is the process validation

- PIC/S

  "Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. "

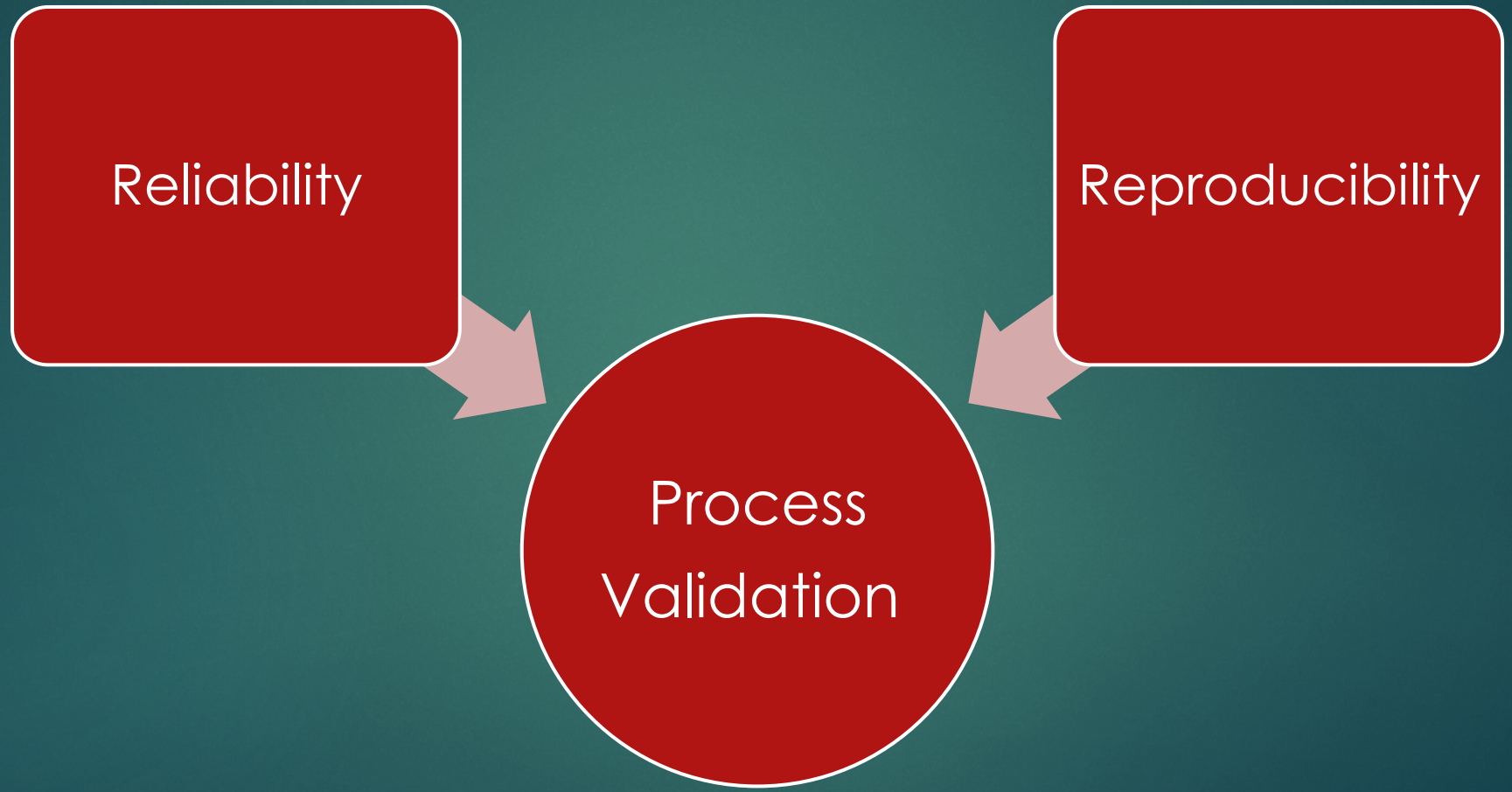
- WHO

  "The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product meeting its predetermined specifications and Quality attributes."

- EMA

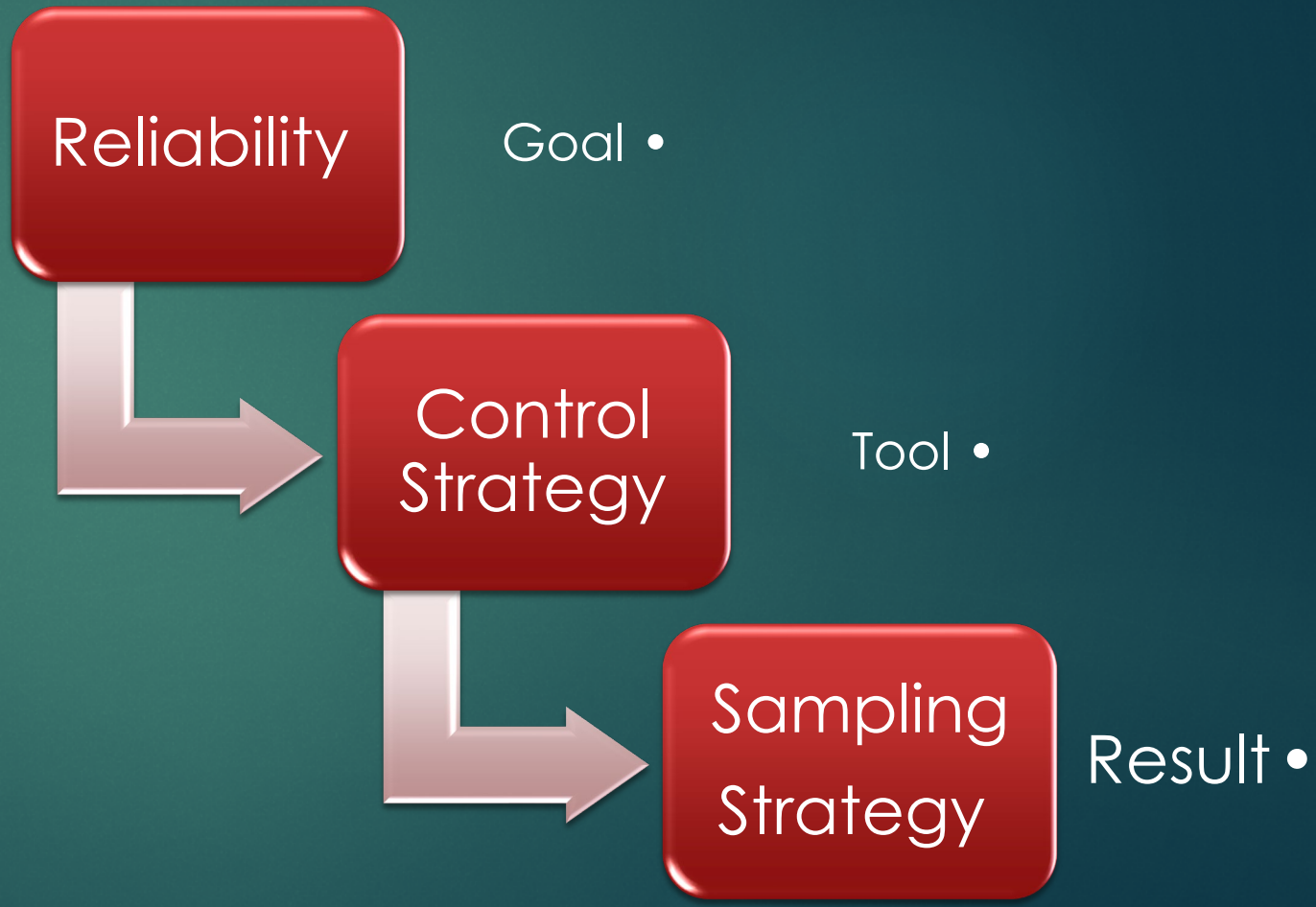
  "The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."

Process Validation Policy



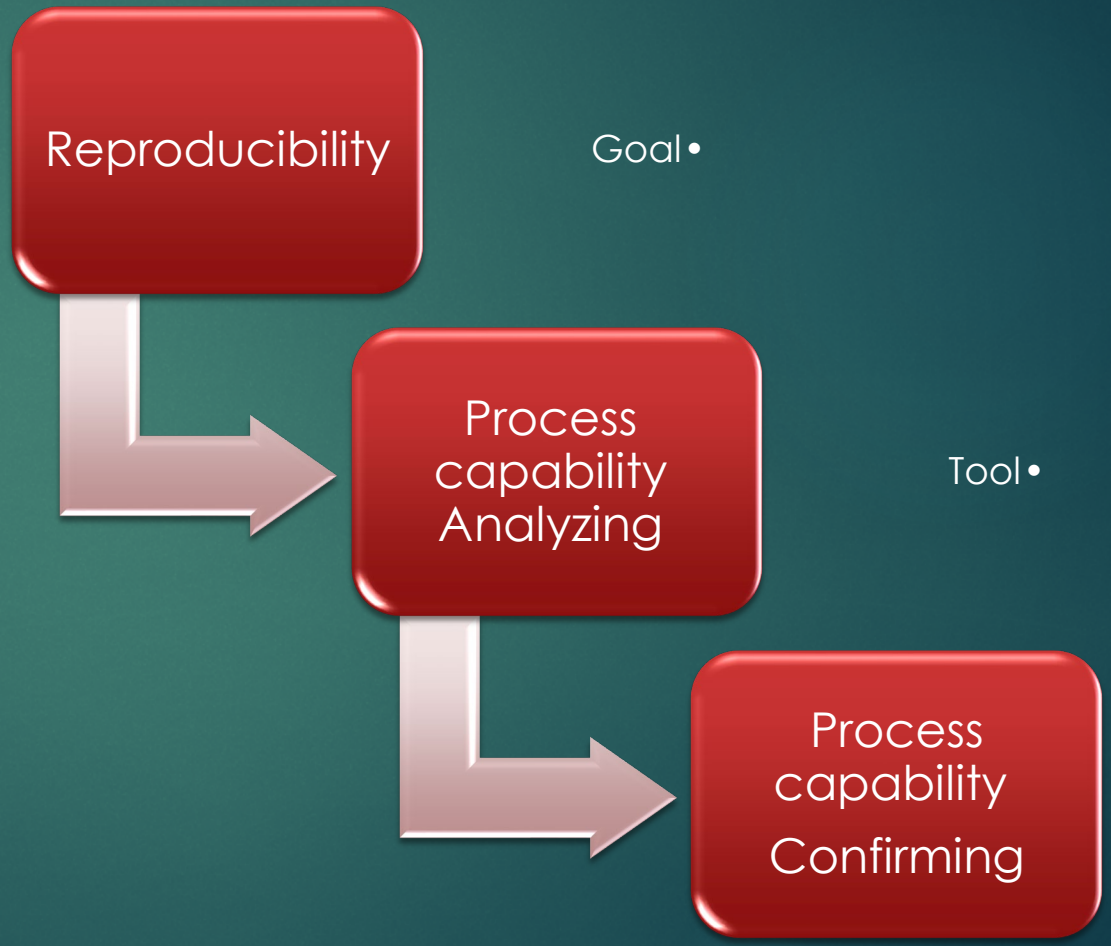
Process Validation Policy
Reliability

- One of the process validation objective is proving reliability of process.
- By establish proper control strategy this goal will achieved.
- The following diagram cleared this item properly:



Process Validation Policy Reproducibility

- One of the process validation objective is proving reproducibility of process.
- By implementing of GMP this goal will achieved.
- The following diagram cleared this item properly:

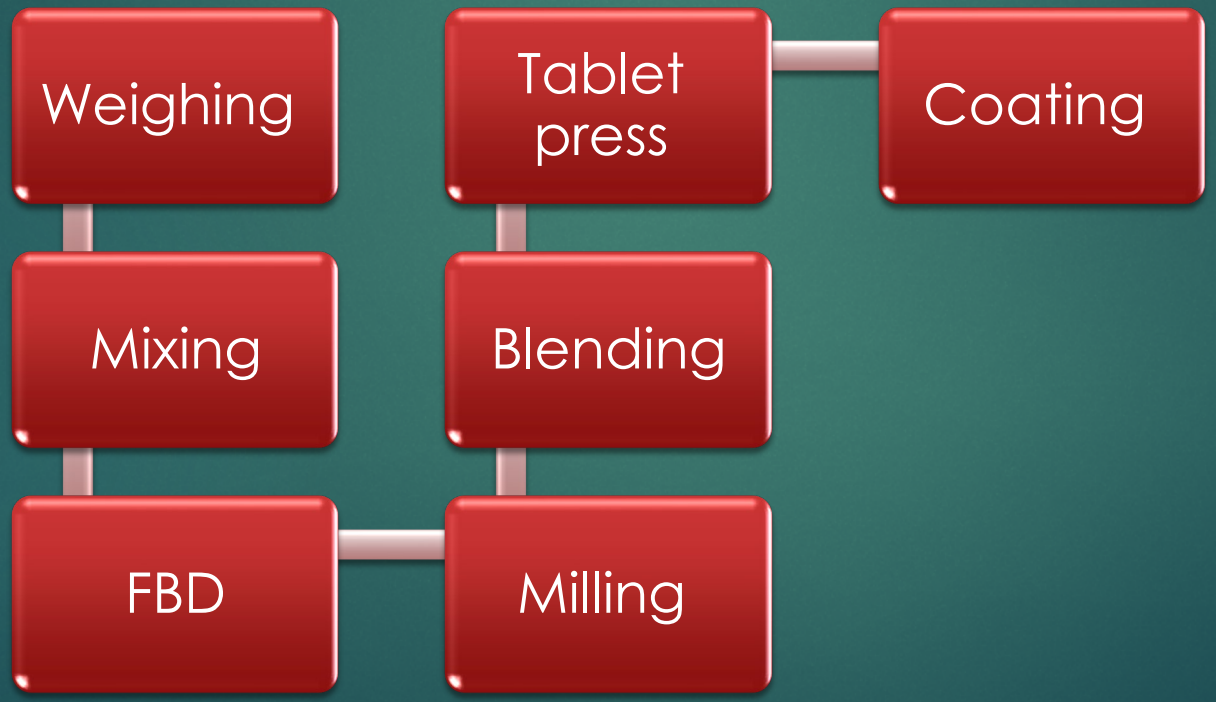


Process Validation Protocol

- The first step for process validation is preparing a protocol for give instruction and outline the principle. Process validation protocols should include:
- A description of the process and a reference to the respective Master Batch Record;
- Functions and responsibilities;
- Summary of the CQAs to be investigated;
- Summary of CPPs and their associated limits;
- Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
- List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
- List of analytical methods and method validation, as appropriate;
- Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
- Additional testing to be carried out, with acceptance criteria;
- Sampling plan and the rationale behind it;
- Methods for recording and evaluating results;
- Process for release and certification of batches (if applicable).

A practical process validation: Amitriptyline process validation

- We want to valid a coating tablet process with wet granulation, first item is description of process. This process is mentioned below as diagram.



Process description

- In 1st step the component of drug are received from warehouse and dispensed to verify compatibility of substance's with requirement.
- During the 2nd sub process we mixed API and excipient component in high-mixing and produce a duff.
- In 3rd sub process we drying the duff with fluid bed dryer. Actually it's will happen by blowing a heated air through the duff.
- In 4th sub process we milling the dried duff and generate a granule.
- In this situation the granule will stick on the equipment part, for solving this problem we should add magnesium stearate to granule. The 5th sub process will do it by blending.
- Now the granule is ready for tablet forming, by tablet press machine in 6th sub process a familiar tablet is produced.
- It is necessary to coat amitriptyline, in 7th sub process at first we prepare the coating solution and coat the tablets by coating machine and finally we produce coated tablet amitriptyline.

Function and responsibility

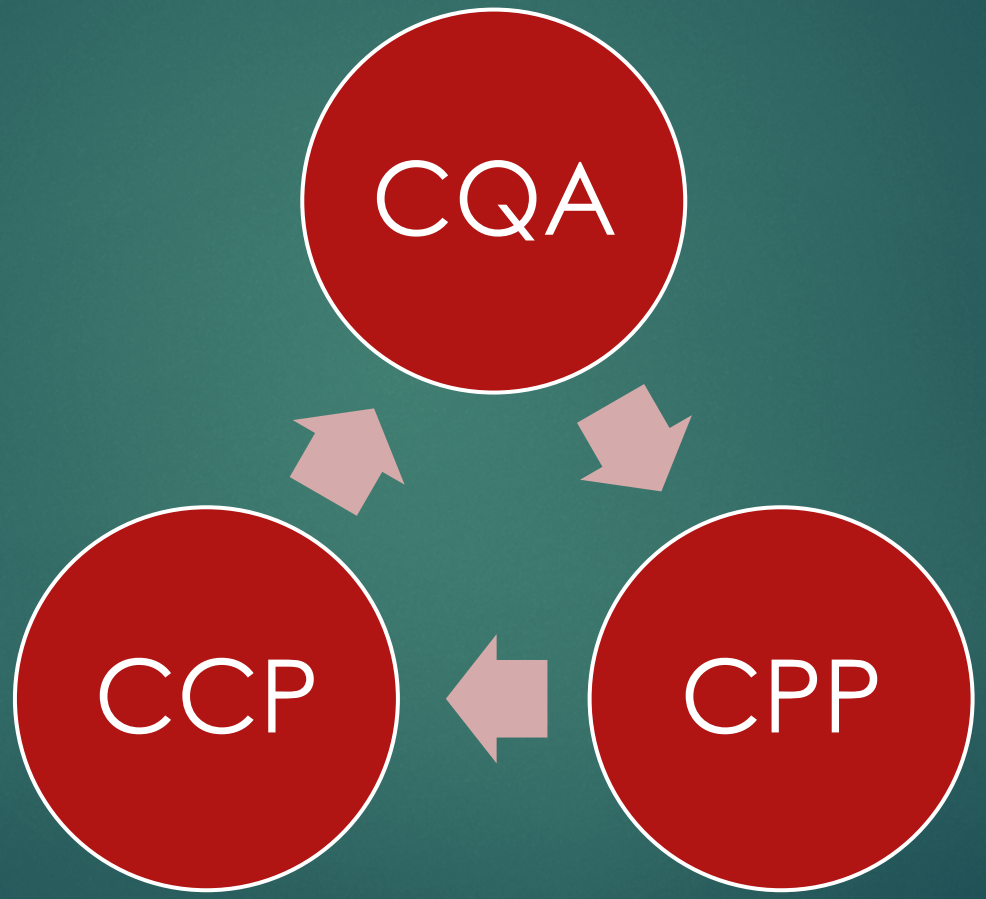
- The responsibility for qualification and validation in pharmaceutical manufacture is a multi-disciplinary one. The current PIC/S GMP Guide states that the heads of the Production and Quality Control departments generally have the responsibility:

  "To ensure that the appropriate validations are done."

Function and responsibility

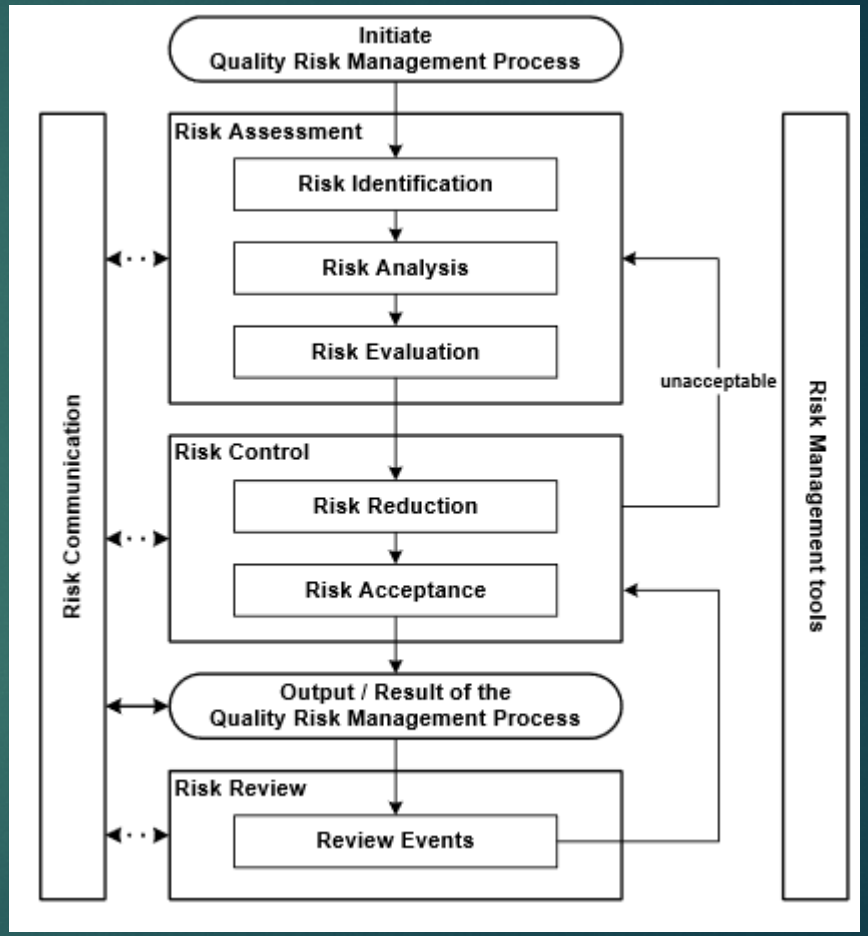
Raw	Duty	Responsible
01	Writing Protocol	Production Manager
02	Review Protocol	QC manager
03	Verifying And Approving Protocol And Report	QA Manager And Qualified Person
04	Execute Protocol And Reporting	Validation Team
05	Monitoring And Verifying Execution	Validation Officer
06	Review Procedure And Result	QA Manager And Qualified Person

Relation between CPP and CQA



CQA investigating

- A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.
- Approach to Identify CQA's: identify a CQA based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute.
- Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.



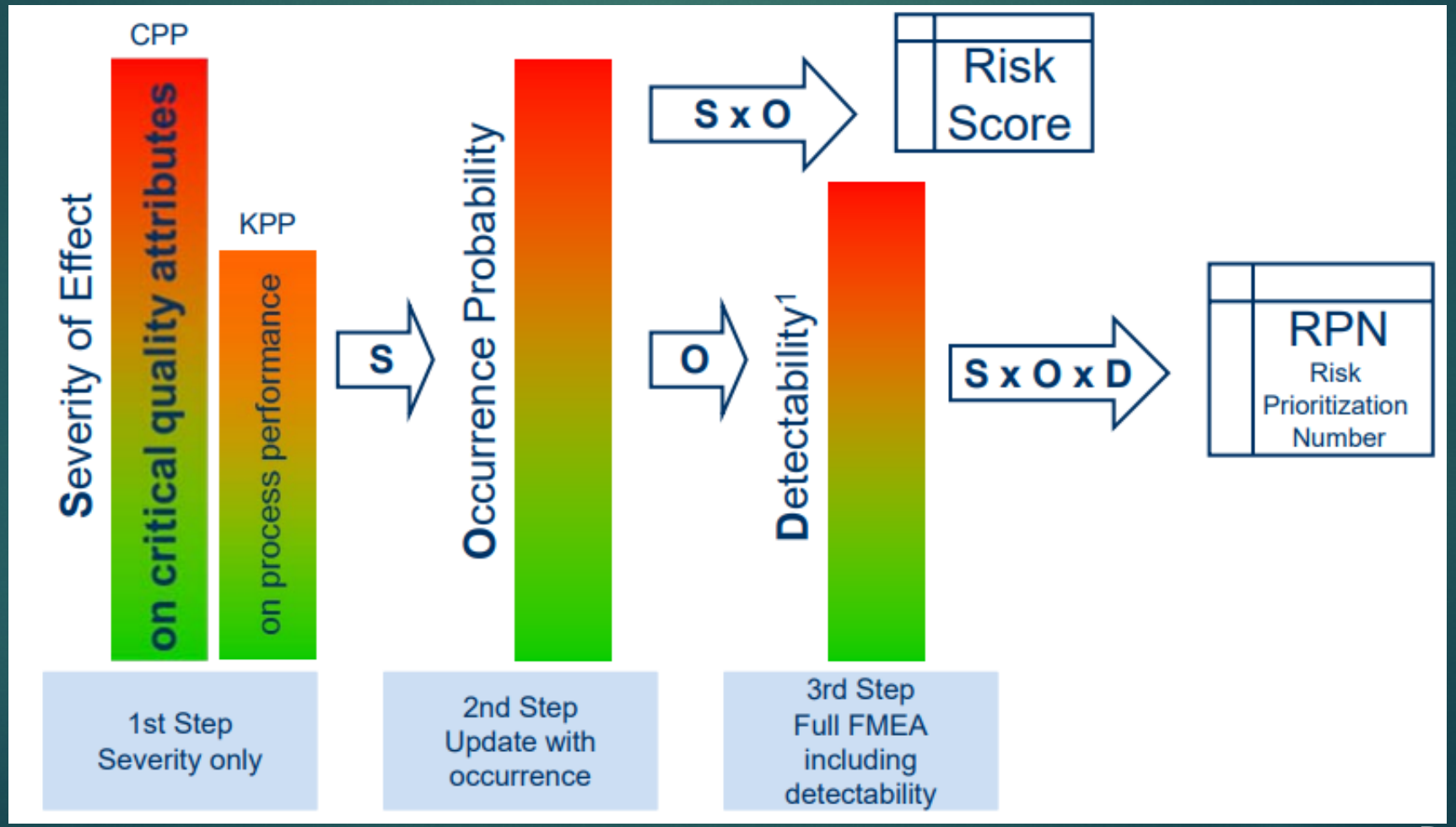
CQA investigating

- Start with list of all possible quality attributes
  - Consider mode of action and molecule type
- Risk-based approach to identify CQAs
  - Links quality attributes to safety and efficacy
  - Establish judgment and documents rationale
- Criticality reflects impact on safety and efficacy
- Keep process considerations separate from CQA assessment
  - CQA impact on safety & efficacy is independent of process capability, process changes shouldn't impact QA criticality
  - makes CQA assessment more modular

CPP investigating

- start with list of all possible process parameter.
  - Consider mode of action and molecule type
- Risk-based approach to identify CPPs
  - Links process parameter to quality attributes.
  - Establish judgment and documents rationale
- Criticality reflects impact on quality attributes.
  - makes CPP assessment more modular

CQA and CPP investigating Approach



Risk Assessment

If the severity be above 4, independence from RPN number, the risk will be categorize as CRITICAL.

And also if the severity be 4, independence from RPN number risk will be categorized as MAJOR.

Detectability	Severity					
		5	4	3	2	1
	1	25	16	9	4	1
	2	50	32	18	8	2
	3	75	48	27	12	3
	4	100	64	36	16	4
	5	125	80	45	20	5
		5	4	3	2	1
	Probability					

CQA investigating

- List of the quality attributes and their risk assessment for high mixing are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Appearance	3	2	3	18	Minor
Homogenous duff	4	2	3	24	Major
Particle size distribution	4	2	2	16	Major

- List of the quality attributes and their risk assessment for FBD are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Appearance	3	3	2	18	Major
Moisture	5	2	3	30	Critical
Particle size distribution	4	2	3	24	Major

CQA investigating

- List of the quality attributes and their risk assessment for miller are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Particle size	5	2	4	40	Critical
Appearance	4	2	3	24	Major

- List of the quality attributes and their risk assessment for blending are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Compression index	4	2	3	24	Major
Appearance	3	3	2	18	Major
Moisture	5	2	3	18	Critical
Assay	5	3	3	45	Critical
Content uniformity	5	3	3	45	Critical

CQA investigating

- List of the quality attributes and their risk assessment for tablet press are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Weight	3	2	5	30	Critical
Appearance	3	2	4	24	Major
Thickness	3	2	2	12	Major
Hardness	5	2	3	30	Critical
Diameter	4	2	2	16	Major
Disintegration	5	3	2	30	Critical
Dissolution	5	2	4	40	Critical
Assay	5	2	4	40	Critical
Content uniformity	5	3	3	40	Critical
Friability	4	4	2	32	Major

CQA investigating

- List of the quality attributes and their risk assessment for tablet coating are mention as table:

Quality Attributes Name	Severity	Probability	Detectability	RPN	Category
Weight	3	2	5	30	Critical
Appearance	3	2	4	24	Major
Thickness	3	2	2	12	Major
Hardness	5	2	3	30	Critical
Diameter	4	2	2	16	Major
Disintegration	5	3	2	30	Critical
Dissolution	5	2	4	40	Critical
Assay	5	2	4	40	Critical
Content uniformity	5	3	3	40	Critical
Friability	4	4	2	32	Major

CPP Investigation

- List of the process parameters for fluid bed dryer have affect on CQA and their risk assessment are mentioned below as table:

Process Parameter Name	Severity	Probability	Detectability	RPN	Category
Air Flow Quantity	5	2	3	30	Critical
Inlet Air Temp.	5	2	3	30	Critical
Outlet Air Temp.	4	2	3	24	Major
Humidity Of Inlet Air	5	2	3	30	Critical
Humidity Of Outlet Air	4	2	3	24	Major
Total Drying Time	5	2	3	30	Critical
Product Temp.	4	2	3	24	Major

CPP Investigation

- List of the process parameters for miller have affect on CQA and their risk assessment are mentioned below as table:

Process parameter Name	Severity	Probability	Detectability	RPN	Category
Screen size	5	3	2	30	Critical
Milling speed	4	2	2	16	Major
Feed rate	4	2	2	16	Major

CPP Investigation

- List of the process parameters for blender have affect on CQA and their risk assessment are mentioned below as table:

Process Parameter Name	Severity	Probability	Detectability	RPN	Category
Blending time	5	2	3	30	Critical
Blender speed	5	2	3	30	Critical
Intensifier bar	4	2	3	24	Major
Method of addition	5	2	3	30	Critical

CPP Investigation

- List of the process parameters for tablet press have affect on CQA and their risk assessment are mentioned below as table:

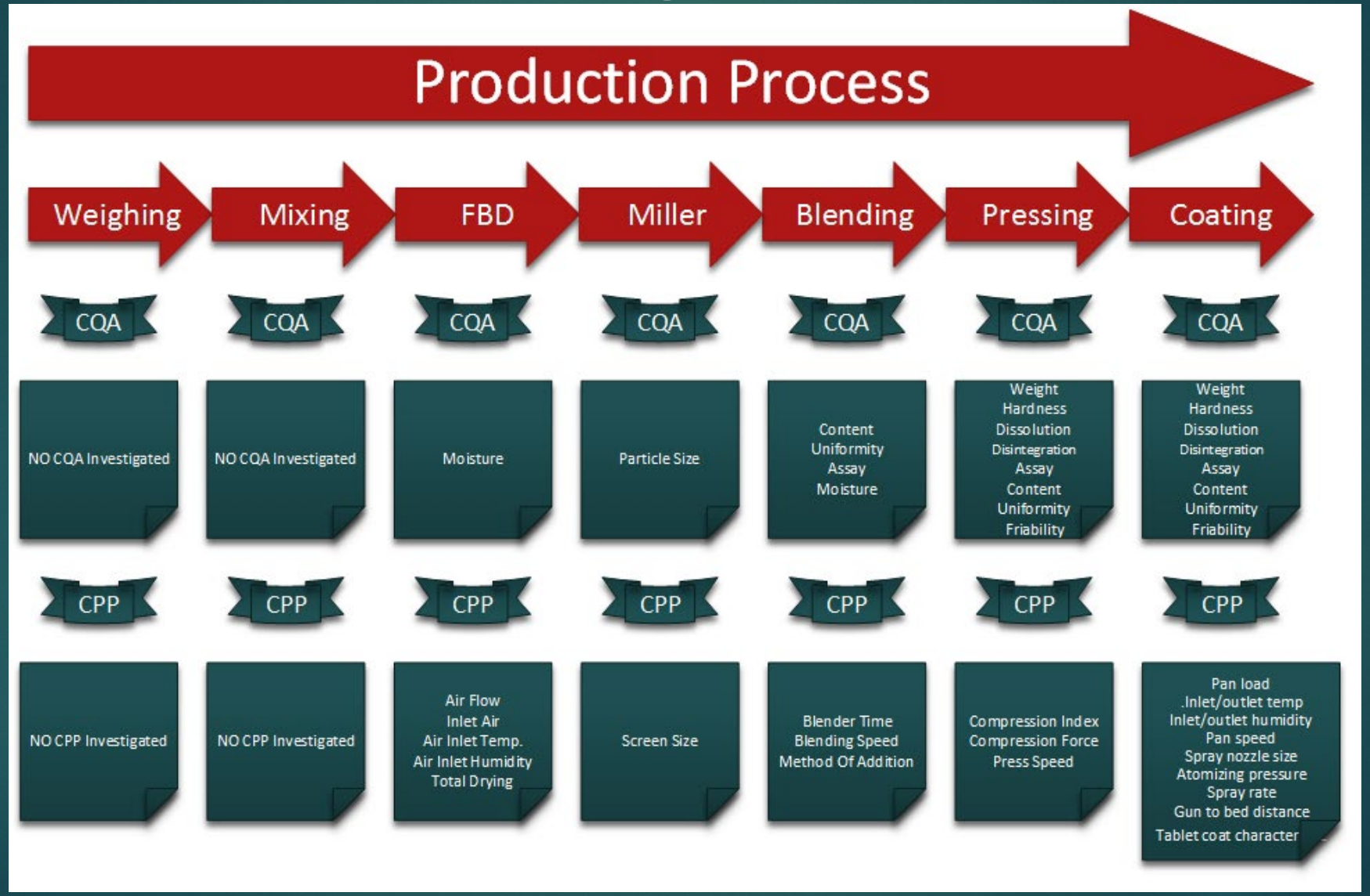
Process Parameter Name	Severity	Probability	Detectability	RPN	Category
Speed of press	5	4	2	40	Critical
Pre-compression	4	2	3	24	Major
Compression force	5	3	3	45	Critical
Feed frame	4	2	3	24	Major
Feeder speed	4	3	2	24	Major

CPP Investigation

- List of the process parameters for tablet coating have affect on CQA and their risk assessment are mentioned below as table:

Process Parameter Name	Severity	Probability	Detectability	RPN	Category
Pan load	5	3	3	45	Critical
Inlet/outlet temp.	5	2	4	40	Critical
Inlet/outlet humidity	5	2	4	40	Critical
Pan speed	5	3	2	30	Critical
Spray nozzle size	5	3	2	30	Critical
Atomizing pressure	5	2	3	30	Critical
Spray rate	5	2	3	30	Critical
Spray angel	4	2	2	16	Major
Gun to bed distance	5	2	3	30	Critical
Tablet coat characteristic	5	2	2	20	Critical

CQA & CPP Investigation



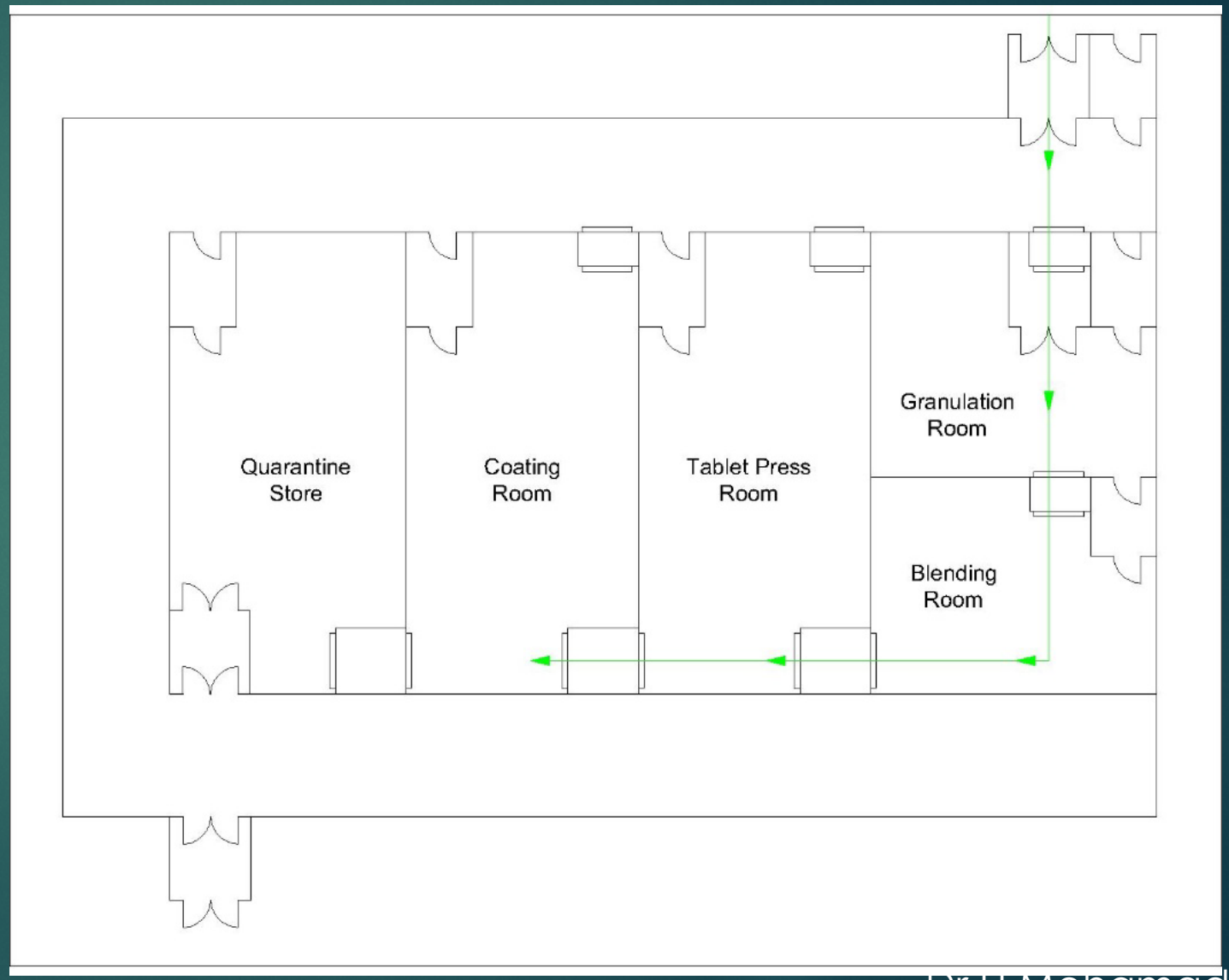
The equipment/facilities to be used

Description of the production areas are stated below as table:

Production Area Description			
Room No.	A(m2)	Classification	Application
PR-001	30	D	Granulation
PR-002	25	D	blending
PR-003	55	D	Tablet pressing
PR-004	55	D	Tablet coating
PR-005	50	CNC	Quarantine Store

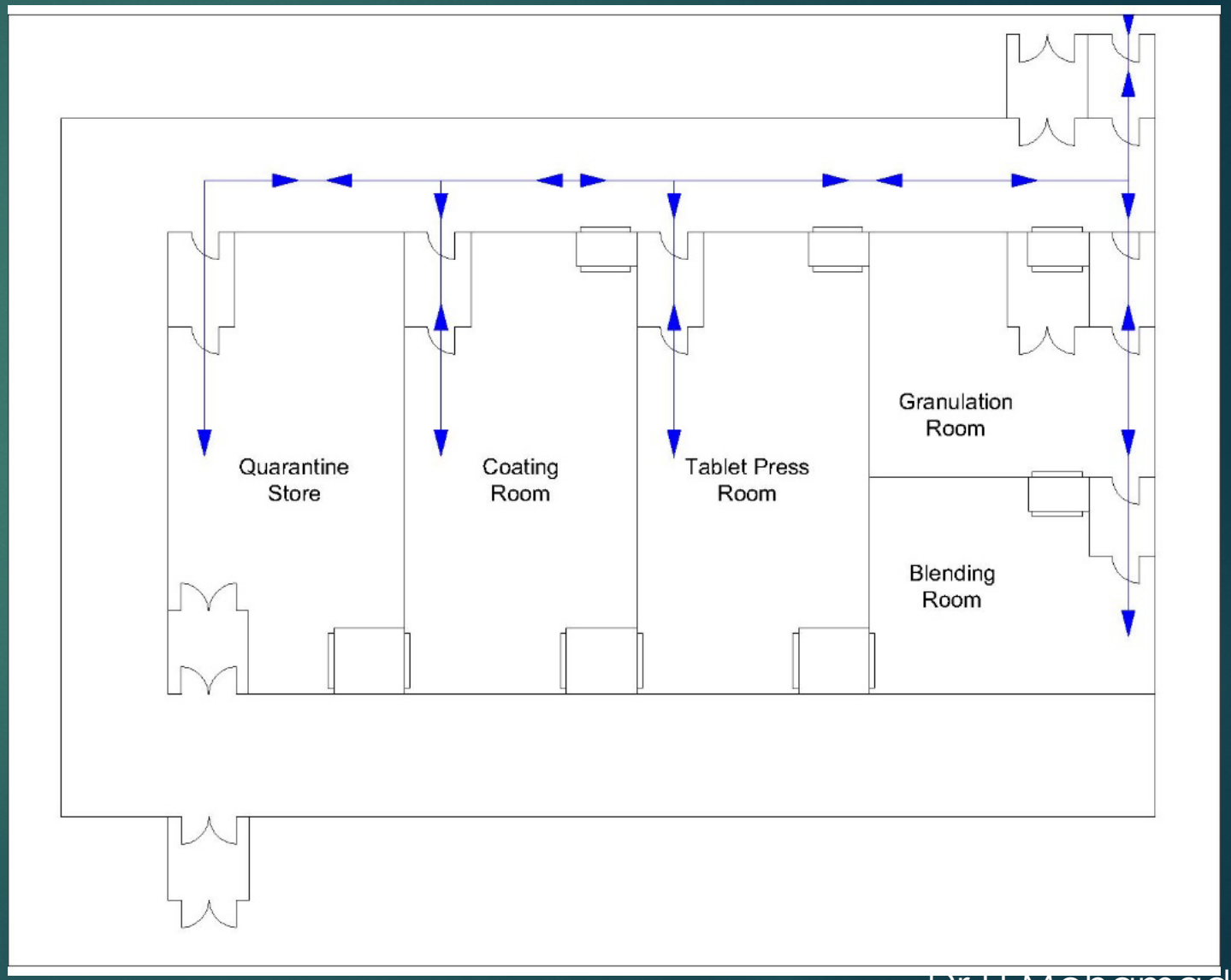
The equipment/facilities to be used

Production Area
Description
Material Flow
Layout



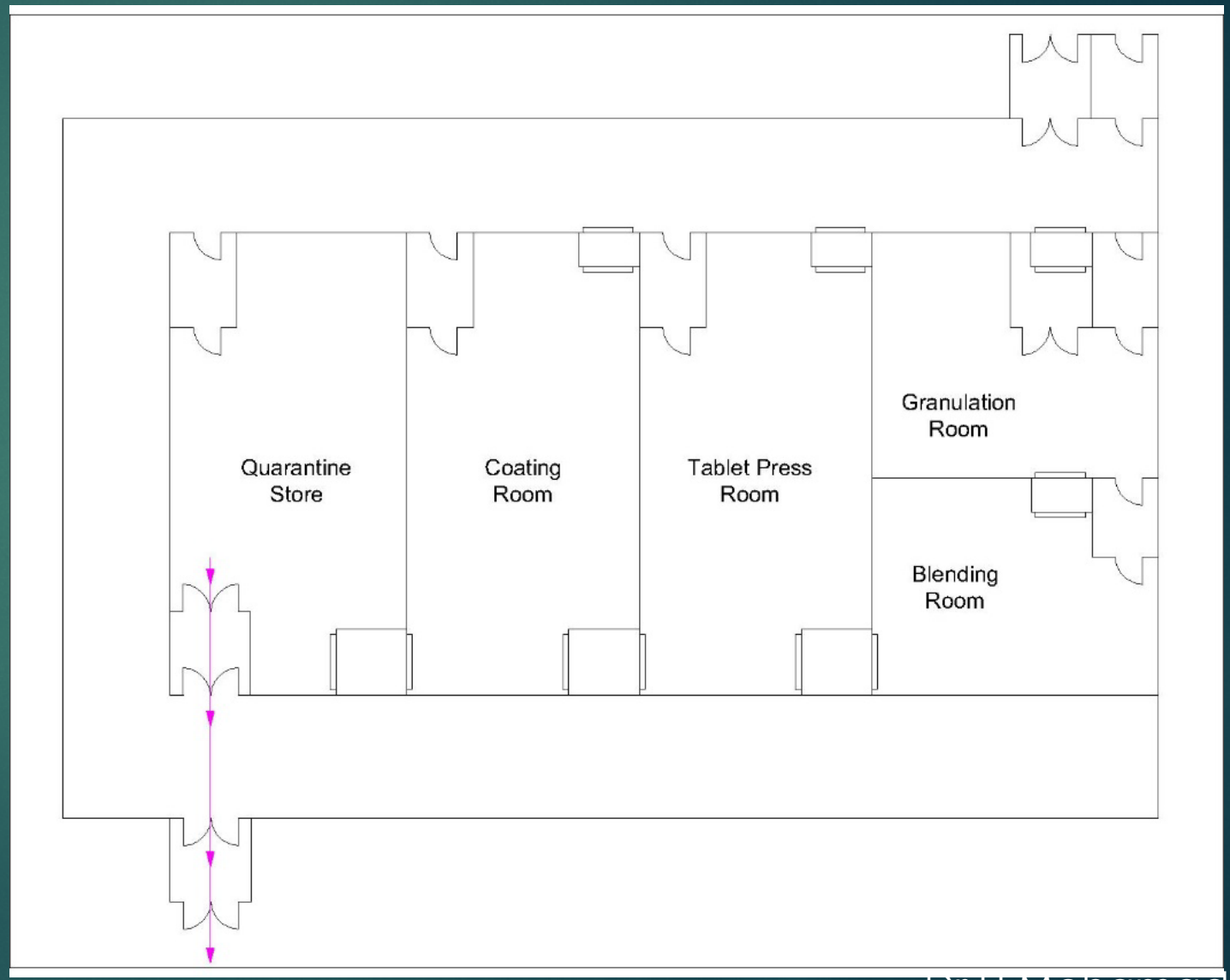
The equipment/facilities to be used

Production Area
Description
Personnel Flow
Layout



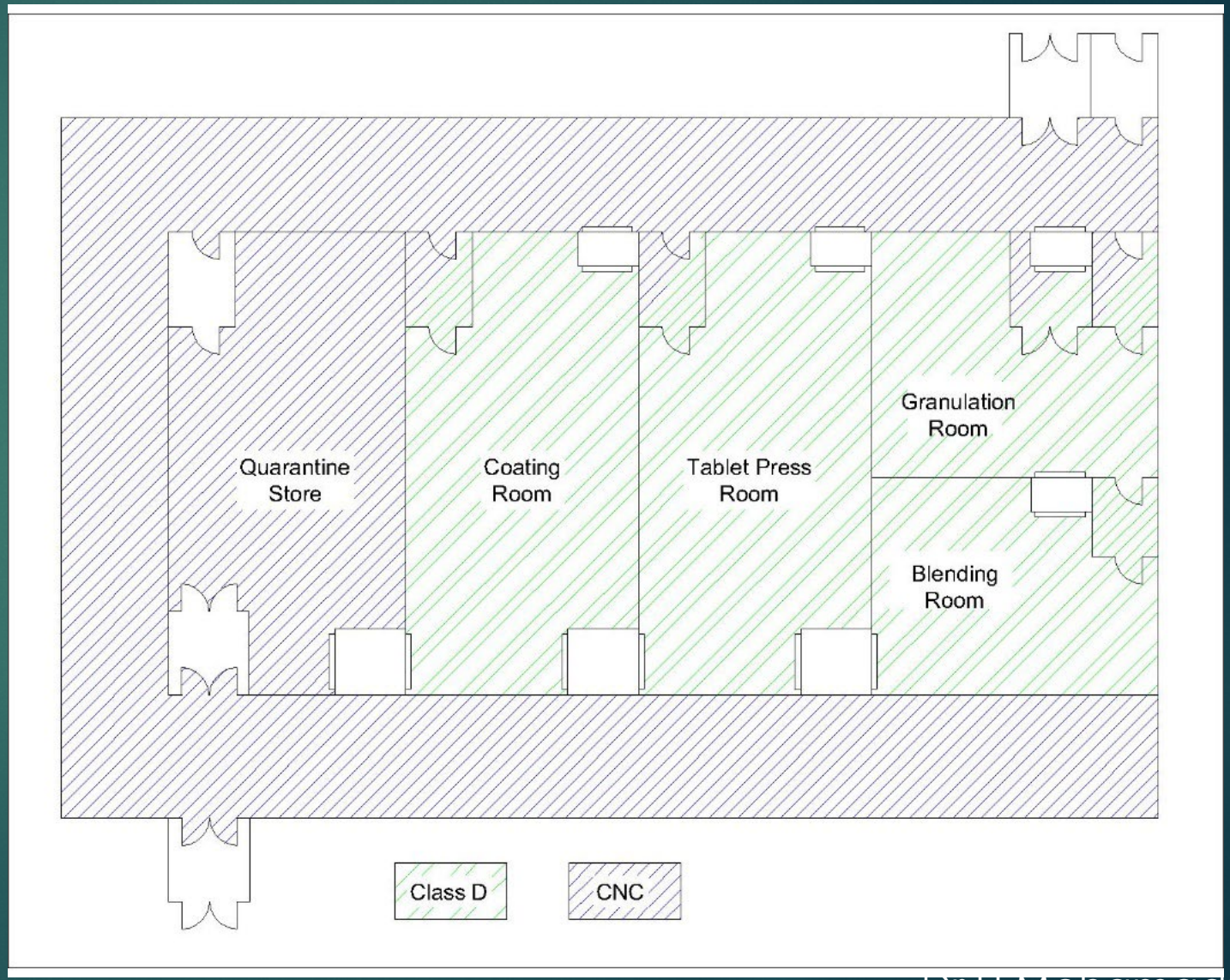
The equipment/facilities to be used

Production Area
Description
Product Flow
Layout



The equipment/facilities to be used

Production Area
Description
Classification
Layout



The equipment/facilities to be used

Production Equipment						
Name	Model	Application	DQ	IQ	OQ	PQ
High Mixing	SDR-132	Mixing	□	□	□	□
FBD	TYD-6054	Fluid Bed Dryer	□	□	□	□
Miller	HG326-J	Miller	□	□	□	□
Blender	ALF5200	Blending	□	□	□	□
Tablet Press	VANTIX	Tablet Pressing	□	□	□	□
Tablet Coating	HERA-122-K	Tablet Coating	□	□	□	□

The equipment/facilities to be used

Utility Equipment						
Name	Model	Application	DQ	IQ	OQ	PQ
HVAC-1	BOR-1452	Air ventilation & conditioning	□	□	□	□
Water Treatment	BRAM-405	Water Treatment	□	□	□	□
Air compressor	ATL-9054	Air compressor	□	□	□	□

The equipment/facilities to be used

Measurment Equipment			
Name	Model	Calibration Status	Verification Status
HPLC	KEN-405	OK	OK
UV	SHI124405	OK	OK
IR	DE4147405	OK	OK
Dispenser	MET-14-F	OK	OK
Friability Meter	HIGRF14	OK	OK
Dissolution	PAR504	OK	OK
Disintegration	HOS1485	OK	OK

List of analytical methods

- All analytical methods used during quality control are mention below:
  1. Identification
  2. Assay
  3. Uniformity test
  4. Dissolution
  5. Disintegration

Description of analytical methods: Identification Test

- Identification test is mentioned in USP pharmacopeia and it's not necessarily to be validated.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General,** *Chloride* ⟨191⟩**:** Meets the requirements

- For further information read SOP ID-QC-SOP-001/00

Description of analytical methods: Assay

- Assay test is mentioned in USP pharmacopeia and it's not necessarily to be validated.

ASSAY

- **PROCEDURE**

Diluted phosphoric acid: Phosphoric acid and water (1:10)

Buffer: 1.42 g/L of dibasic sodium phosphate (Na_2HPO_4) in water, adjusted with *Diluted phosphoric acid* to a pH of 7.7

Mobile phase: Methanol and *Buffer* (7:3)

System suitability stock solution A: 1 mg/mL of USP Amitriptyline Related Compound A RS in methanol

System suitability stock solution B: 0.4 mg/mL of USP Amitriptyline Hydrochloride RS, 0.6 mg/mL each of USP Amitriptyline Related Compound B RS, USP Cyclobenzaprine Hydrochloride RS, and USP Nortriptyline Hydrochloride RS in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Amitriptyline Hydrochloride RS in *Mobile phase*

System suitability solution: 1 µg/mL of amitriptyline hydrochloride, 0.5 µg/mL of amitriptyline related compound A, and 1.5 µg/mL each of amitriptyline related compound B, cyclobenzaprine hydrochloride, and nortriptyline hydrochloride from suitable volumes of *Standard solution*, *System suitability stock solution A*, and *System suitability stock solution B* in *Mobile phase*

Sample solution: 0.2 mg/mL of Amitriptyline Hydrochloride in *Mobile phase*

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: 1.5 times the retention time of amitriptyline

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—For relative retention times, see *Table 1*.]

Suitability requirements

Resolution: NLT 1.5 between amitriptyline related compound B and nortriptyline, *System suitability solution*

Relative standard deviation: NMT 2.0% for the amitriptyline peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amitriptyline hydrochloride ($C_{20}H_{23}N \cdot HCl$) in the portion of Amitriptyline Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Amitriptyline Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Amitriptyline Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

- For further information read SOP ID-QC-SOP-002/00

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Description of analytical methods: Uniformity Test

- This analytical test is like assay but these test have difference in making analyt and location of sampling.
- The procedure of uniformity test are mentioned in USP pharmacopeia and it's not necessarily to be validated.
- For further information read SOP ID-QC-SOP-003/00

Description of analytical methods: Dissolution and Disintegration Test

- This analytical test is not mentioned in USP and it's should be validated.
- For further information read analytical method validation protocol ID-RD-PRT-001/00 and SOP ID-QC-SOP-004/00

Process Control Strategy Bracketing Approach

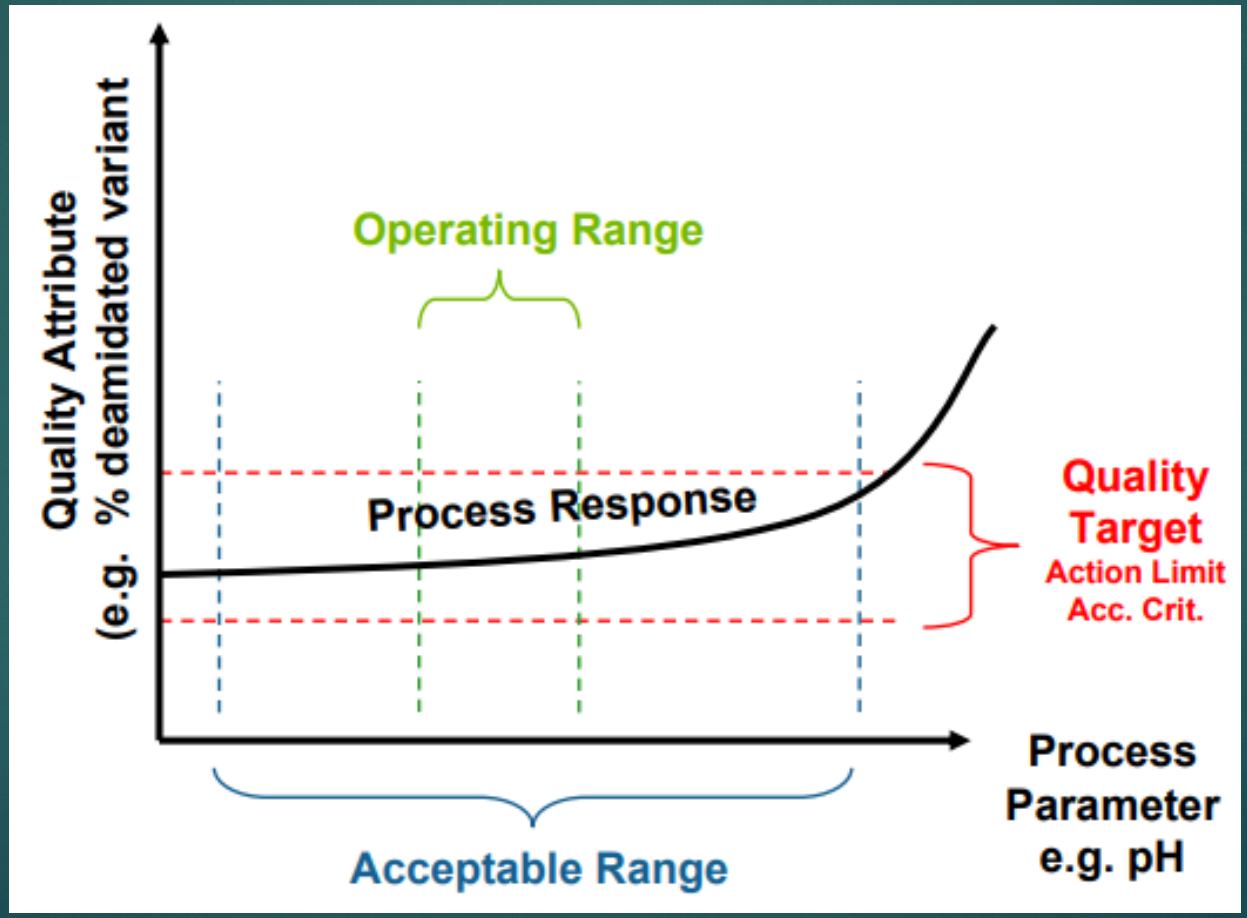
- **PIC/S**
- "A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size, and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells. Bracketing can be applied to different container sizes or different fills in the same container closure system."

Process Control Strategy Bracketing Approach

- The CQA's in mixing, FBD, Milling and blending could be tested at the final stage. According to bracketing approach we can combine these stage as granulation sub process.

Process Control Strategy

- Criticality of attributes and process parameters is needed for establishing, understanding and evaluating a risk-based control strategy.



Proposed Process Quality Controls

- Risk assessment for quality control in granulation process.

Risk Name	Severity	Probability	Detectability	RPN	Category
Content uniformity of component	5	2	4	40	Critical
Enough amount of component in granule	5	2	4	40	Critical
Verify component identity	5	4	2	40	Critical
Appearance and physical characteristic	4	2	3	24	Major
Amount of granule moisture	5	2	3	30	Critical
Particle size distribution	5	2	3	30	Critical

Proposed Process Quality Controls

- Analytical test description for granulation process

Analytical Test Description			
Test	Acceptance Criteria (Pharmacopeia)	Acceptance Criteria (Operational)	Acceptance Criteria (Validation)
Assay	90-110%	95-105%	97-103%
Content uniformity	85-115%	90-110%	97-103%
Identification	Compatible with ref. graph	Compatible with ref. graph	Compatible with ref. graph
Appearance	-	Compatible with CTD spec.	Compatible with CTD spec.
Moisture	<4%	<4%	<4%

Proposed Process Quality Controls

- Risk assessment for quality control in TABLET PRESS process.

Risk Name	Severity	Probability	Detectability	RPN	Category
Content uniformity of component	5	2	4	40	Critical
Enough amount of component in tablet	5	2	4	40	Critical
Verify component identity	5	4	2	40	Critical
Appearance and physical characteristic	4	2	3	24	Major
Microbial risk	5	2	3	30	Critical

Proposed Process Quality Controls

- Analytical tests description for tablet press are stated next page as table:

Analytical Test Description

Test	Acceptance criteria (Pharmacopeia)	Acceptance criteria (Operational)	Acceptance criteria (Validation)
Assay	90-110%	95-105%	97-103%
Content uniformity	85-115%	90-110%	95-105%
Identification	Compatible with ref. graph	Compatible with ref. graph	Compatible with ref. graph
Appearance	-	Compatible with CTD spec.	Compatible with CTD spec.
Color	-	Compatible with CTD spec.	Compatible with CTD spec.
Thickness	-	3.2-3.6	3.2-3.6
Weight	160±7.5%	160±5%	160±5%
Hardness	-	4-10Kpa	4-10Kpa
Friability	<1%	<1%	<1%
Diameter	-	8-8.1 mm	8-8.1 mm
Dissolution	≥75%	≤75%	≤75%
Disintegration	<15min	<15min	<15min
Microbial count	<1000CFU	<800CFU	<600CFU

Proposed Process Quality Controls

- Risk assessment for quality control in tablet coating process.

Risk Name	Severity	Probability	Detectability	RPN	Category
Content uniformity of component	5	2	4	40	Critical
Enough amount of component in tablet	5	2	4	40	Critical
Verify component identity	5	4	2	40	Critical
Appearance and physical characteristic	4	2	3	24	Major
Microbial risk	5	2	3	30	Critical

Proposed Process Quality Controls

- Analytical tests description for tablet coating are stated next page as table:

Analytical Test Description			
Test	Acceptance criteria (Pharmacopeia)	Acceptance criteria (Operational)	Acceptance criteria (Validation)
Assay	90-110%	95-105%	97-103%
Content uniformity	85-115%	90-110%	95-105%
Identification	Compatible with ref. graph	Compatible with ref. graph	Compatible with ref. graph
Appearance	-	Compatible with CTD spec.	Compatible with CTD spec.
Color	Compatible with CTD spec.	Compatible with CTD spec.	Compatible with CTD spec.
Thickness	-	3.2-3.6	3.2-3.6
Weight	166±7.5%	166±5%	166±5%
Hardness	-	4-14Kpa	4-14Kpa
Friability	<1%	<1%	<1%
Diameter	-	8-8.2 mm	8-8.2 mm
Dissolution	≥75%	≤75%	≤75%
Disintegration	<30min	<30min	<30min
Microbial count	<1000CFU	<800CFU	<600CFU

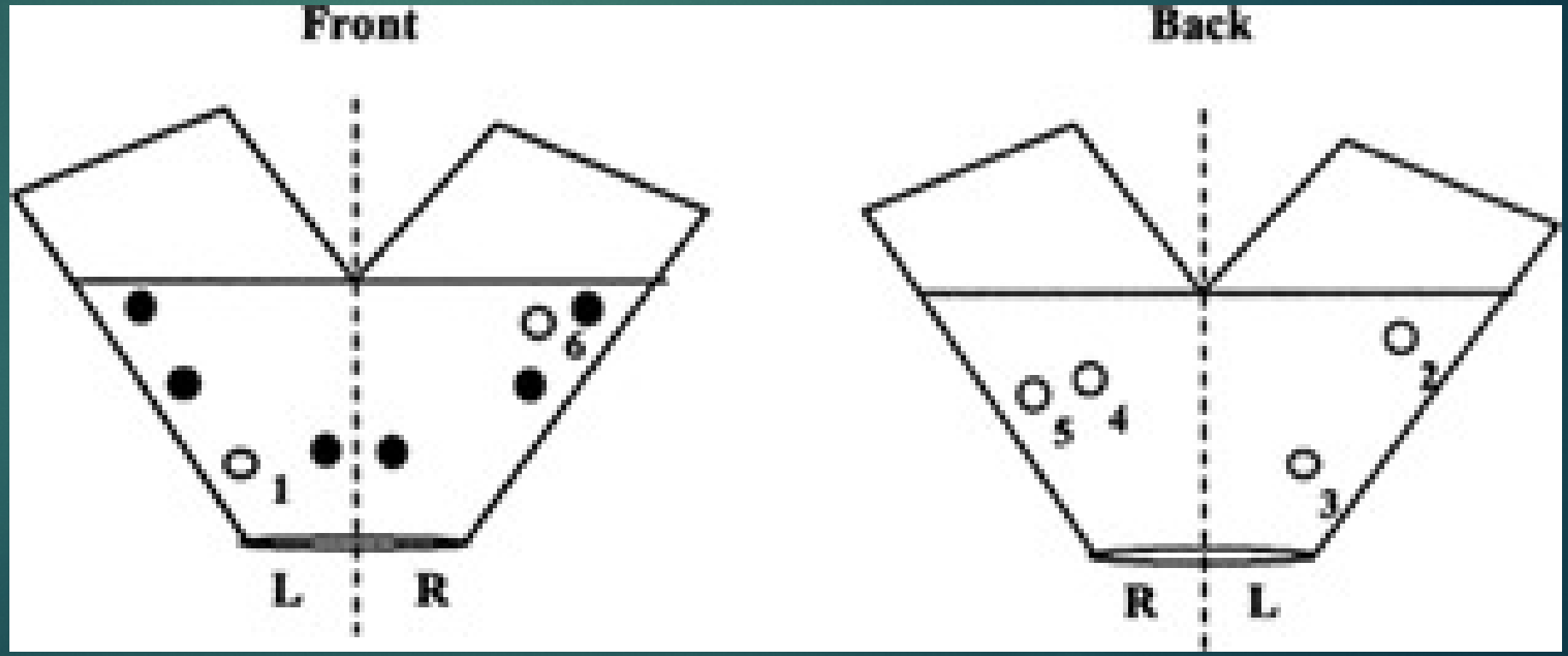
Proposed in-process controls with acceptance criteria

IPQC Test Description			
Test	Acceptance criteria(GRANUL)	Acceptance criteria(UNCOATED)	Acceptance criteria(COATED)
Appearance	Compatible with CTD spec.	Compatible with CTD spec.	Compatible with CTD spec.
Color	Compatible with CTD spec.	Compatible with CTD spec.	Compatible with CTD spec.
Thickness	-	3.2-3.4	3.2-3.6
Weight	-	160±5%	166±5%
Hardness	-	4-10Kpa	4-14Kpa
Friability	-	<1%	<1%
Diameter	-	8-8.1 mm	8-8.2 mm
Moisture	<4%	-	-

Sampling Description				
Stage	Location	Amount	Test	Frequently
Granulation	Blender	Every Point 40gr	Particle Size Distribution Moisture Content Uniformity Compression Index	15min
Tablet Press Tablet Coating	Tablet Press Tablet Coating	200 Tab	Weight Thickness Hardness Friability Disintegration Dissolution Assay Content Uniformity	15min

Sampling plan

- Location of sampling in blender are shown below as schematic diagram.



Batch releasing

- Batches of medicinal products should only be released for sale or supply to the market after certification by a QP. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.
- There are 3 way for batch releasing:
    1. Real time releasing
    2. Parametric release
    3. Process analytical technology

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- There are 3 way for batch releasing:
    1. Real time releasing
    2. Parametric release
    3. Process analytical technology(PAT)

Batch Releasing
Real Time Releasing

- Before a medicinal product is released for sale, the Qualified Person responsible for its release should take into account, among other aspects, the conformity of the product to its specification7 . In the case of approved RTRT, this conformity would not routinely be supported by results of end product testing. Nevertheless a specification has to be established and each batch of a product should comply with it if tested.

Batch Releasing
Parametric Releasing

- Parametric release is based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring during manufacturing, without direct measurement of quality attributes. It can be used as an operational alternative to end product testing for the drug product in certain cases when approved by the competent authority.

Batch Releasing
PAT Releasing

- Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.
- The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design

Process Capability Analysis Introduction

- Process Capability Indices: The behavior of a process (as related to inherent variability) in the state of statistical control is used to describe its capability. To compare a process with customer requirements (or specifications), it is common practice to think of capability in terms of the proportion of the process output that is within product specifications or tolerances.
- Process capability analysis is a statically tool for measurement and analysis of parameters and attributes parameters identified in the control strategy to verify continued operation within a state of control.
- A "state of statistical control" is achieved when the process exhibits no detectable patterns or trends, such that the variation seen in the data is believed to be random and inherent to the process.

Process capability analysis Definition

- Range, R: The largest observation minus the smallest observation in a set of values or observations.
- Process Capability Index, C_p: An index describing process capability in relation to specified tolerance.
- Short Term Standard Deviation, σ_{ST}: The inherent variation present when a process is operating in a state of statistical control, expressed in terms of standard deviation.

Process capability analysis Definition

- Minimum Process Capability index,C_{pk}: Smaller of the upper process capability index and the lower process capability index.
- Lower Process Capability Index, C_{pkl}: Describing process capability in relation to the lower specification limit.
- Upper Process Capability Index, C_{pku}: Index describing process capability in relation to the upper specification limit.

Process Capability Analysis

- Process Capability Index, C_P:
- The process capability index relates the process capability to the customer's specification tolerance. The process capability index, C_P, is:

$$C_p = \frac{\text{Specification Tolerance}}{\text{Process Capability}} = \frac{USL - LSL}{6\sigma_{ST}}$$

- where USL = upper specification limit and LSL = lower specification limit.
- The relationship between C_P and the percent defective product produced by a centered process (with a normal distribution) is:

C_p	Percent Defective	Parts per Million	C_p	Percent Defective	Parts per Million
0.6	7.19	71900	1.1	0.0967	967
0.7	3.57	35700	1.2	0.0320	318
0.8	1.64	16400	1.3	0.0096	96
0.9	0.69	6900	1.33	0.00636	64
1.0	0.27	2700	1.67	0.00006	0.57

Process Capability Analysis

- One can see that any process with a $C_P < 1$ is not as capable of meeting customer requirements (as indicated by % defectives) as a process with values of $C_P > 1$.

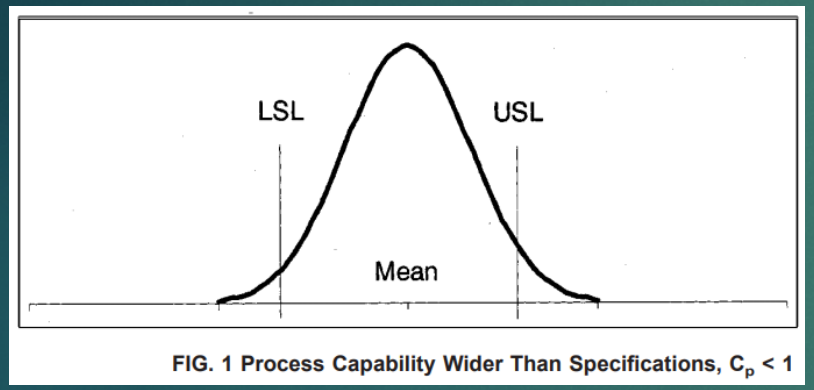

FIG. 1 Process Capability Wider Than Specifications, $C_p < 1$

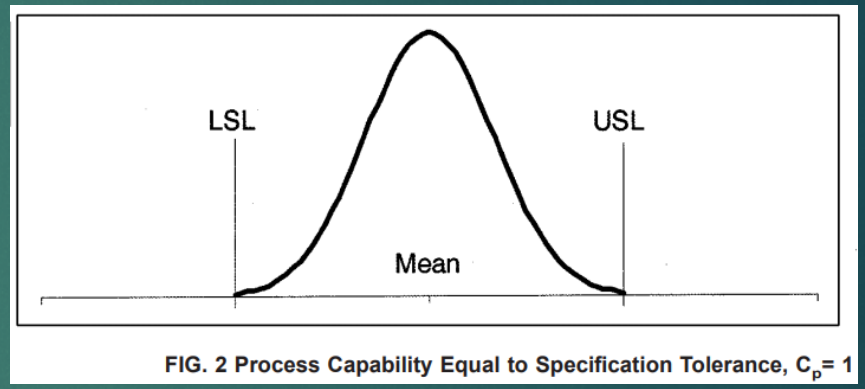

FIG. 2 Process Capability Equal to Specification Tolerance, $C_p = 1$

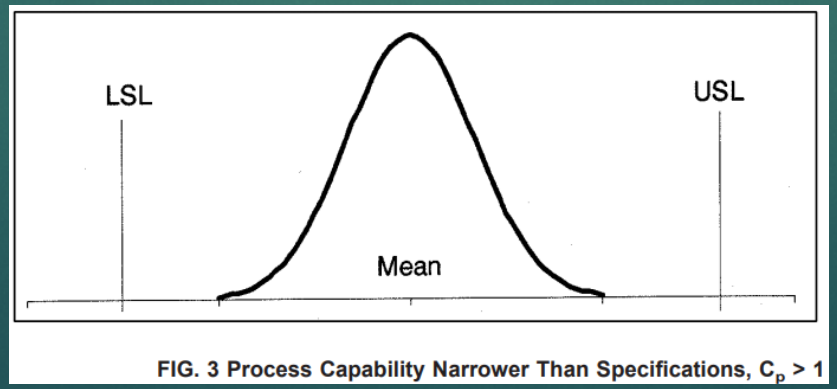

FIG. 3 Process Capability Narrower Than Specifications, $C_p > 1$

Process Capability Analysis

- Process Capability Indices Adjusted For Process Shift:
- C_{Pk} is a process capability index that considers the process average against a single or double-sided specification limit. It measures whether the process is capable of meeting the customer's requirements by considering:
    1. The specification limit
    2. The current process average
    3. The current σ_{ST}

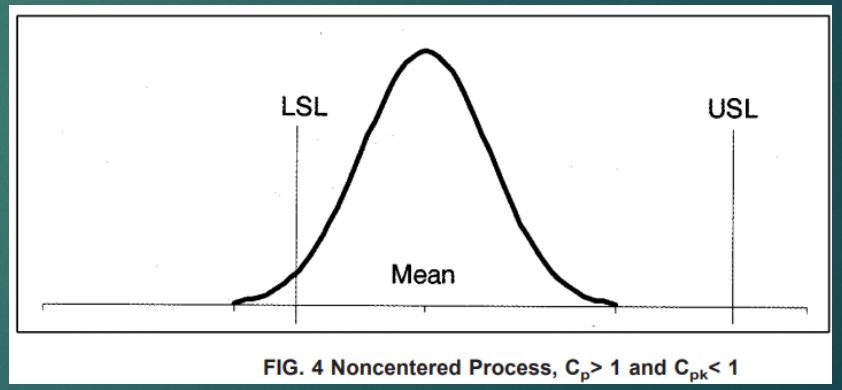

FIG. 4 Noncentered Process, $C_p > 1$ and $C_{pk} < 1$

Process Capability Analysis

- Under the assumption of normality, C_{Pk} is calculated as:

$$C_{pk} = \min[C_{pku}, C_{pkl}] \qquad \hat{C}_{pk} = \min[\hat{C}_{pku}, \hat{C}_{pkl}]$$

- where the estimated upper process capability index is defined as:

$$\hat{C}_{pku} = \frac{USL - \bar{X}}{3\,\hat{\sigma}_{ST}}$$

- and the estimated lower process capability index is defined as:

$$\hat{C}_{pkl} = \frac{\bar{X} - LSL}{3\,\hat{\sigma}_{ST}}$$

Process Capability Analysis

- The relationship between C_P and C_{Pk} can be summarized as:
  - C_{Pk} can be equal to but never larger than C_P ,
  - C_P and C_{Pk} are equal only when the process is centered on target.
  - If C_P is larger than C_{Pk} , then the process is not centered on target.
  - If both C_P and C_{Pk} are >1, the process is capable and performing within the specifications.
  - If both C_P and C_{Pk} are <1, the process is not capable and not performing within the specifications.
  - If C_P is >1 and C_{Pk} is <1, the process is capable, but not centered and not performing within the specifications.

Change Control

- The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.
- Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.
- Changes should be authorized and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.
- Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.
- Following implementation, and where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

Revalidation

- In the following case the revalidation should be implemented:
  - Any change in manufacturing process which has affect on product quality.
  - Any change in batch size.
  - Any change in final product formulation.
  - Any change on production site which has affect on product quality.
  - Any change on production equipment or facilities which has affect on product quality.
  - Any change in primary packaging
  - Any change in source of API.
  - Expiration of validation period