



# **Manufacturing Process Considerations for Immediate & Modified Release Products**

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# Outline

- Process selection for Immediate Release Products
- Manufacturing process train & risk assessment
- Some process consideration for MR products
- SUPAC related to process and equipments
- Conclusion

# Initial Considerations for Process Selection

- **Drug load:** Low, medium, high
- **Solubility of API:** High or low
- **Chemical and physical stability of API:**
  - Aqueous stability: Wet granulation versus direct compression
  - Thermal stability: possibility of form conversion, degradation
- **Formulation:** Impact on CQAs, stability
  - API & Excipient Compatibility: possibility of degradation with the process selected
- **In-process measurement:** On-line/in-line/at-line or off-line

Keep an end in mind: Is the process suitable & scalable?

# Typical In-Process Controls for IR/MR Manufacturing Processes

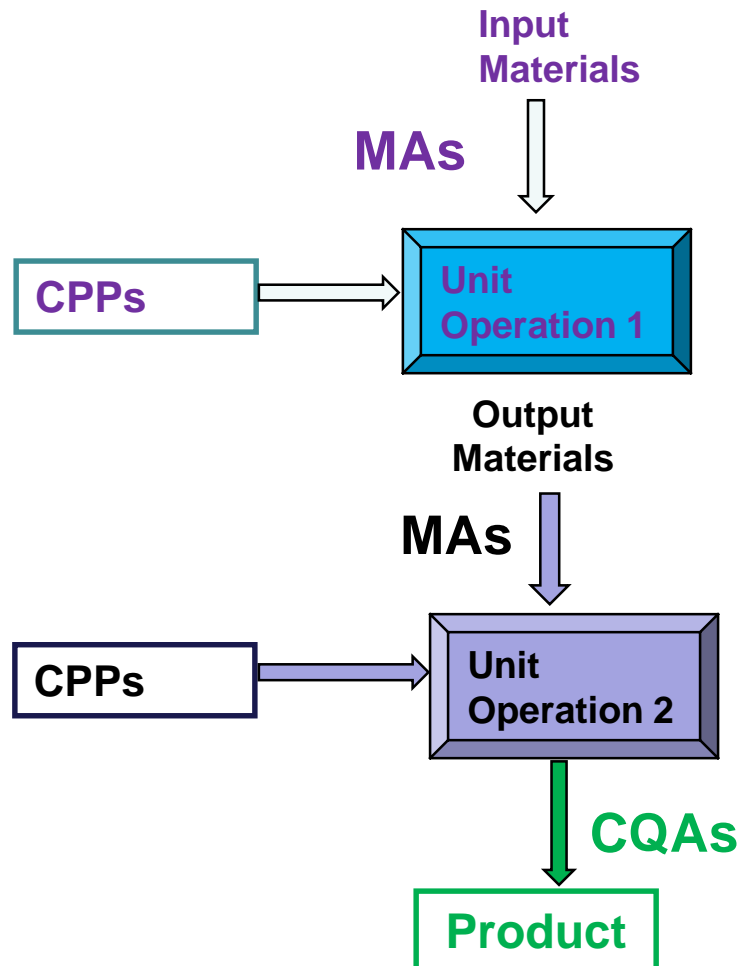
- **Blending:** Blend uniformity, content uniformity
- **Milling:** Particle size distribution, flow properties
- **Wet granulation:** Granulation end point, flow properties
- **Drying:** Loss on drying
- **Compression:** Hardness, thickness, friability, dissolution
- **Coating:** Weight gain, loss on drying  
Non-functional or functional (coming up later)

# Typical Process Parameters

(not an exhaustive list)

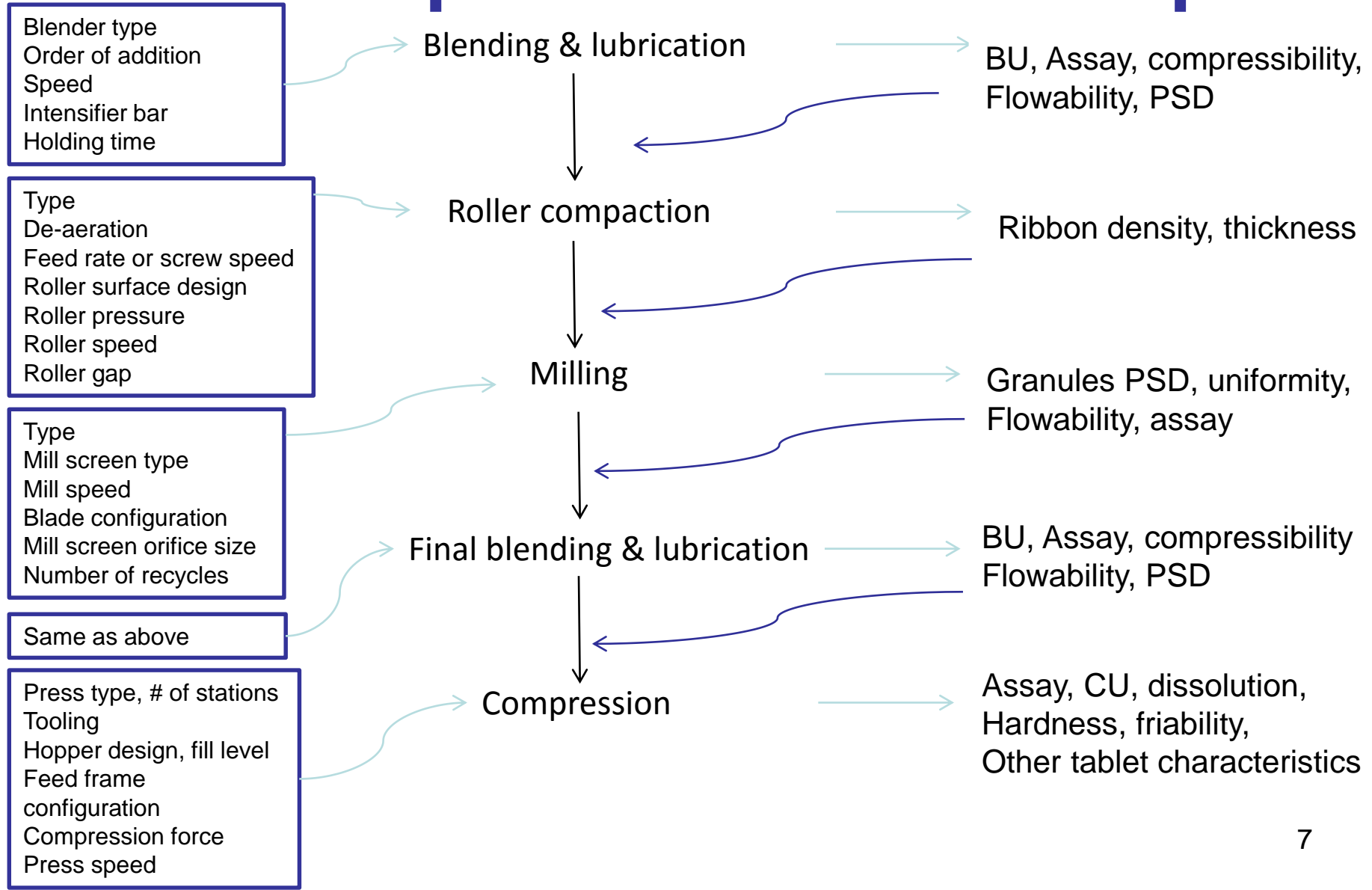
- **Blending:** Speed, order of addition , % occupancy, blend time (also consider sampling plan)
- **Milling:** Screen size, milling speed, number of recycles
- **Wet granulation:** granulation spray rate
- **Drying:** drying temperature
- **Compression:** Compression force, press speed  
(Also consider press type, # of stations, tooling, hopper design, fill level, feed frame configuration)
- **Coating:** More information in MR product section

# Manufacturing Process Train



*MA: Material Attribute*  
*CPP: Critical Process Parameter*  
*CQA: Critical Quality Attribute*

# Example of a Process Map



# Roller compaction & Milling Variables

## Process variables:

### Roller compactor:

Type  
Deaeration  
Feed rate or screw speed  
Roller surface design  
Roller pressure  
Roller speed

### Roller gap

### Mill:

Type  
Mill screen type  
Mill speed  
Blade configuration  
Mill screen orifice size  
Number of recycles

## Input material variables:

### Roller compaction:

PSD of Blend  
Blend uniformity  
Blend compressibility/flowability  
Lubricant level

### Milling:

Compact/ribbon density

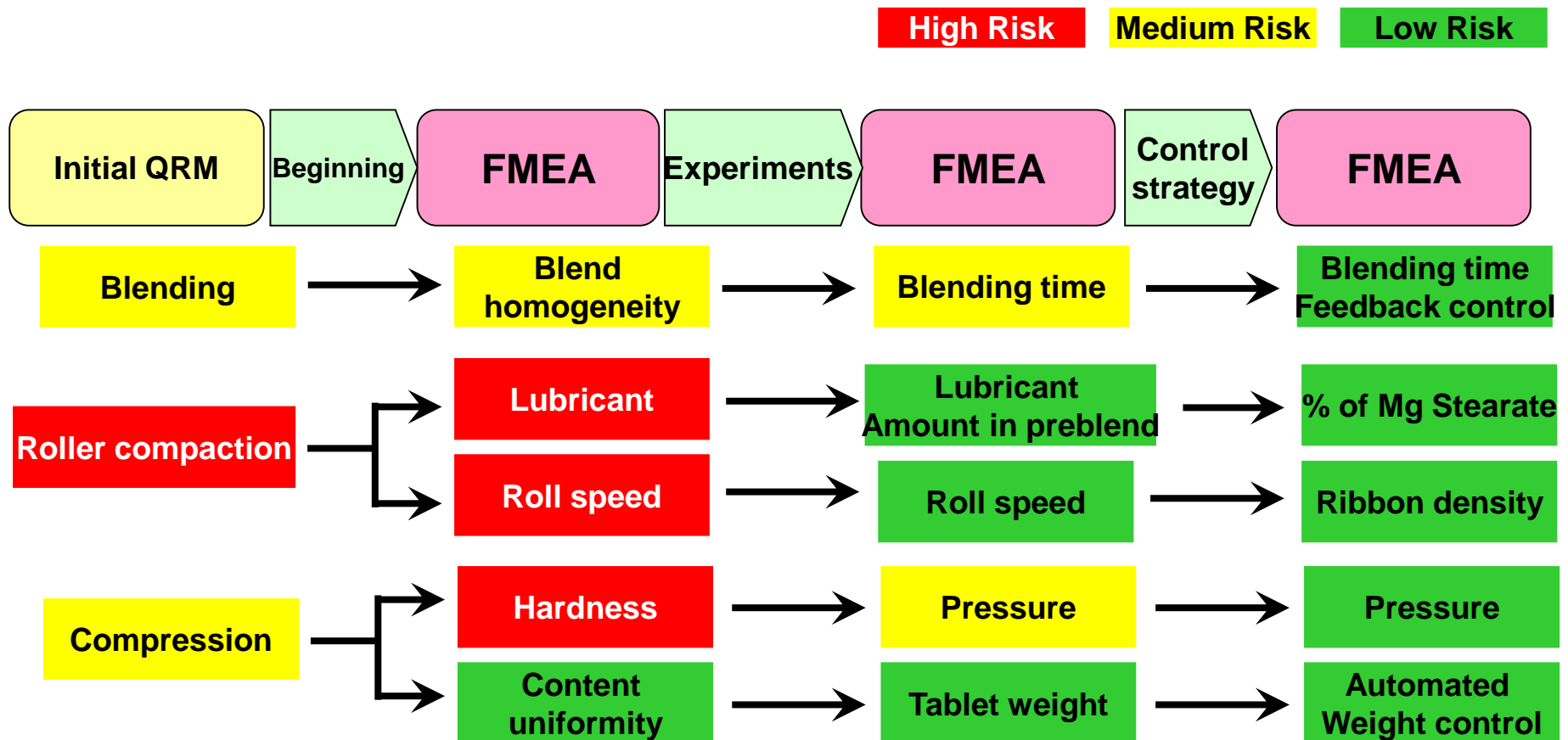




# Overall Risk Assessment for Process

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*
BU	Pre-Mix	H
	Roller compaction	M
	Milling	M
	Final Blending	M
Content Uniformity	Pre-Mix	L
	Roller compaction	H
	Milling	H
	Final Blending	M
	Compression	L
		L
Assay/Stability	Pre-Mix	L
	Roller compaction	
	Milling	
	Final Blending	
	Compression	
Dissolution	Pre-Mix	H
	Roller compaction	
	Milling	
	Final Blending	
	Compression	
Microbial Contamination	Pre-Mix	L
	Roller compaction	L
	Milling	L
	Final Blending	L
	Compression	L

# Iterative Risk Assessment for Process



# Multi-layer Tablets

- Rationale for multi-layer tablet and compatibility of layers
- Selection of manufacturing processes for granules in each layer;
- Adjustment of tablet weight - individual layers could be large;
- Optimization of formulation and manufacturing process
  - Disintegrant and lubricant levels
  - Blending time and moisture content of final blend
  - Tablet hardness
- Selection of dissolution method and medium
- Possible scale-up issues: Delamination potential

# MR - Process Considerations

- **Functional coating**
  - Weight gain during coating
  - Amount of solids in the coating dispersion
  - Distance between spray gun and tablet bed
  - Spray rate and pattern
  - Spray atomizing pressure
  - Pan Speed
  - Inlet air temperature
  - Inlet and outlet air flows
  - Tablet-bed temperature
  - Homogeneity of coating
  - Limit on oversized and fines for various coating layers
- **Matrix design**
  - Similar considerations as IR products (blending, granulation, compression)

# SUPAC: Manufacturing Process Changes

- Changes to parameters (e.g. mixing times, operating speeds) **within** application/validation ranges
- Changes to parameters (e.g. mixing times, operating speeds) **outside** application/validation ranges
- **Change in the type of process**, such as from granulation technique to direct compression of dry powder

# SUPAC: Manufacturing Equipment Changes

- Change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients
- Change to alternate equipment of the **same design and operating principles** of the same or of a different capacity.
- Change to equipment of **different design and different operating principles**

# What to Submit for Processes

- Process selection rationale
- Manufacturing process description
- Identification of high risk unit operations
- Comprehensive control strategy
- A table comparing process parameters, equipment's, in-process controls between batches manufactured across different scales
- Objective controls for processes
- Non-ambiguous instructions in batch records
- Scale up information

# Process Parameters and In-process Controls for Robust Manufacture

- Extremely important to ensure process remains under the state of control
- Increase in process understanding
- Designing a robust process & product

One of the most frequently cited deficiency for IR or MR products relates to lack of adequate in-process controls



# Summary



# Acknowledgements

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Please evaluate this session:

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