Small Molecule Case Studies

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Learning Objectives

Provide insight into chemistry, manufacturing and controls assessment concerning:

- Risk assessment
- Development data
- Facilities and equipment

Poll Question:

What is the most challenging aspect of creating your chemistry, manufacturing and controls (CMC) section of your application?

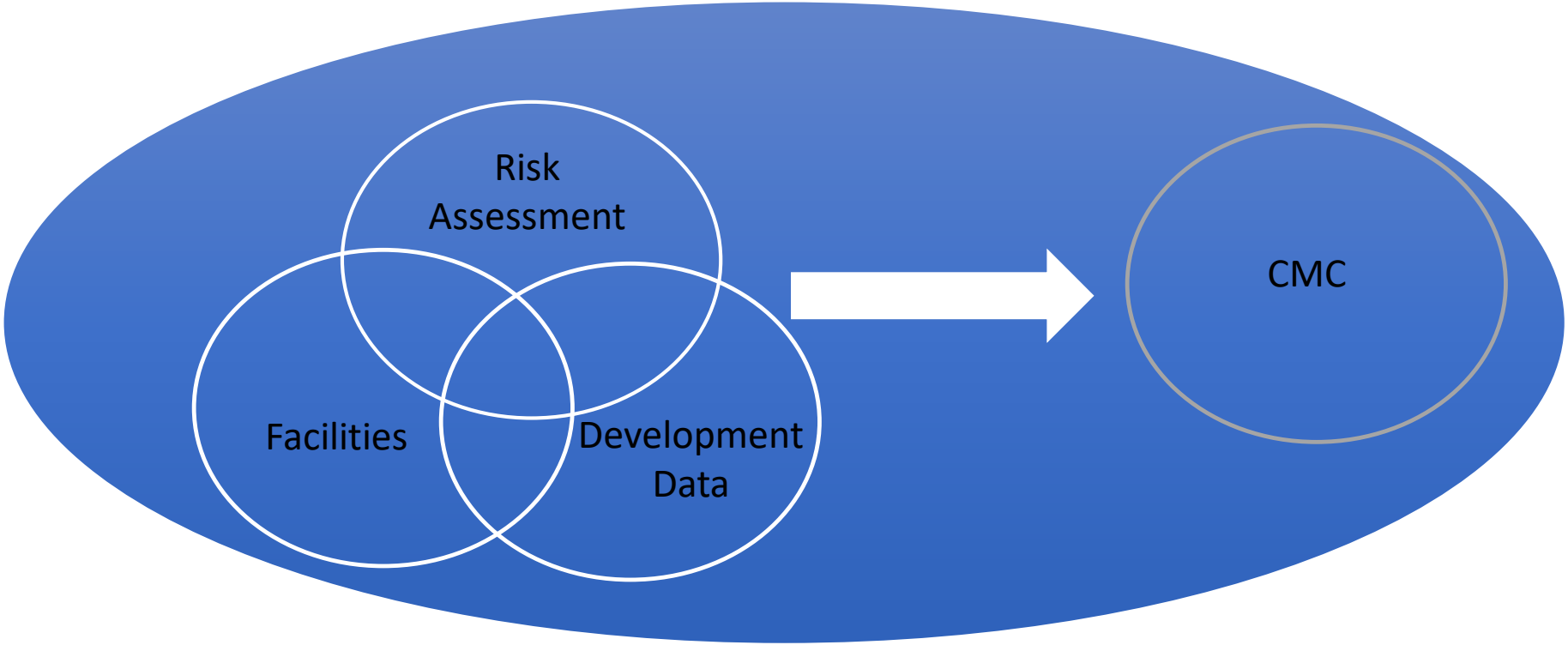
A. **Development data**

B. **Risk assessment**

C. **Critical Process Parameters**

D. **Acceptance Criteria**

Application Chemistry, Manufacturing and Controls Assessment



Case Study #1: Lozenge

- Low drug load
- Dry blending/Direct compression
- Facility has no history for dry blending or compression operations

Initial Risk Assessment

Unit Operation	Critical Quality Attribute	Process Risk	Facility Risk	Considerations
Pre-lubrication	• Assay • Blend Uniformity	Medium	High	• Low drug load • No dry mix process experience • No tablet experience • No observations for 2 previous inspections • No quality defects
Lubrication	• Assay • Blend Uniformity	Medium	High	
Compression	• Assay • Content Uniformity • Dissolution	High	High	• No compression experience • Compression equipment never been inspected

Critical Material Attributes

- Drug Substance
  - Poor flowability
  - Hygroscopic
  - 3-tier particle size distribution controlled
- Excipient (85% of tablet)
  - Good flowability
  - 3-tier particle size distribution

Blending Development

- Critical process parameters defined
  - Mixing speed and time
- Data included % occupancy

Blending Development

- Data not summarized
- Blend uniformity data not robust

Compression

- Critical process parameters defined
  - Speed, pre-compression and main compression forces defined
- Content uniformity via stratified sampling

Compression

- Process parameters adjusted for exhibit batches
- Pre-compression force not sufficient to produce passing tablets

Pre-approval Inspection Decision?

- Good inspectional history
- No quality defect signals
- No experience with proposed manufacturing operations

Assessor recommended a PAI

Lessons Learned

- Organize and summarize development data
- Development data should support controls
- Include deviation and failure investigations

Case Study #2: Capsule

- Prompt-release
- Drug-coated sugar spheres
- Facility has experience with capsules

Initial Risk Assessment

Unit Operation	Critical Quality Attribute	Process Risk	Facility Risk	Considerations
Drug solution mixing	Assay	Low	High	• Low drug load • Inspectional history • Quality defect signals
Drug Coating	Assay	High	High	• Critical process parameters
Drying	Related substances	Low	High	• Parameters based upon experience
Encapsulation	Assay Content Uniformity	Medium	High	• Critical process parameters

Critical Material Attributes

- Drug Substance
  - Solubility - highly soluble in water

Drug coating development

- Critical process parameters defined (DOE)
  - product temperature, air flow, atomization air pressure and spray rate
- In-process controls

Drug coating development

- Critical process parameters ranges not used in exhibit batches
- Spray rate appeared to be wide

Encapsulation

- Critical process parameter
  - Machine speed
- In-process controls
  - Target capsule weight
  - Weight variation of capsule content
  - Average weight of the empty capsule
  - Capsule locking length

Pre-approval Inspection Decision?

- Recent inspection covered high risk operation
- Quality defect signals

Assessor did not recommended a PAI

Lessons Learned

- Exhibit batch process parameters should match development conclusions
- Is “for information only” data a control?
- Provide justification

Call to Action

- Consider your operation holistically
- Ensure decisions are science-based
- Summarize your development data

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Challenge Question #1

What are the three 3 fundamental questions used to define risk for risk assessment purposes?

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Challenge Question #2

What is the aim of pharmaceutical development?

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product.