How to Identify Critical Quality Attributes and Critical Process Parameters

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Outline

- Brief introduction on Quality by Design (QbD)
- Example approach to identify critical quality attributes (CQA)
- Example approach to identify critical material attributes (CMA) and critical process parameters (CPP)
- Illustrative examples
- Concluding remarks

What is Quality by Design (QbD)?

- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8 R2)

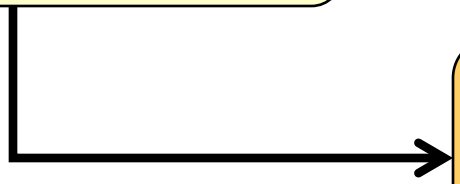
	Systematic Approach
Predefined objectives	▪ Define Quality Target Product Profile (QTPP) ▪ Identify Critical Quality Attributes (CQA)
Product and process understanding	▪ Identify critical material attributes (CMA*) and critical process parameters (CPP) ▪ Establish the functional relationships that link CMA/CPP to CQA
Process control	▪ Develop appropriate Control Strategy, including justifications
Sound science	▪ Science-driven development (scientific literature, prior knowledge, DOEs etc.)
Quality risk management	▪ Risk-based development (ICH Q9)

** CMA definition will be given later.*

What is a Quality Target Product Profile (QTPP)?

ICH Q8(R2) Definition: A **prospective** summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy.

TPP: labeled use, safety and efficacy



QTPP: quality characteristics to ensure safety and efficacy as promised in the label

Guidance for Industry
Q8, Q9, & Q10 Questions and Answers

The Quality Target Product Profile (QTPP) provides an understanding of what will ensure the quality, safety, and efficacy of a specific product for the patient

EXAMPLE QTPP

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

QbD for ANDAs: An Example for IR Dosage Forms. April 2012.
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM304305.pdf

Points to Consider
Guide for ICH Q8/Q9/Q10 Implementation

The Quality Target Product Profile (QTPP) describes the design criteria for the product, and should therefore form the basis for development of the CQAs, CPPs, and control strategy.

Definitions

- Critical Quality Attributes (CQA)
  - 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 (ICH Q8)
- Critical Process Parameter (CPP)
  - A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)
- *Critical Material Attribute (CMA)**
  - *A physical, chemical, biological or microbiological property or characteristic of an **input material** that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.*

*CMA is not defined in ICH guidance, but used here for discussion purposes

Approach to Identify CQAs

1. Consider all DP quality attributes; physical attributes, identification, assay, content uniformity, dissolution and drug release, degradation products, residual solvents, moisture, microbial limits, etc.
2. Identify a CQA based on the **severity of harm** to a patient (safety and efficacy) resulting from failure to meet that quality attribute.
   - Identified before taking into account risk control
   - Does not change as a result of risk management

EXAMPLE QTPP

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Drug product quality attributes	Physical Attributes Identification Assay Content Uniformity Dissolution Degradation Products Residual Solvents Water Content Microbial Limits	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients [illegible] organic solvent will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variability, so this CQA will be evaluated throughout product and process development.
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl [illegible] w/v SLS	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process [illegible] dissolution profile. This CQA [illegible] development.

Not a CQA

CQA

QbD for ANDAs: An Example for IR Dosage Forms. April 2012.

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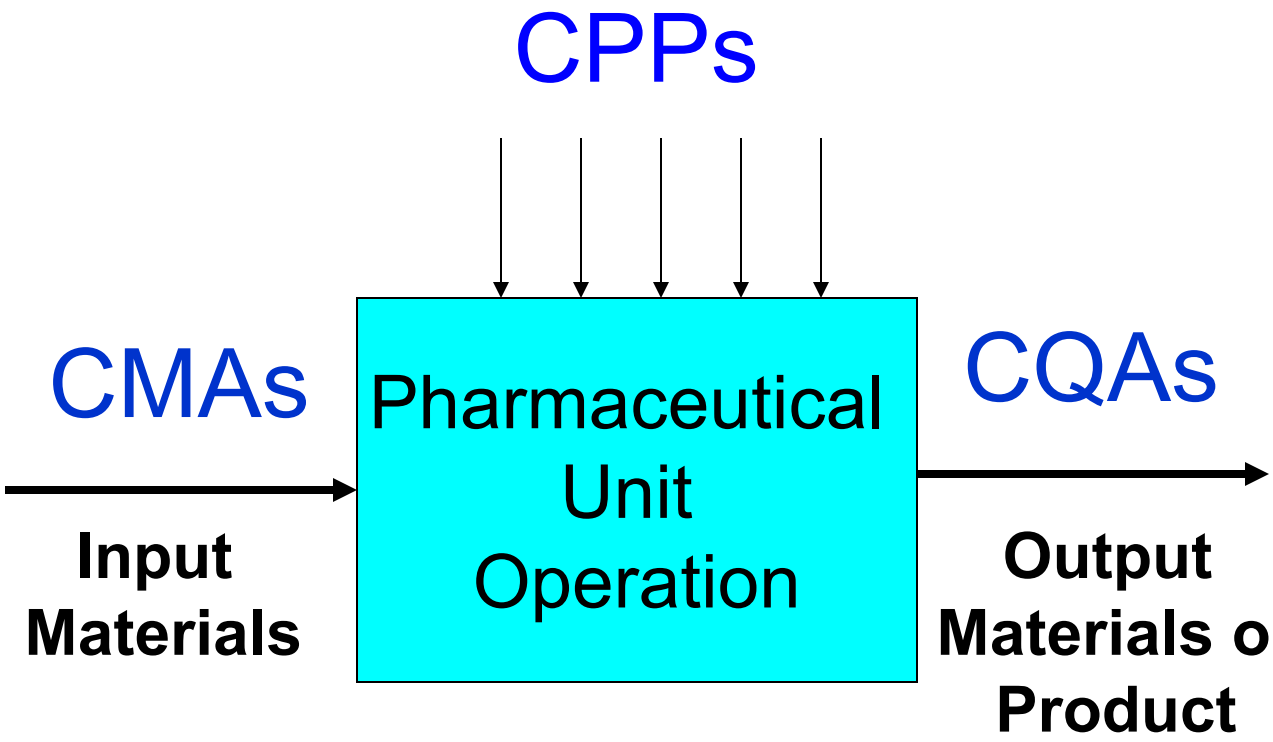
Relationship between CMAs, CPPs and CQAs



$$CQAs = f(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Linking Patient - Product - Process

Patient

Product

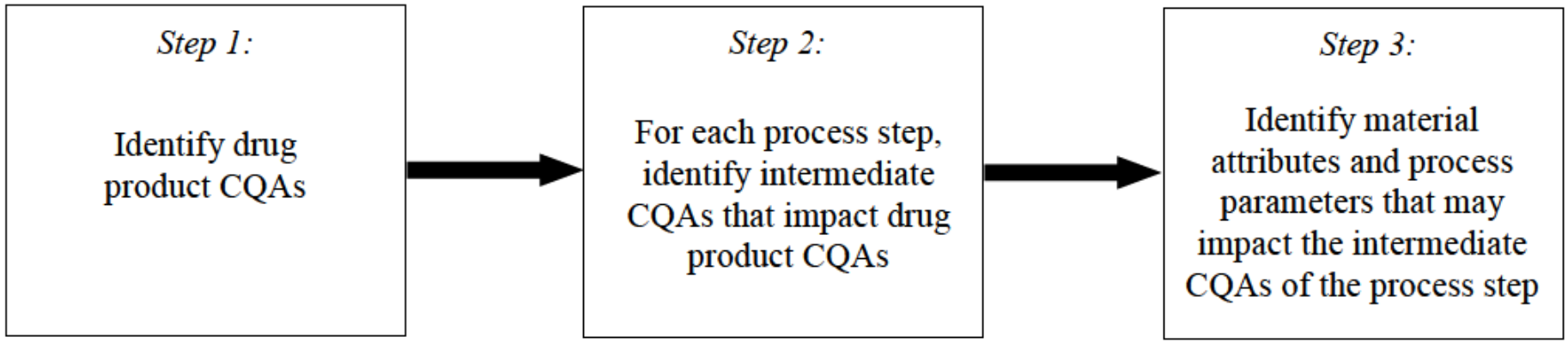
Formulation /Process

Clinical Outcome (Safety & Efficacy)

Critical Quality Attributes (CQA)

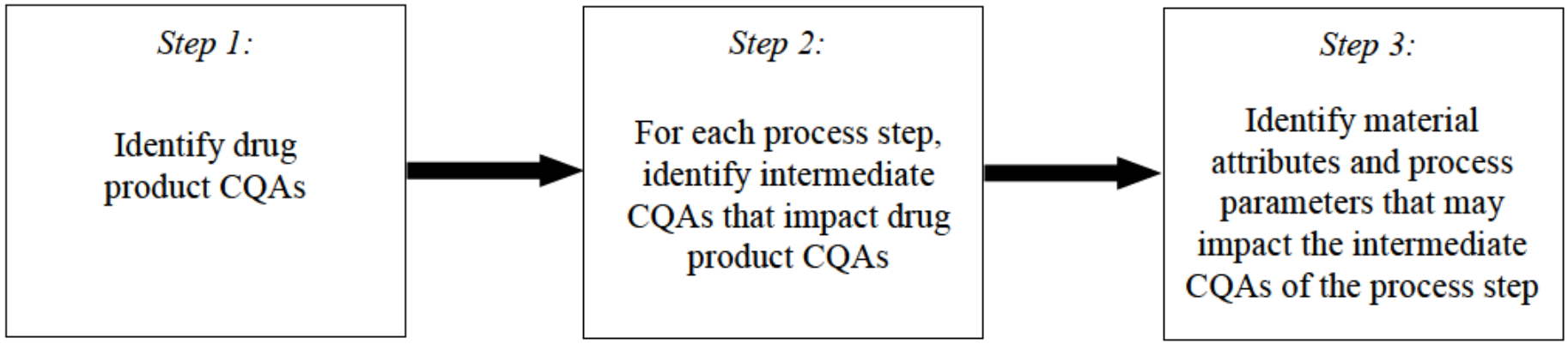
Critical Material Attributes (CMA)
Critical Process Parameters (CPP)

Example Approach to Identify Material Attributes and Process Parameters



Useful tools:
Risk assessment, prior knowledge, established science…..

Example Approach to Identify Material Attributes and Process Parameters



Drug Product CQAs:
Content Uniformity

→

Intermediate CQAs:
Blend Uniformity

→

Process Variables:
1. Particle size distribution
2. Loading level
3. Number of revolutions

Identifying Potentially High Risk MAs or PPs

Input material attributes	Process parameters	Quality attributes
	Blending/mixing	
• Particle size • Particle size distribution • Fines/oversize • Particle shape • Bulk/tapped/true density • Cohesive/adhesive properties • Electrostatic properties • Moisture content	• Type and geometry of mixer • Mixer load level • Order of addition • Number of revolutions (time and speed) • Agitating bar (on/off pattern) • Discharge method • Holding time • Environment temperature and RH	• Blend uniformity • Potency • Particle size • Particle size distribution • Bulk/tapped/true density • Moisture content • Flow properties • Cohesive/adhesive properties • Powder segregation • Electrostatic properties

- Special considerations for unique DS/DP properties
  - e.g. RH can be potentially high risk for a hygroscopic formulation

Yu et al, Understanding Pharmaceutical Quality by Design, *The AAPS Journal, 2014 , 16(4) 771- 783*

Example Approach to Determine Criticality

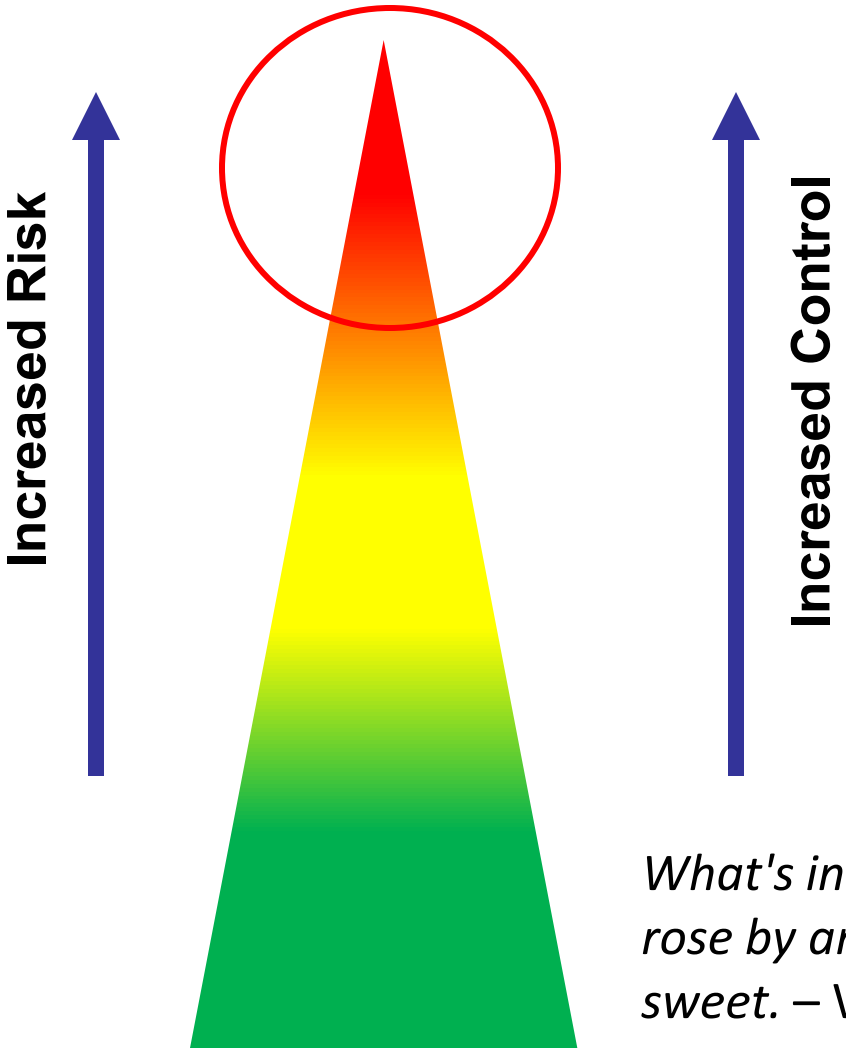
Once potentially high risk variables are identified:

- Identify levels or ranges of these potentially high risk attributes and/or parameters.
- Design and conduct experiments, using DOE when appropriate.
- Analyze the experimental data to determine if a material attribute or process parameter is critical.
  - If variability has an impact, then need to monitor and/or control
- Develop a control strategy.

Key Points from EMA-FDA QbD Pilot

- Pilot program aimed at a parallel assessment of CMC sections which are relevant to QbD
- The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality.
- Agencies are amenable to the applicant using their own terminology in the pharmaceutical development section to communicate development findings
- However, in the 3.2.P.3.3 “Description of the Manufacturing Process and Process Controls” and 3.2.P.3.4 “Control of Critical Steps and Intermediates” sections, the description of all parameters that have an impact on a CQA should be classified as critical.

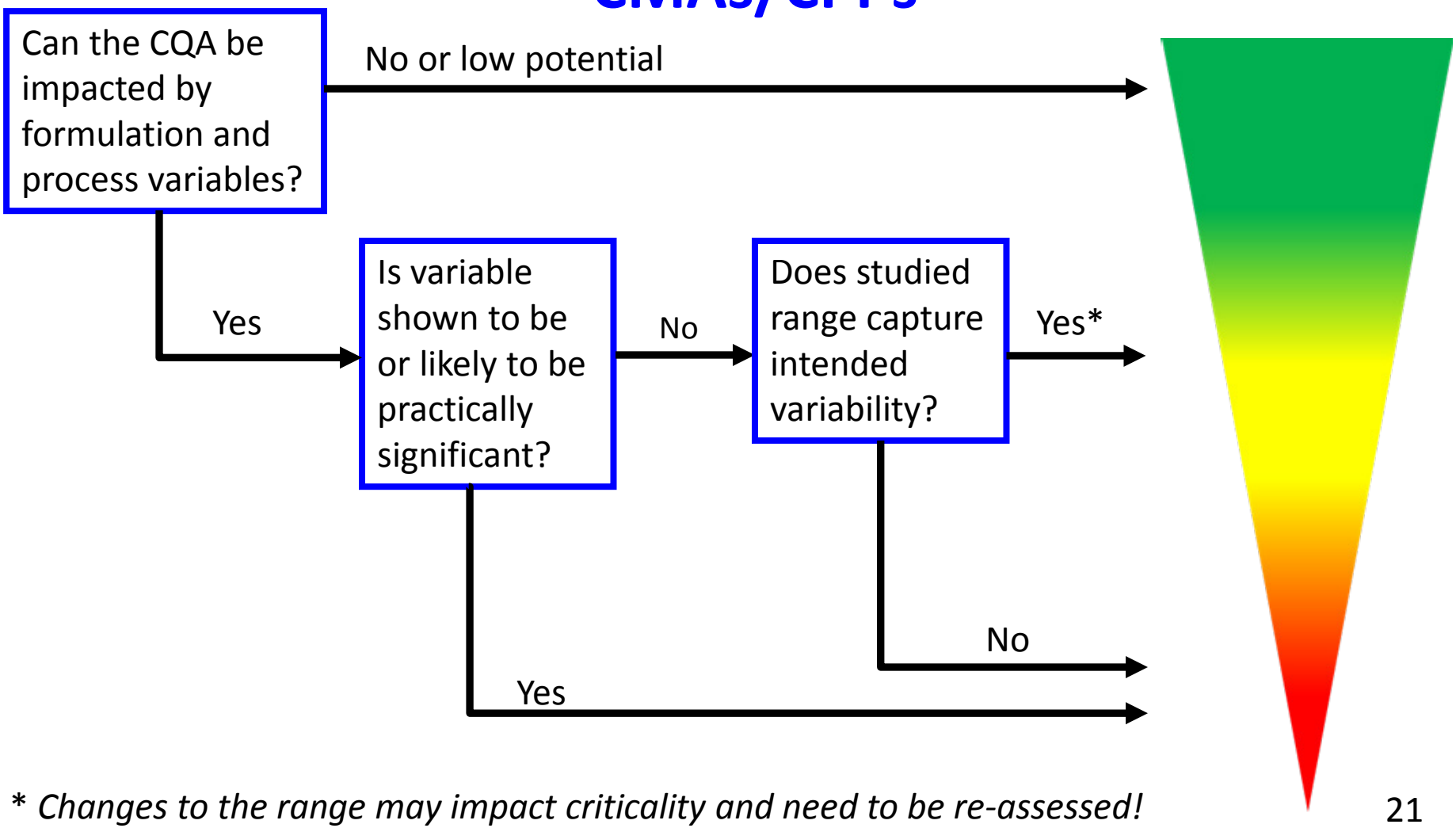
Criticality



1. Continuum
2. Focus on the vital few
3. The control strategy (the established range) is important
4. If underlying assumptions change, then criticality can change

What's in a name? That which we call a rose by any other name would smell as sweet. – William Shakespeare

Schematic Flow Diagram for Identification of CMAs/CPPs



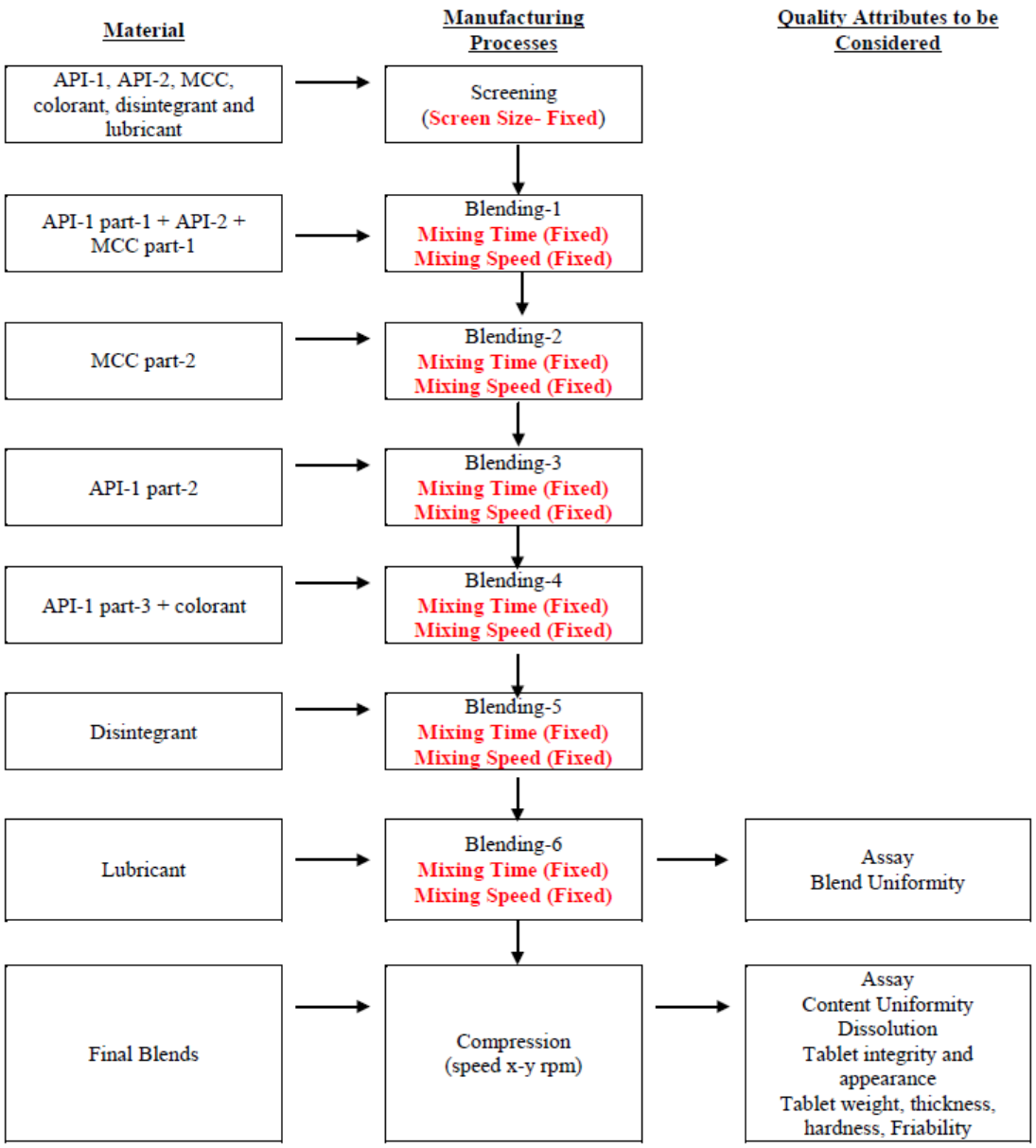
* *Changes to the range may impact criticality and need to be re-assessed!*

Illustrative Examples

Example-1

- A fixed-dose combination IR tablet:
  - API-1: ~80% of the tablet weight
  - API-2: ~1% of the tablet weight
  - Diluent (microcrystalline cellulose): ~ 14% of the tablet weight
  - Other excipients: disintegrant, colorant, and lubricant
  - Content Uniformity (CU) of API-2 is a high risk CQA

Process Flow Diagram



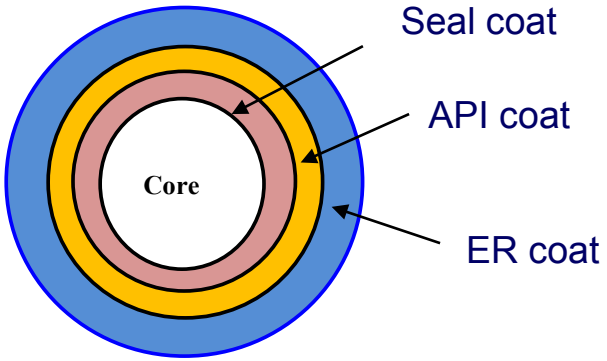
Process Understanding and Control

- Process understanding:
  - Ranked all blending steps as medium risk; hence, no development study was conducted
  - Provided testing results of one lab scale batch (4-quart V-blender, 1.2 kg) and exhibit batch (20 cu. ft. 184 kg)
- Applicant's control strategy: fix all MAs and PPs for all blending steps
- Agency's comment: All MAs and PPs are **potentially critical** due to limited characterization of the sources of variability and inadequate understanding of the impact of CMAs and CPPs on the drug product CQAs

Knowledge is power ! - Francis Bacon

Example -2

- An Extended–Release (ER) Capsule
- API: 100 mg
  - highly soluble, excellent chemical stability, no polymorphism
- Manufacturing Process:
  - Seal-coated sugar sphere core
  - API coated pellets
  - **ER polymer coated pellets**
  - Encapsulation and packing
- Dissolution is a high risk CQA



ER Polymer Layer Formulation

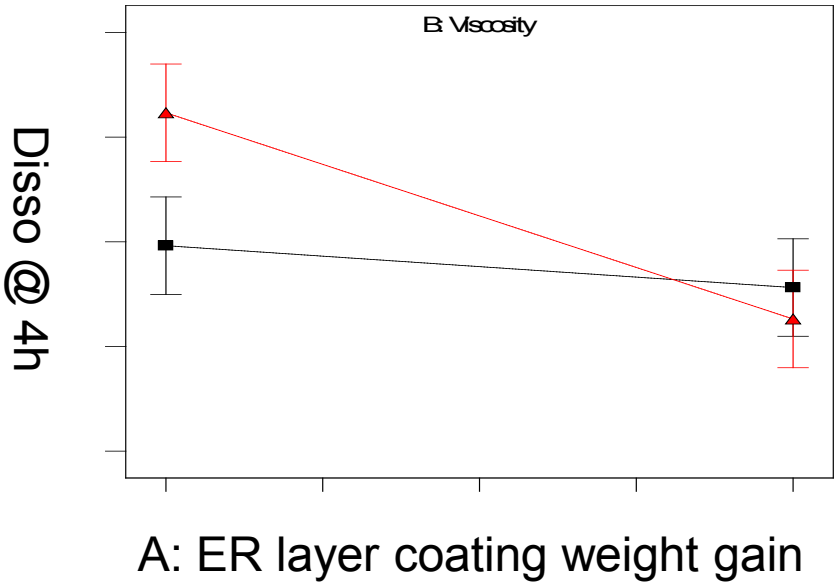
- ER polymer layer:
  - Polymer-1 (release controlling, water insoluble)
  - Polymer-2 (pore former, water soluble)
  - Plasticizer B
  - Colorant
- Formulation feasibility studies
  - Trial with IR pellets + ER pellets (abandoned)
  - Effect of Polymer 1 viscosity
  - Effect of Polymer 2 type
  - Effect of plasticizer type: Plasticizer A vs. B (hydrophobic vs. hydrophilic)

Formulation Optimization

- One-factor-at-a-time (OFAT) approach
  - Polymer-2 quantity
  - Polymer-2 viscosity
  - ER layer coating weight gain
- Applicant's conclusion: No impact on dissolution; hence, these factors are not critical
- Agency's comments: Any interaction? How's the range justified? Coating process variability?

Further Studies

- ER layer coating weight gain and Polymer-2 viscosity have strong interaction.
- Both factors are critical!
- Control strategy:
  - Using fixed amount of Polymer-1 and Polymer-2
  - Tighten the Polymer-2 viscosity to the studied ranges instead of compendial limits



Don't use insufficiently powered studies to force a favorable conclusion of non-criticality. The narrow range of 'non-critical process parameter' is still potentially critical.

Example-3

- Oral IR tablet: EQ 5mg base
- API loading: ~4%
- Diluents: microcrystalline cellulose (~60%) and lactose monohydrate (~30%)
- Other excipients: disintegrant and lubricant
- Manufacturing Process:
  - blending, milling, blend lubrication
  - roller compaction and milling, blend lubrication
  - compression and aqueous based film coating
- Content Uniformity is a high risk CQA

Summary of MAs and PPs Evaluated

Focus Area	Unit Operation	Parameters	Measured Attributes	Study Scale and Type
1	Blend	Drug substance particle size	Uniformity of dosage units [a]	Small scale multivariate; Multivariate modeling; Pilot/production scale confirmation (univariate)
		Bin load		
		Blender revolutions		
2	Mill	Mill screen size		Small scale univariate; Pilot/production scale univariate
		Mill speed		
3	Lubrication Blend	Blender revolutions		Small scale multivariate
4	Roller Compact /Mill	Roll force	Ribbon solid fraction Granule particle size distribution Granule compactibility	Small scale multivariate; Pilot/production scale confirmation (univariate)
		Gap width		
		Roll speed		
		Mill screen size		
5	Lubrication Blend	Blender revolutions	Uniformity of dosage units [a]	Small scale multivariate
6	Compression	Compression force	Uniformity of dosage units Tablet core hardness Tablet core friability Tablet core weight variability Tablet core disintegration Tablet core dissolution Punch sticking potential	Small scale multivariate; Pilot/production scale confirmation (univariate); Multivariate modeling for Uniformity of dosage units;
		Dwell time		
7	Film Coating	Pan load	Tablet appearance Tablet water content	Pilot/production scale multivariate and univariate; Multivariate thermodynamic modeling; Image analysis modeling
		Spray rate		
		Exhaust Air temperature		
		Coating weight gain		

Process Development

Table 3.2.P.2.3-6 Summary of Initial Mixing Process Studies (FA1-FA3)

Table 3.2.P.2.3-7 Summary of 2^{12-8} Multivariate Study Design

Table 3.2.P.2.3-8 Summary of 2^{5-2} Roller Compaction Multivariate Study

Table 3.2.P.2.3-11 Summary of the 2^{5-1} Multivariate Study for Roller Compaction (FA4)

Table 3.2.P.2.3-14 Summary of 2^{4-1} Compression Multivariate Study

Process Step (Focus Area)	Parameter	Measured Attributes at Various Compression Force Levels
Roller Compact and Mill (FA4)	Ribbon Solid Fraction: x – y	Compression Profile Tablet core properties Hardness Thickness Solid Fraction Friability Disintegration Dissolution (selected runs)
	Mill Screen Size: x – y mm	
Lubrication Blend (FA5)	Lubrication Time: x – y min	
Compression (FA6)	Dwell Time: x – y ms	

So What is Critical?

- The applicant's conclusion:
  - No critical process parameters, intermediates or process steps have been identified within the ranges studied during development.
- The Agency did not focus so much on the terminology, but…
- Paid a lot of attention to the studied ranges and verified if these ranges are captured in the control strategy, process description, and master batch record….

Control Strategy

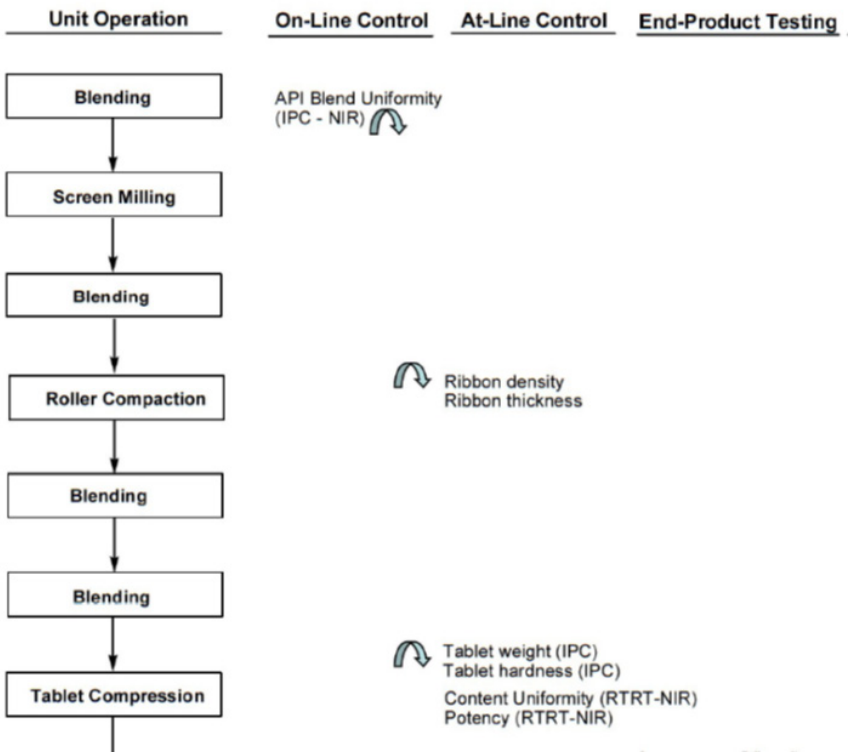
Process Step (Focus Area)	Process Parameters					Related Key/Critical Attributes
	Equipment Used	Parameter Studied	Range Studied	Target	Designation	
Formulation – Input Material		Drug Substance Particle Size Distribution (µm)				Uniformity of Dosage Units (CQA)
Blending (FA1)	Diffusion Mixer	Bin Loading (%)				
		Blend Revolutions				
Milling (FA2)	Screening Mill	Mill Screen Opening Size (mm)				Uniformity of Dosage Units (CQA)
		Impeller Tip Speed, (m/min)				
Intragranular Lubrication Blend (FA3)	Diffusion Mixer	Bin Loading (%) [a]				
		Blend Revolutions				
Dry Granulating and Mill (FA4)	Roller Compactor and Screening Mill (Gerteis)	Roll Force (kN/cm)				Ribbon Solid Fraction (KQA) Granule Particle Size (KQA) Max. Tablet Hardness (KQA)
		Gap Width (mm)				
		Mill Screen Size (mm)				Granule Particle Size (KQA)
		Roll Speed (rpm)				
Extragranular Lubrication Blend (FA5)	Diffusion Mixer	Bin Loading (%) [a]				
		Blend Revolutions				
Compression (FA6)	Tablet Press	Compression Force (kN) (Based on tablet hardness)				
		Compression Speed (dwell time) (ms)				
Film Coating (FA7)	Pan Coater	Pan Fill (%) [b] (GC1500 Pan Load in kg)				
		Exhaust Air Temperature (°C)				Tablet Water Content (KQA)
		Exhaust Air Humidity (%)				
		Coating Weight Gain (%)				

** Changes to the range may impact criticality and need to be re-assessed!*

Example-4

- Oral IR tablet: 2.5 mg and 5 mg
- Drug substance: BCS high solubility, non-hygroscopic, only one crystalline form known, excellent chemical stability
- API loading: 2.4%
- Diluents: microcrystalline cellulose (~40%) and lactose monohydrate (~50%)
- Other excipients: disintegrant, wetting agent, and lubricant
- Manufacturing Process:
  - blending, screening, lubrication, roller compaction, milling, blending and lubrication, compression, and film-coating
- Content Uniformity is a high risk CQA

Process Understanding and Control Strategy

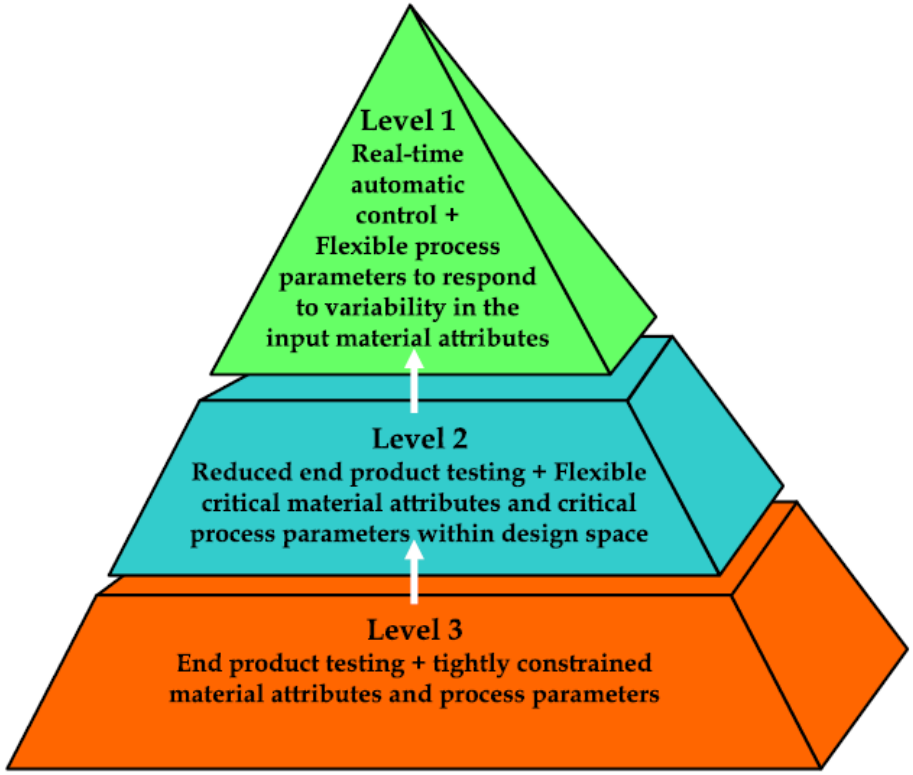


- In-line NIR method to determine BU and blending endpoint
- At-line NIR method for tablet Assay and CU (Large N)
- Other traditional in-process controls: ribbon density, ribbon thickness, core tablet weight & hardness

So What is Critical?

- Flexible for input material attributes and process parameters
- Agency looked carefully at the NIR method, model development, validation, lifecycle maintenance plan
- The established NIR method, instrument details, spectral acquisition and sampling, spectral data processing, calculation/reporting and the acceptance criteria are included in P.3.4 "*Controls of Critical Steps and Intermediates*".

Impact on Post-Approval Changes



Control Strategy Implementation Options

- Level 1: **flexible** input material attributes and process parameters; **real-time automatic controls** assure that CQAs consistently conform to the established acceptance criteria
- Level 2: flexible material attributes and process parameters **within** the established design space
- Level 3: **any significant change** in these MAs and PPs warrants regulatory oversight

Yu, et al. Understanding Pharmaceutical Quality by Design, The AAPS Journal, 2014, 16(4): 771-783

Concluding Remarks

- Systematic approach, begin with the end in mind
- Identify CQAs based on patient's needs: **safety and efficacy**
- Use **science- and risk-based approach** to identify material attributes and/or process parameters that may impact CQAs
- Prioritize development studies and focus on the **vital few potentially high risk** material attributes and process parameters
- Establish an appropriate **control strategy**
- Consider discussing **lifecycle management plans**

Acknowledgements

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Thank You for Your Attention!