Implementation of ICH Q8, Q9, Q10

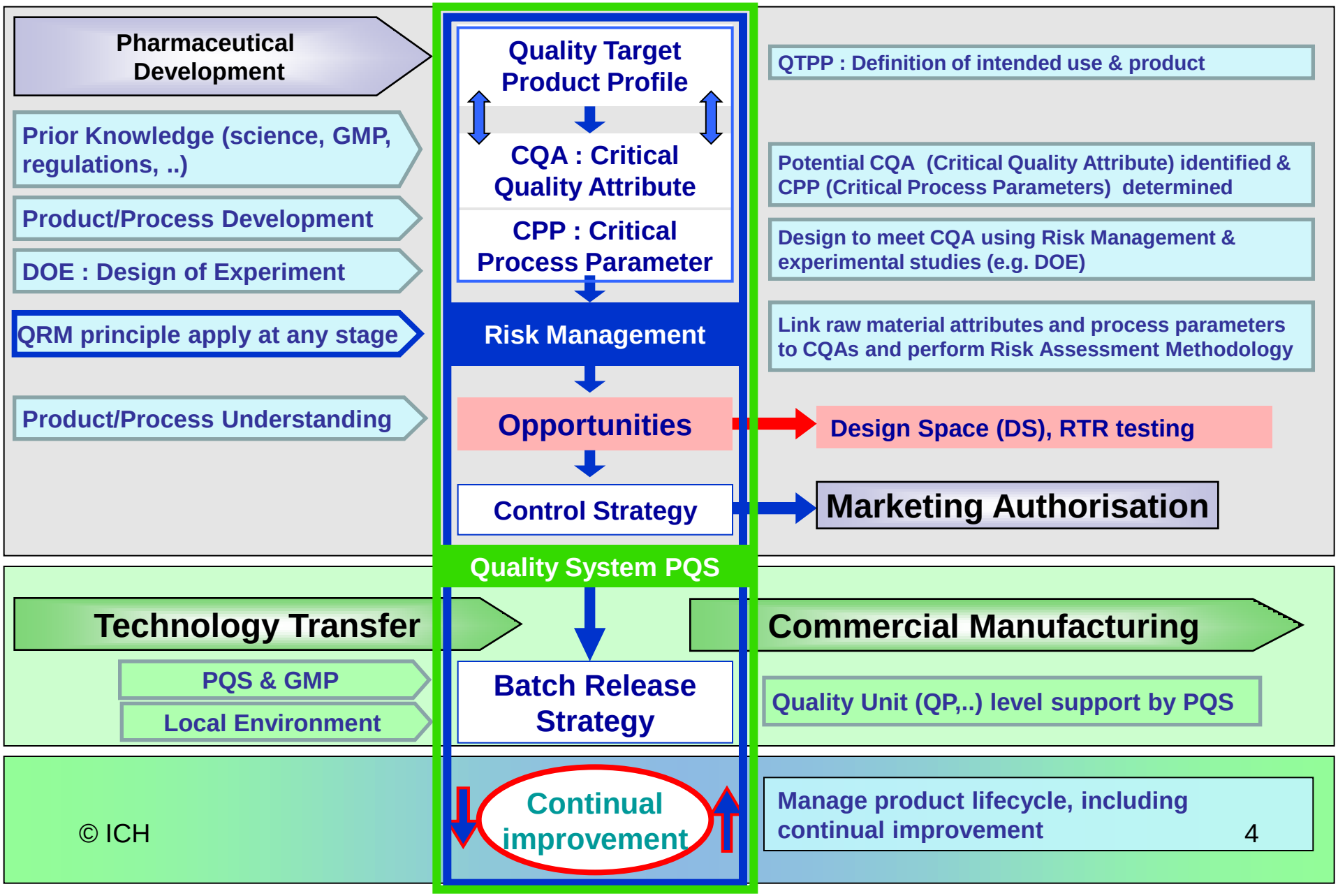
Product Development: Case Study Overview

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Outline of Presentation

- Key Steps for Quality by Design
- Case Study Organization
- Introducing API and Drug Product
  - Discussion of concepts of Quality Target Product Profile, processes, composition
- Description of API & Drug Product process development
  - Discussion of illustrative examples of detailed approaches from the case study
- Batch release

Key Steps for a product under Quality by Design (QbD)



Purpose of Case Study

- **Illustrative example**
  - Covers the concepts and integrated implementation of ICH Q8, 9 and 10
  - Not the complete content for a regulatory filing

Note: *this example is not intended to represent the preferred or required approach.*

Case Study Organization

Basis for Development Information

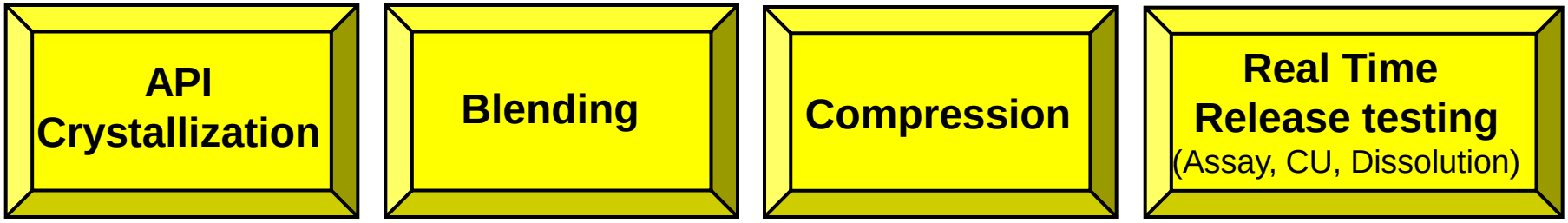
- Fictional active pharmaceutical ingredient (API)
- Drug product information is based on the ‘Sakura’ Tablet case study
  - Full Sakura case study can be found at http://www.nihs.go.jp/drug/DrugDiv-E.html
- Alignment between API and drug product
  - API Particle size and drug product dissolution
  - Hydrolytic degradation and dry granulation /direct compression

Organization of Content

- Quality Target Product Profile (QTPP)
- API properties and assumptions
- Process and Drug product composition overview
- Initial risk assessment of unit operations
- Quality by Design assessment of selected unit operations

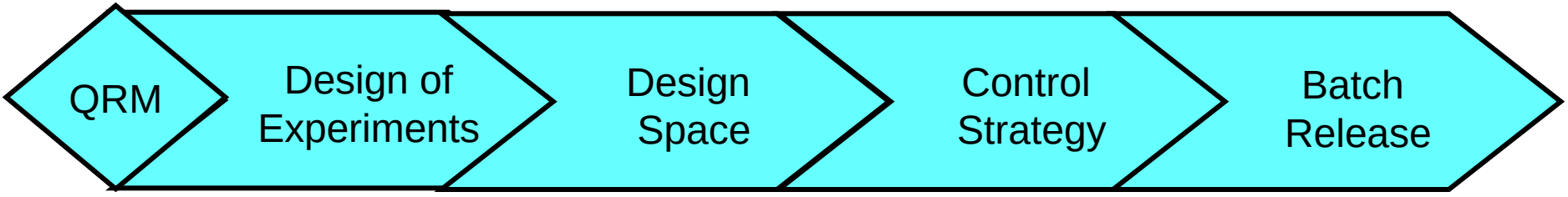
Technical Examples

	Process focus	Quality attribute focus
• API	- Final crystallization step	- Particle size control
• Drug Product	- Blending - Direct compression	- Assay and content uniformity - Dissolution

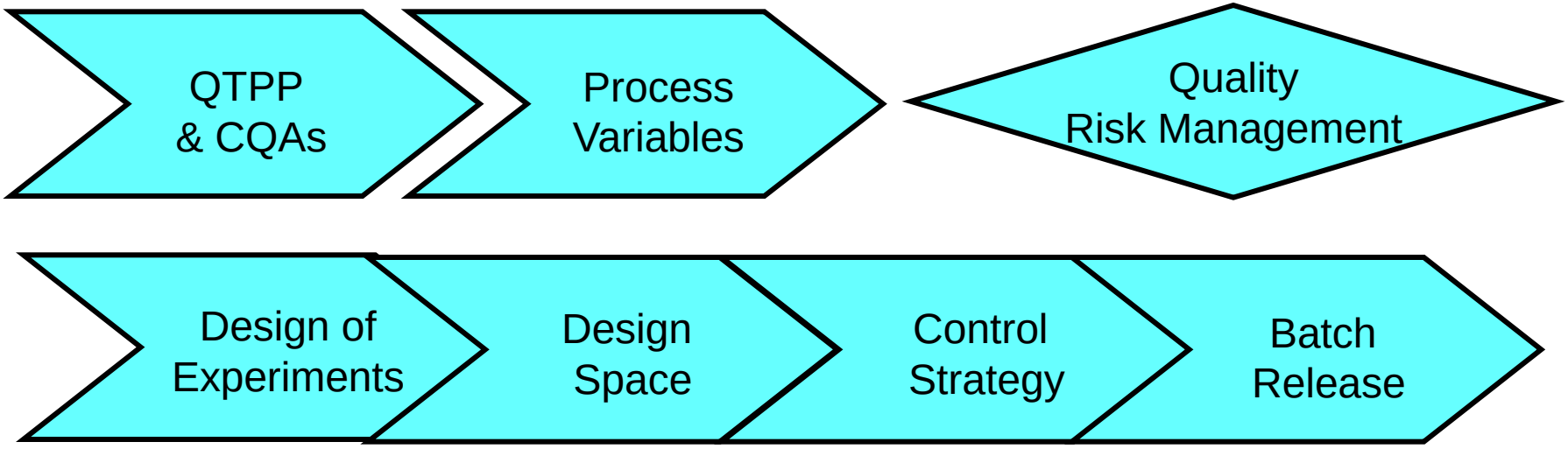


Process Step Analysis

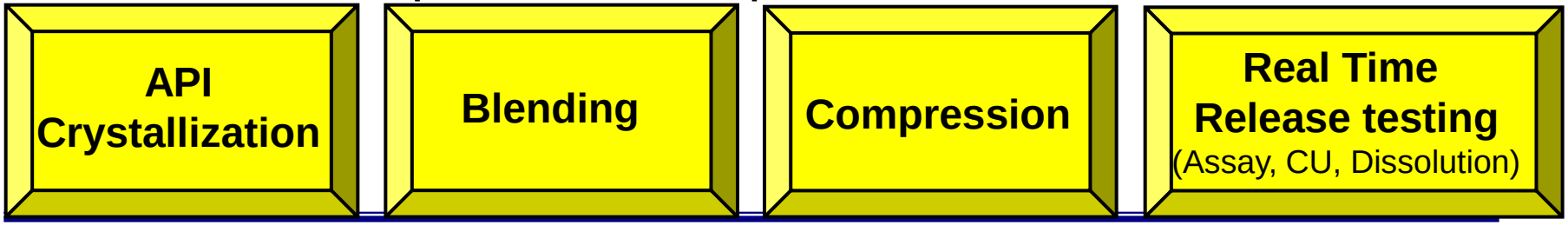
- For each example
  - Risk assessment
  - Design of experiments
    - *Experimental planning, execution & data analysis*
  - Design space definition
  - Control strategy
  - Batch release



QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



Introducing API and Drug Product

Assumptions

- API is designated as Amokinol
  - Single, neutral polymorph
  - Biopharmaceutical Classification System (BCS) class II – low solubility & high permeability
  - API solubility (dissolution) affected by particle size
  - Degrades by hydrolytic mechanism
- In vitro-in vivo correlation (IVIVC) established – allows dissolution to be used as surrogate for clinical performance
- Drug product is oral immediate release tablet

Assumptions & Prior Knowledge

- API is designated as Amokinol
  - Single, neutral polymorph
  - Biopharmaceutical Classification System (BCS) class II – low solubility & high permeability
  - API solubility (dissolution) affected by particle size
    - Crystallization step impacts particle size
  - Degrades by hydrolytic mechanism
    - Higher water levels and elevated temperatures will increase degradation
    - Degradates are water soluble, so last processing removal point is the aqueous extraction step
    - Degradates are not rejected in the crystallization step
- In vitro-in vivo correlation (IVIVC) established – allows dissolution to be used as surrogate for clinical performance
- Drug product is oral immediate release tablet

Quality Target Product Profile (QTPP)

Safety and Efficacy Requirements

Tablet	Characteristics / Requirements	Translation into Quality Target Product Profile (QTPP)
Dose	30 mg	Identity, Assay and Uniformity
Subjective Properties	No off-taste, uniform color, and suitable for global market	Appearance, elegance, size, unit integrity and other characteristics
Patient Safety – chemical purity	Impurities and/or degradates below ICH or to be qualified	Acceptable hydrolysis degradate levels at release, appropriate manufacturing environment controls
Patient efficacy – Particle Size Distribution (PSD)	PSD that does not impact bioperformance or pharm processing	Acceptable API PSD Dissolution
Chemical and Drug Product Stability: 2 year shelf life (worldwide = 30°C)	Degradates below ICH or to be qualified and no changes in bioperformance over expiry period	Hydrolysis degradation & dissolution changes controlled by packaging

QTPP may evolve during lifecycle – during development and commercial manufacture - as new knowledge is gained e.g. new patient needs are identified, new technical information is obtained about the product etc.

API Unit Operations

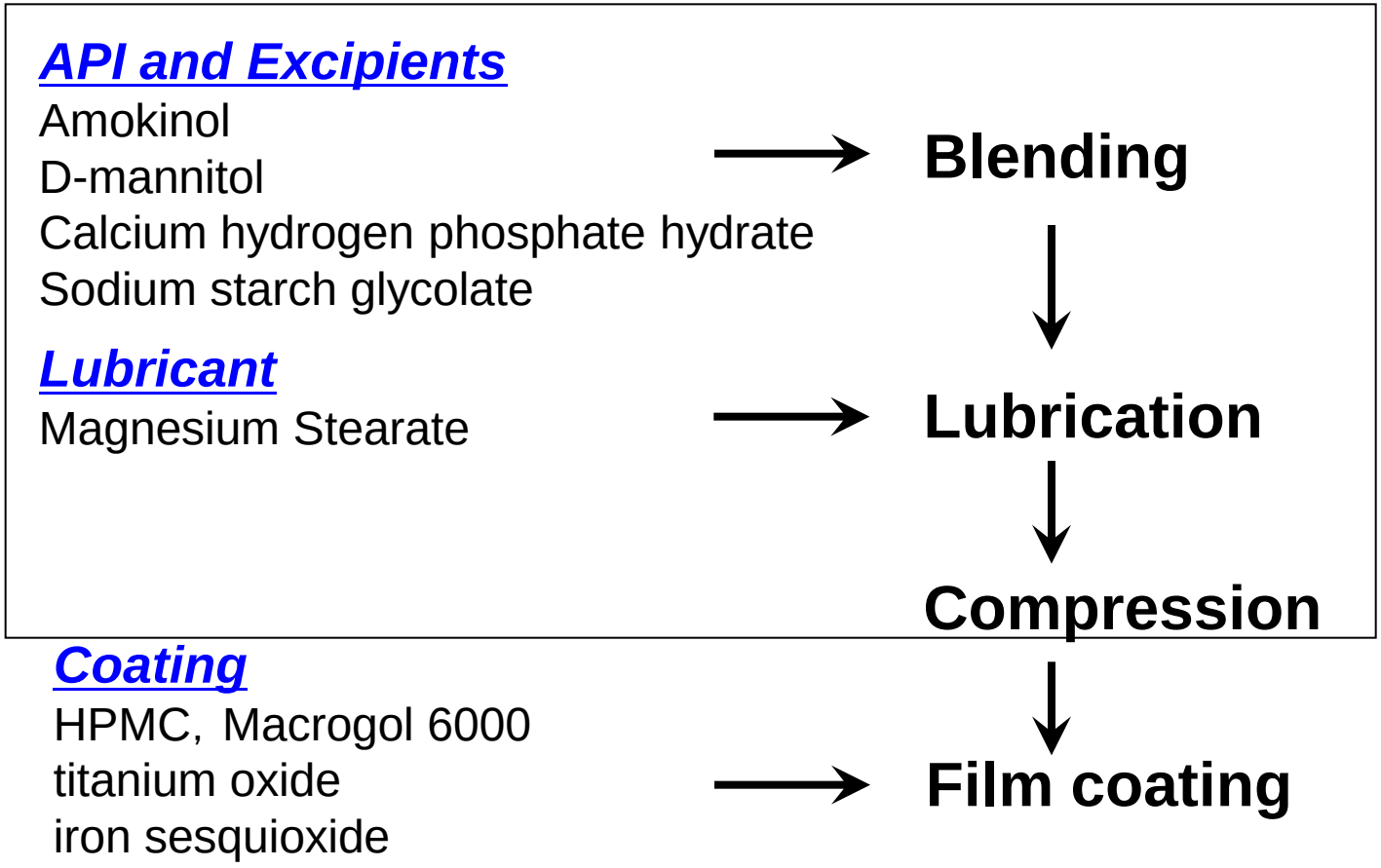
Understand formation & removal of impurities

Coupling Reaction	Coupling of API Starting Materials
Aqueous Extractions	Removes unreacted materials. Done cold to minimize risk of degradation
Distillative Solvent Switch	Removes water, prepares API for crystallization step
Semi Continuous Crystallization	Addition of API in solution and anti-solvent to a seed slurry
Centrifugal Filtration	Filtration and washing of API
Rotary Drying	Drying off crystallization solvents

Tablet Formulation

Function	Specification	Excipient	Sakura Tablet 30 mg
Active ingredient	Separate specification	Amokinol	30 mg / tablet (100 mg)
Excipient	Pharmacopoeial or other compendial specification	Calcium hydrogen phosphate hydrate	Appropriate amount
Excipient		D-mannitol	10 mg
Disintegrant		Sodium starch glycolate	5 mg
Lubricant		Magnesium stearate	2 mg
Coating agent		HPMC	2.4 mg
Polishing agent		Macrogol 6000	0.3 mg
Coloring agent		Titanium oxide	0.3 mg
Coloring agent		Iron sesquioxide	Trace amount

Drug Product Process



Overview of API and Drug Product Case Study Elements

Representative Examples from the full Case Study

Overall Risk Assessment for Process

- no impact to CQA
- known or potential impact to CQA
- current controls mitigate risk
- known or potential impact to CQA
- additional study required

* includes bioperformace of API, and safety(API purity)

CQA	Process Steps: Drug Substance						Process Steps: Drug Product					
	Coupling Reaction	Aqueous Extractions	Distillative Solvent Switch	Semi-Continuous Crystallization	Centrifugal Filtration	Rotary Drying	Manufacture Moisture Control	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance*												
Dissolution												
Assay												
Degradation												
Content Uniformity												
Appearance												
Friability												
Stability-chemical												
Stability-physical												

Product Development: Case Study Overview

Overall Risk Assessment for Process

- no impact to CQA
- known or potential impact to CQA
- current controls mitigate risk
- known or potential impact to CQA
- additional study required

* includes bioperformace of API, and safety(API purity)

Process Steps

CQA	Drug Substance						Drug Product					
	Coupling Reaction	Aqueous Extractions	Distillative Solvent Switch	Semi-Continuous Crystallization	Centrifugal Filtration	Rotary Drying	Manufacture Moisture Control	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance*												
Dissolution												
Assay												
Degradation												
Content Uniformity												
Appearance												
Friability												
Stability-chemical												
Stability-physical												

API Semi-Continuous Crystallization

- Designed to minimize hydrolytic degradation (degradate below qualified levels)
  - Univariate experimentation example
    - FMEA of crystallization process parameters
      - > High risk for temperature, feed time, water level
    - Test upper end of parameter ranges (represents worst case) with variation in water content only and monitor degradation
    - Proven acceptable upper limits defined for above parameters

Note that in this case study, the distillative solvent switch prior to crystallization and crystallization itself are conducted at lower temperatures and no degradation occurs in these steps

API Semi-Continuous Crystallization

- Designed to control particle size
  - Multivariate DOE example leading to predictive model
    - FMEA of parameters using prior knowledge
      - > High risk for addition time, % seed, temperature, agitation
    - DOE: half fraction factorial using experimental ranges based on QTPP, operational flexibility & prior knowledge
    - Design space based on predictive model obtained by statistical analysis of DOE data
- Particle size distribution (PSD) qualified in formulation DOE and dissolution studies

Product Development: Case Study Overview

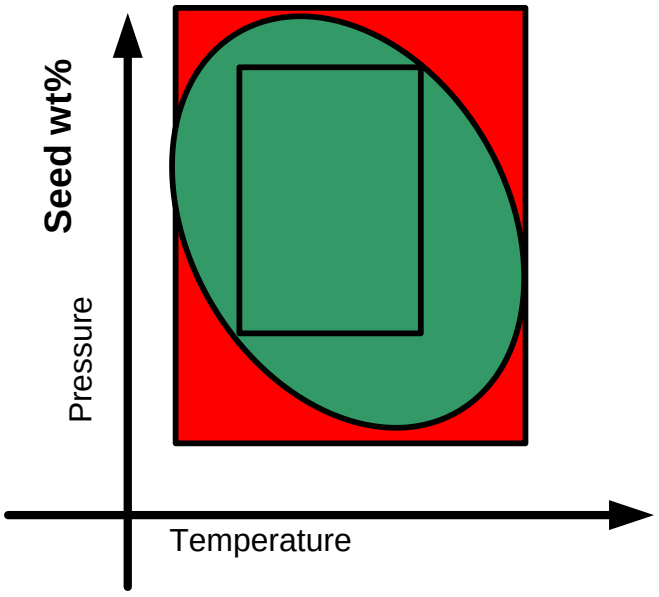
Risk Assessment:

Particle Size Distribution (PSD) Control

What is the **Impact** that ---------- will have on PSD? 1) minimal 5) moderate 9) significant						
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely						
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely						
Unit Operation	**Parameter**	IMPACT	PROB.	Detect	RPN	**Comments**
Crystallization	Feed Temperature	1	5	1	5	Prior knowledge (slowness of crystallization kinetics) ensures that the hot crystallizer feed will be well di[illegible] before crystallizing. Hence no im[illegible] crystal size.
Crystallization	Water content of Feed	1	5	5	25	Prior knowledge (solubility data) [illegible] do not affect crystalliation kinetics.
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Fast addition could result in uncontrolled crystallization. Detection of short addition time could occur too late to prevent this uncontrolled crystallization, and thus impact final PSD.
Crystallization	Seed wt percentage	9	5	5	225	Prior knowledge (Chemical Engineering theory) highlights seed wt percentage variations as a potential source of final PSD variation
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after air attrition milling
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

To be investigated in DOE

Options for Depicting a Design Space



- Oval = full design space represented by equation
- Rectangle represent ranges
  - Simple, but a portion of the design space is not utilized
  - Could use other rectangles within oval
- Exact choice of above options can be driven by business factors

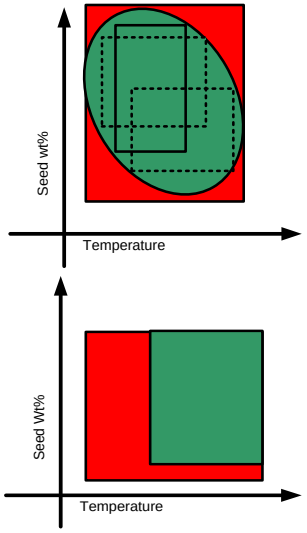
Large square represents the ranges tested in the DOE.
Red area represents points of failure
Green area represents points of success.

- For purposes of this case study, an acceptable design space based on ranges was chosen

Options for Expanding a Design Space

- **Why expand a Design Space?**
  - Business drivers can change, resulting in a different optimum operating space

- **When is DS Expansion possible?**
  - **Case A:** When the original design space was artificially constrained for simplicity
  - **Case B:** When some edges of the design space are the same as edges of the knowledge space



API Crystallization: Design Space & Control Strategy

- Control Strategy should address:
  - Parameter controls
    - Distillative solvent switch achieves target water content
    - Crystallization parameters are within the design space
  - Testing
    - API feed solution tested for water content
    - Final API will be tested for hydrolysis degradate
    - Using the predictive model, PSD does not need to be routinely tested since it is consistently controlled by the process parameters

Design Space / Control Strategy Parameter controls & Testing

Particle Size	Crystallization	Temperature	20 to 30ºC	Control between 23 and 27ºC
Particle Size	Crystallization	Feed Time	5 to 15 hours	Control via flow rate settings
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes in agitator size result in change to speed setting
Particle Size	Crystallization	Seed Wt%	1 to 2 wt%	Controlled through weigh scales and overcheck
Hydrolysis Degradate	Distillation / Crystallization	Water Content	< 1 vol%	Control via in-process assay

Particle size will be tested in this example, since the result is included in the mathematical model used for dissolution.

Drug Product

- Immediate release tablet containing 30 mg Amokinol
- Rationale for formulation composition and process selection provided
- In vitro-in vivo correlation (IVIVC) determination
  - Correlation shown between pharmacokinetic data and dissolution results
  - Robust dissolution measurement needed
    - For a low solubility drug, close monitoring is important

Example from Case Study

Drug Product Direct Compression

2.3.P.3.3 Manufacturing Process

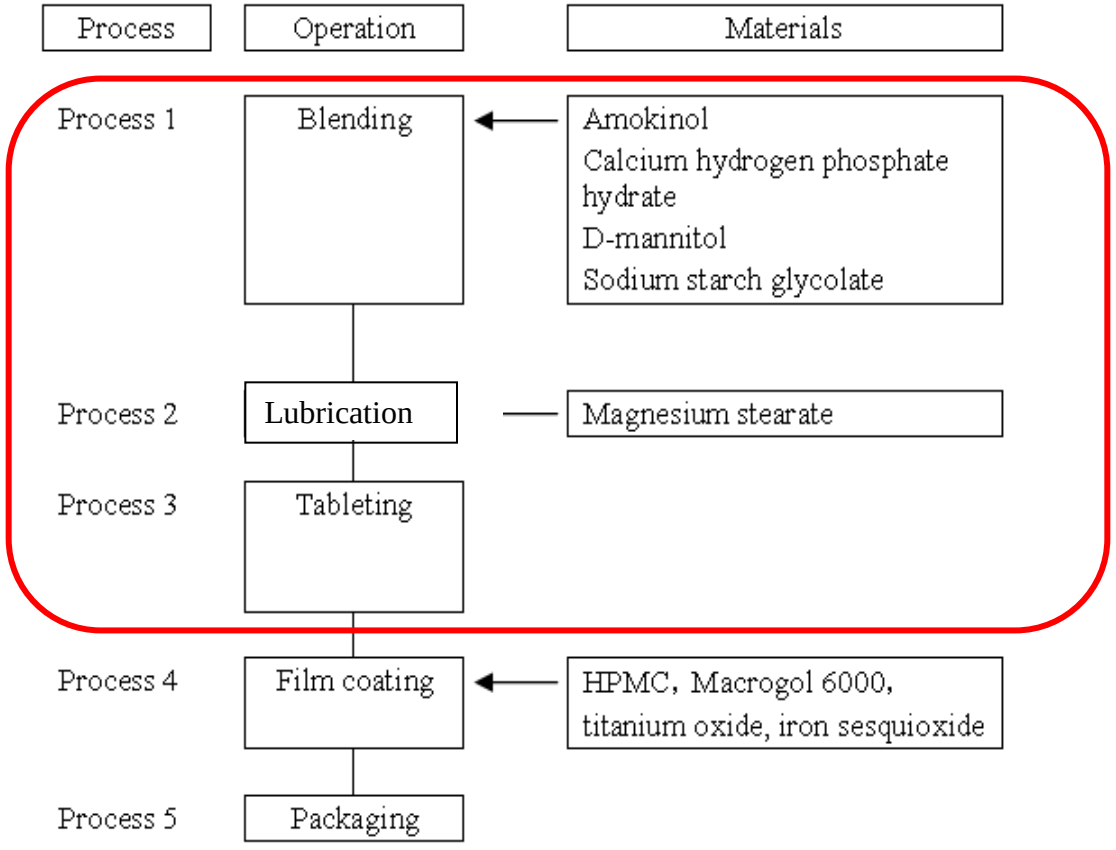


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

Focus of Story

Initial Quality Risk Assessment

- Impact of Formulation and Process unit operations on Tablet CQAs assessed using prior knowledge
  - Also consider the impact of excipient characteristics on the CQAs

	Drug substance particle size	Moisture content in manufacture	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance							
Dissolution							
Assay							
Degradation							
Content uniformity							
Appearance							
Friability							
Stability-chemical							
Stability-physical							

- Low risk
- Medium risk
- High risk

Drug Product CQA – *Dissolution Summary*

- Quality risk assessment
  - High impact risk for API particle size, filler, lubrication and compression
    - Fillers selected based on experimental work to confirm compatibility with Amokinol and acceptable compression and product dissolution characteristics
  - API particle size affects both bioavailability & dissolution
- Multivariate DOE to determine factors that affect dissolution and extent of their impact
- Predictive mathematical model generated
  - Confirmed by comparison of results from model vs. actual dissolution testing
- Possible graphical representations of this design space

Predictive Model for Dissolution

A mathematical representation of the design space

Prediction algorithm:

$$\text{Diss} = 108.9 - 11.96 \times \text{API} - 7.556\times10^{-5} \times \text{MgSt} - 0.1849 \times \text{LubT} - 3.783\times10^{-2} \times \text{Hard} - 2.557\times10^{-5} \times \text{MgSt} \times \text{LubT}$$

Factors include: API PSD, lubricant (magnesium stearate) specific surface area, lubrication time, tablet hardness (via compression force)

Confirmation of model

	Batch 1	Batch 2	Batch 3
Model prediction	**89.8**	**87.3**	**88.5**
Dissolution testing result	**92.8 (88.4–94.2)**	**90.3 (89.0-102.5)**	**91.5 (90.5-93.5)**

Continue model verification with dissolution testing of production material, as needed

Dissolution: Control Strategy

- **Controls of input material CQAs**
  - API particle size
    - Control of crystallisation step
  - Magnesium stearate specific surface area
    - Specification for incoming material
- **Controls of process parameter CPPs**
  - Lubrication step blending time within design space
  - Compression force (set for tablet hardness) within design space
    - Tablet press force-feedback control system
- **Prediction mathematical model**
  - Use in place of dissolution testing of finished drug product
  - Potentially allows process to be adjusted for variation (e.g. in API particle size) and still assure dissolution performance

Drug Product CQA - *Assay & Content Uniformity Summary*

- **Quality risk assessment**
  - Potential impact for API particle size, moisture control, blending, and lubrication
  - Moisture will be controlled in manufacturing environment
- **Consider possible control strategy approaches**
  - Experimental plan to develop design space using input material and process factors
  - In-process monitoring
- **Assay assured by weight control of tablets made from uniform powder blend with acceptable API content by HPLC**
  - Blend homogeneity by on-line NIR to determine blending endpoint, includes feedback loop
  - API assay in blend tested by HPLC
  - Tablet weight by automatic weight control with feedback loop

Blending Process Control Options

- Decision on conventional vs. RTR testing

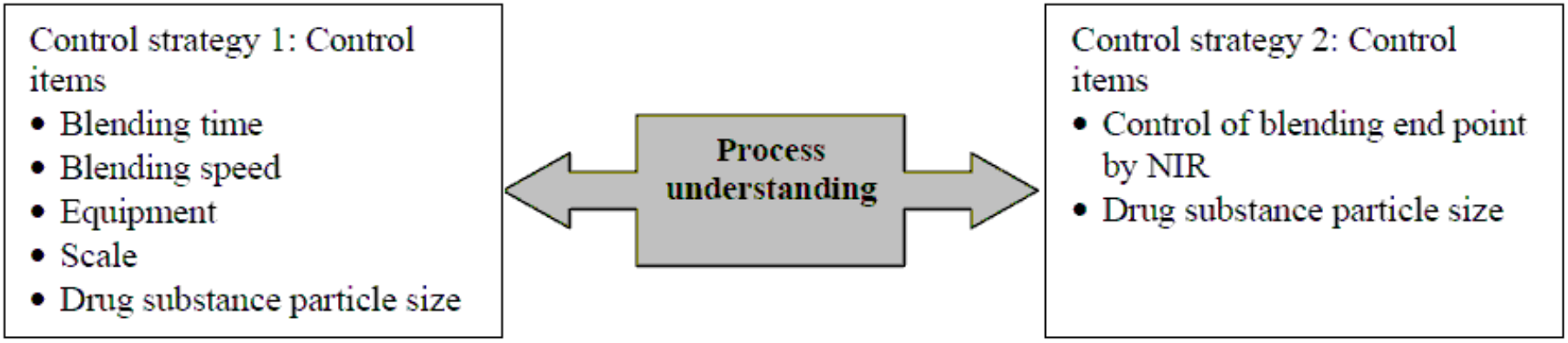


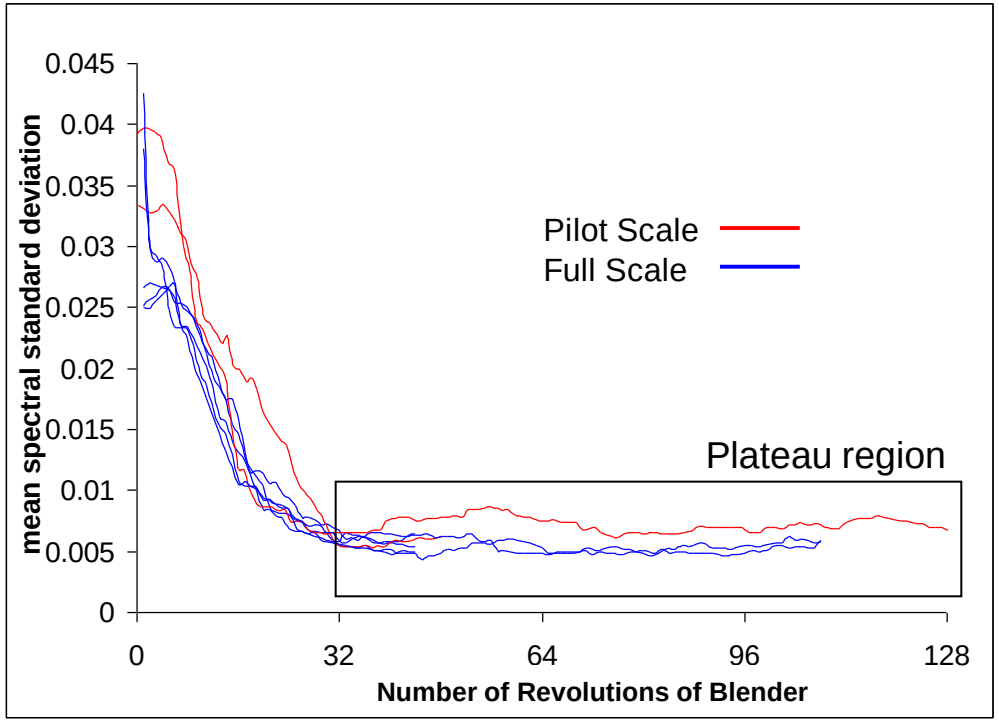
Figure 2.3.P.2.3-7 Control Strategy for Blending Process

Note) In the case of employment of control strategy 1, it is possible that drug substance partcle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.

Process Control Option 2

Blend uniformity monitored using a process analyser

- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
  - Assays tablets to confirm uniformity
  - Conducts studies to try to segregate API

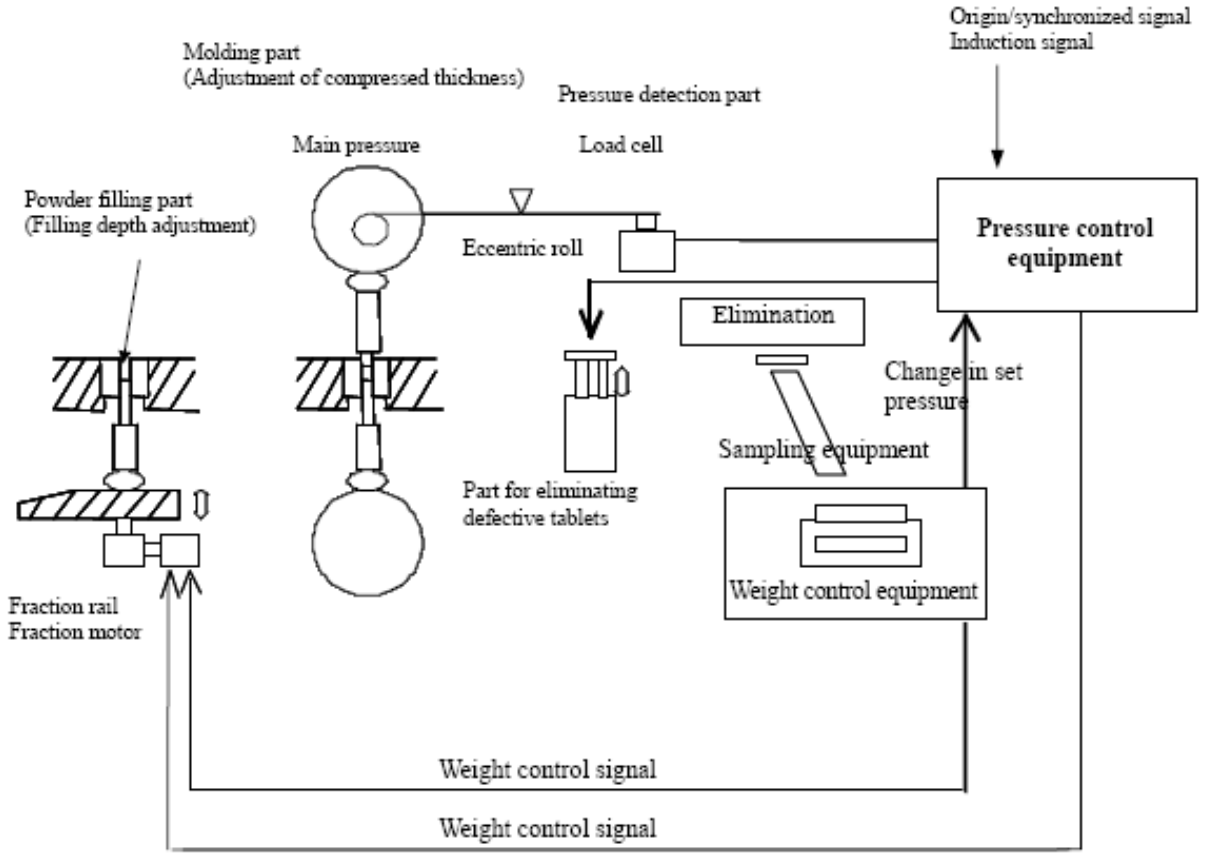


Data analysis model will be provided
Plan for updating of model available

Acknowledgement: adapted from ISPE PQLI Team

Product Development: Case Study Overview

Tablet Weight Control in Compression Operation



Conventional automated control of Tablet Weight using feedback loop:

Sample weights fed into weight control equipment which sends signal to filling mechanism on tablet machine to adjust fill volume and therefore tablet weight.

Batch Release Strategy

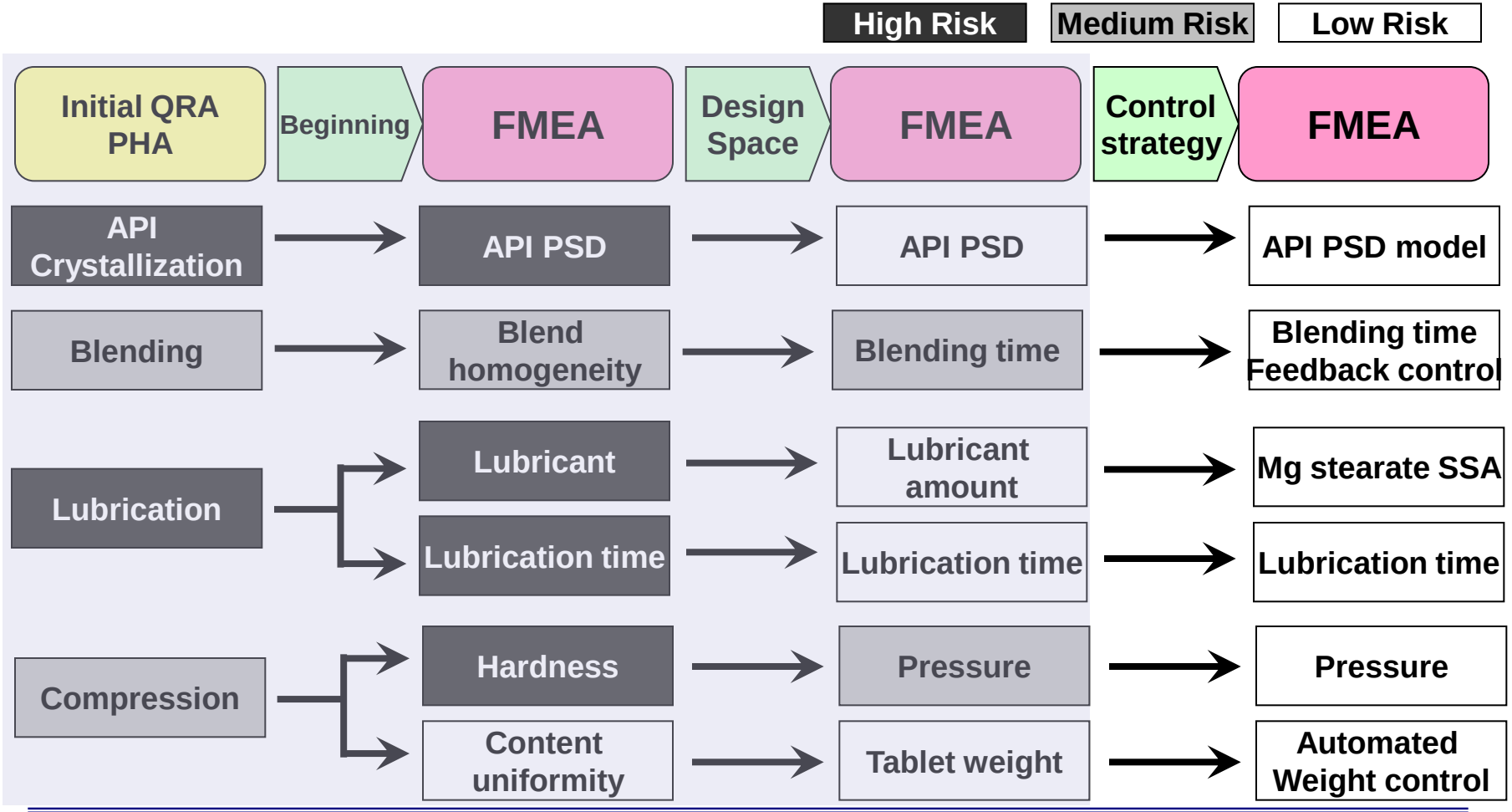
- **Finished product not tested for assay, CU and dissolution**
- **Input materials** meet specifications and are tested
  - API particle size distribution
  - Magnesium stearate specific surface area
- **Assay calculation**
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop), %RSD of 10 tablets
- **Content Uniformity**
  - On-line NIR criteria met for end of blending (blend homogeneity)
  - Tablet weight control results checked
- **Dissolution**
  - Predictive model using input and process parameters calculates for each batch that dissolution meets acceptance criteria
  - Input and process parameters used are within the filed design space
    - Compression force is monitored for tablet hardness
- **Water content**
  - NMT 3% in finished product (not covered in this case study)

Drug Product Specifications

- *Use for stability, regulatory testing, site change, whenever RTR testing is not possible*
- **Input materials meet specifications and are tested**
  - API PSD
  - Magnesium stearate specific surface area
- **Assay calculation** (drug product acceptance criteria 95-105% by HPLC)
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop)
    - For 10 tablets per sampling point, <2% RSD for weights
- **Content Uniformity** (drug product acceptance criteria meets compendia)
  - On-line NIR criteria met for end of blending (blend homogeneity)
  - Tablet weight control results checked
- **Dissolution** (drug product acceptance criteria min 85% in 30 minutes)
  - Predictive model using input and process parameters for each batch calculates whether dissolution meets acceptance criteria
  - Input and process parameters are all within the filed design space
    - Compression force is controlled for tablet hardness
- **Water content** (drug product acceptance criteria NMT 3 wt% by KF)

Product Development: Case Study Overview

Iterative risk assessments



Conclusions

- Better process knowledge is the outcome of QbD development
- Provides the opportunity for flexible change management
- Use Quality Risk Management proactively
- Multiple approaches for experimental design are possible
- Multiple ways of presenting Design Space are acceptable
  - Predictive models need to be confirmed and maintained
- Real Time Release Testing (RTRT) is an option
  - Opportunity for efficiency and flexibility