Implementation of ICH Q8, Q9, Q10

Case Study

Disclaimer

The information within this presentation is based on the ICH Q-IWG members expertise and experience, and represents the views of the ICH Q-IWG members for the purposes of a training workshop.

Purpose of Case Study

This case study is provided as an example to help illustrate the concepts and integrated implementation of approaches described in ICH Q8, Q9 and Q10. It is not intended to be the complete information on development and the manufacturing process for a product that would be presented in a regulatory filing, but focuses mainly on Quality by Design aspects to facilitate training and discussion for the purposes of this workshop.

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

Basis for Development Information

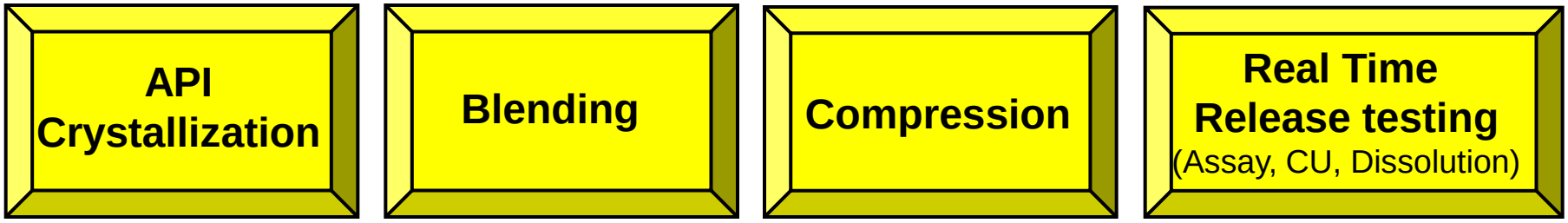
- Fictional active pharmaceutical ingredient (API)
- Drug product information is based on the ‘Sakura’ Tablet case study
  - Full Sakura case study can be found at http://www.nihs.go.jp/drug/DrugDiv-E.html
- Alignment between API and drug product
  - API Particle size and drug product dissolution
  -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

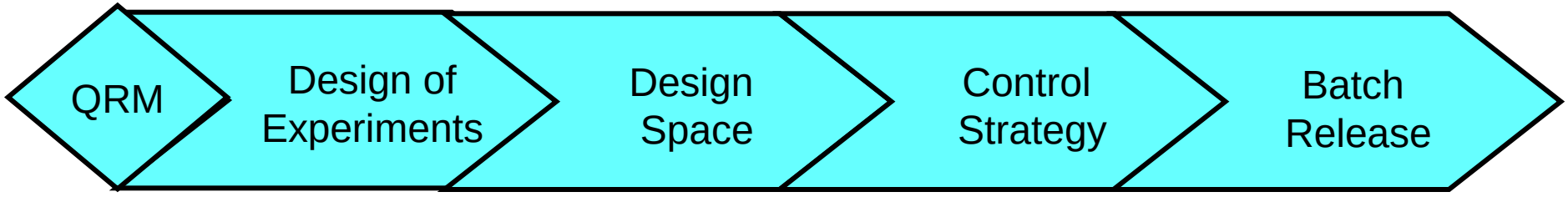
Technical Examples

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

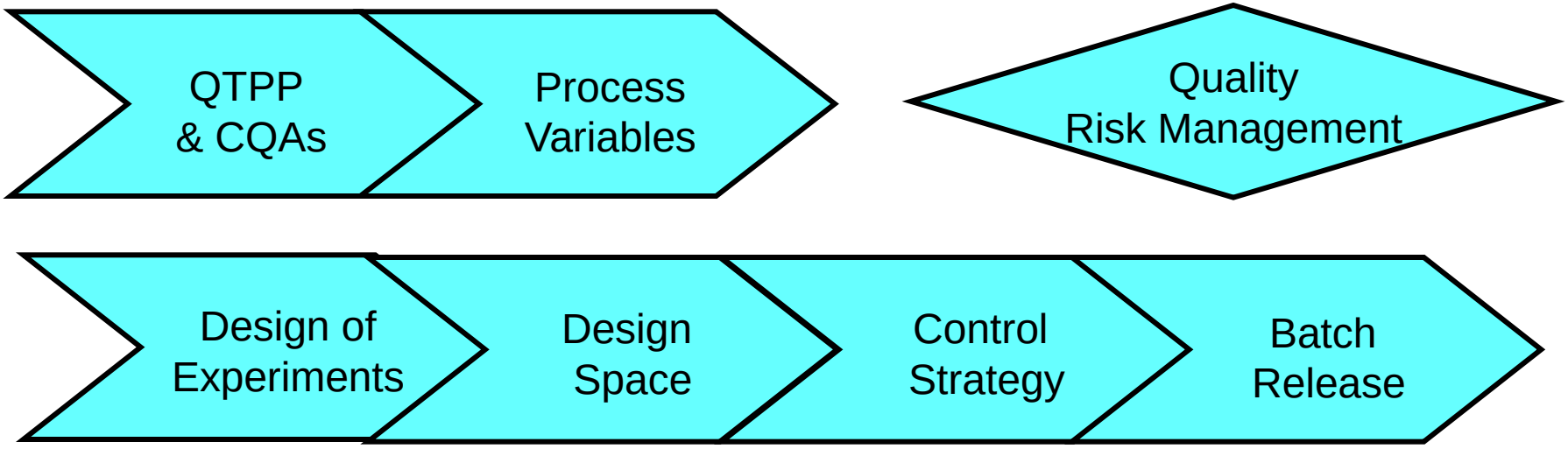


Process Step Analysis

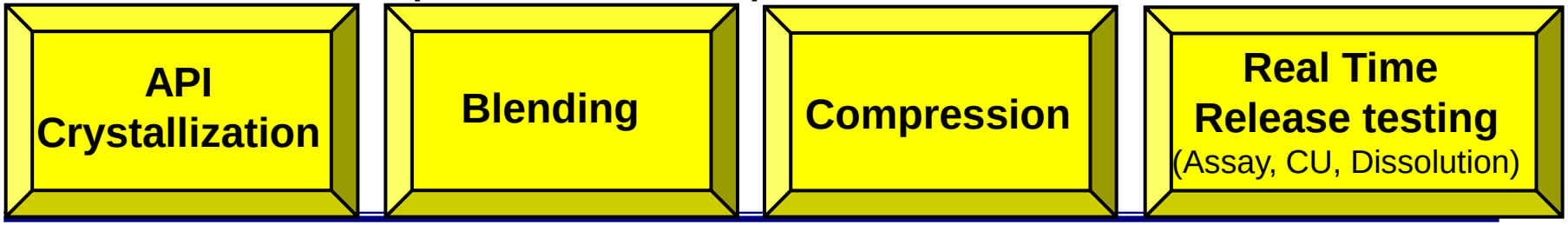
- For each example
  - Risk assessment
  - Design of experiments
  - Design space definition
  - Control strategy
  - Batch release



QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



Case Study

Quality Target Product Profile

defines the objectives for development

Dosage form and strength	Immediate release tablet taken orally containing 30 mg of active ingredient
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution
Description and hardness	Robust tablet able to withstand transport and handling
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm

- QTPP: 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 of the drug product. (ICH Q8 (R2))

Case Study

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.

Assumptions for the case

- API is designated as Amokinol
  - Single, neutral polymorph
  - Biopharmaceutical Classification System (BCS) class II – low solubility & high permeability
  - Dissolution rate affected by particle size
  - Potential for hydrolytic degradation
- In vitro-in vivo correlation (IVIVC) established – allows dissolution to be used as surrogate for clinical performance

API Unit Operations

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

2.3.P.1 Description and Composition of the Drug Product (Sakura Tablet, Film-coated Tablet)

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

API and Excipients

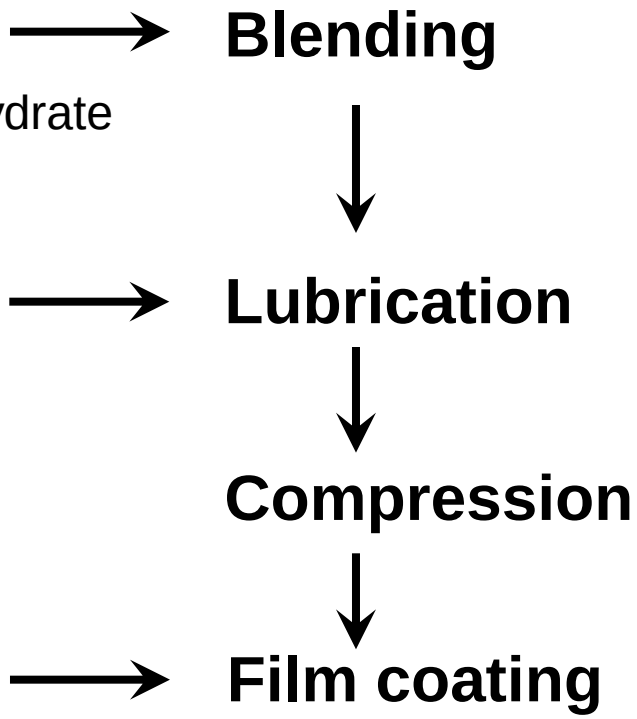
Amokinol
D-mannitol
Calcium hydrogen phosphate hydrate
Sodium starch glycolate

Lubricant

Magnesium Stearate

Coating

HPMC, Macrogol 6000
titanium oxide
iron sesquioxide



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)

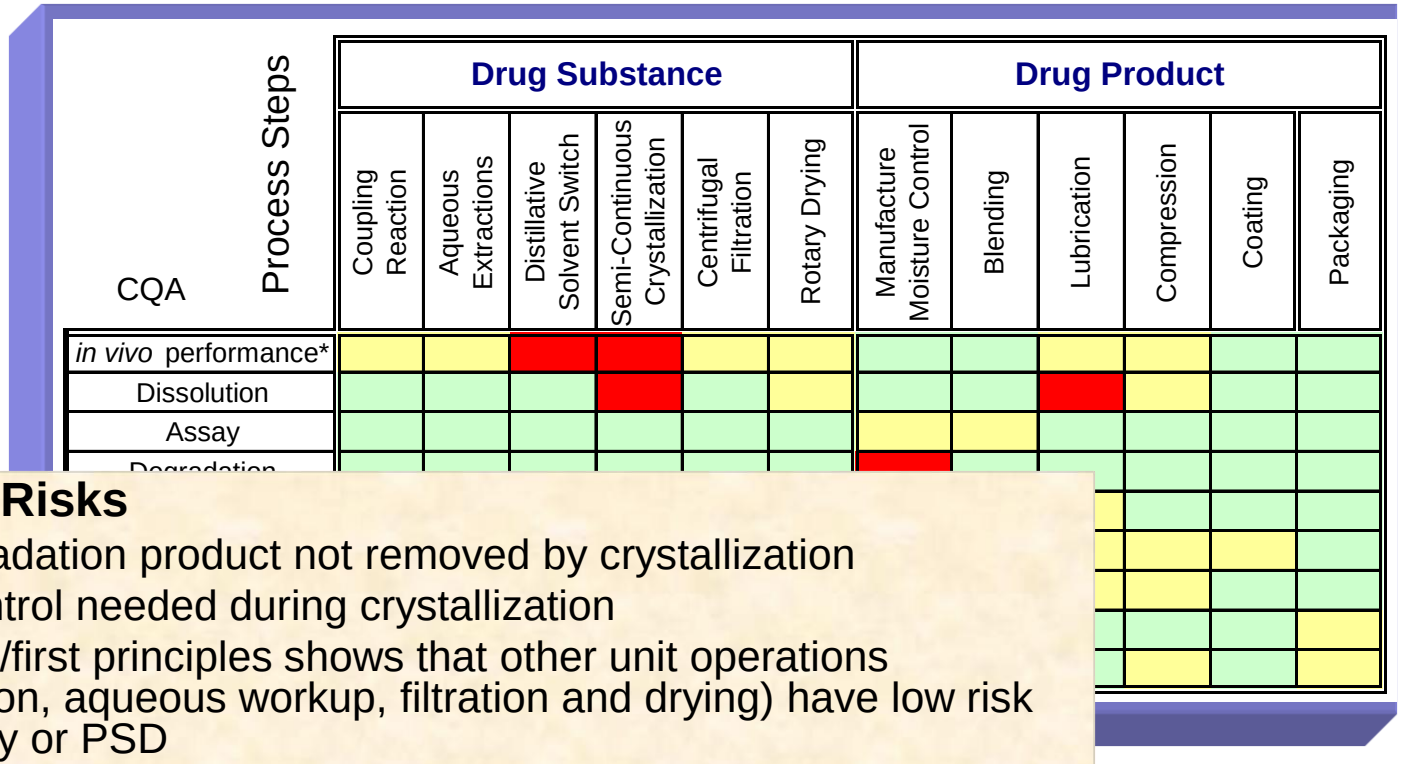
Process Steps

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												

Case Study

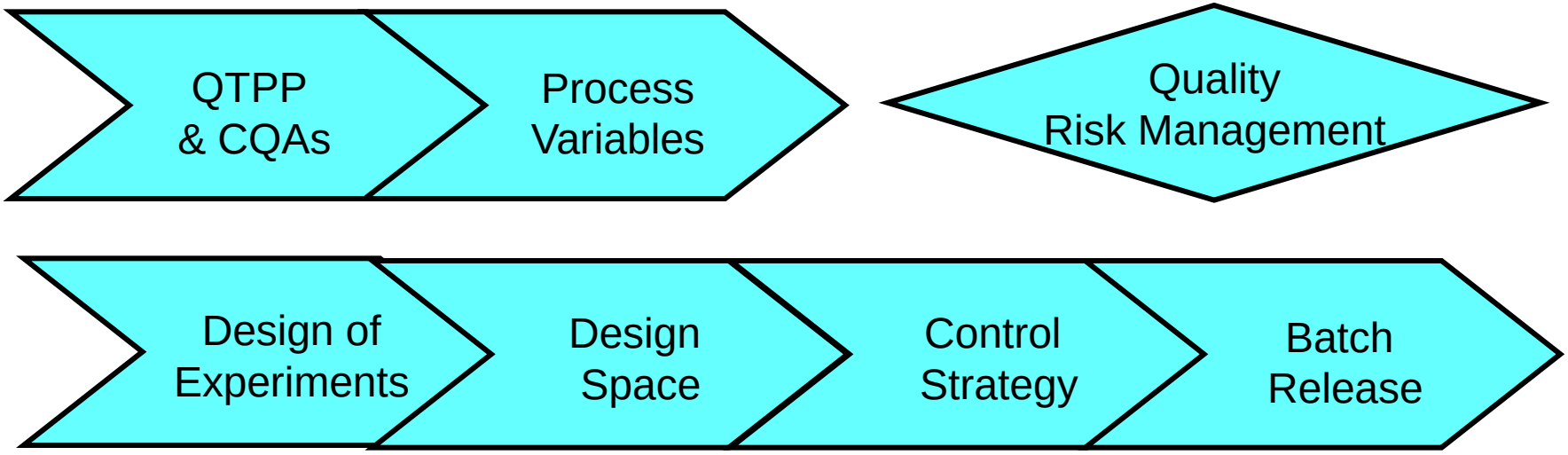
Initial Risk Assessment

- Focus on Impact to CQA's



- **Drug Substance Risks**
  - Hydrolysis degradation product not removed by crystallization
  - Particle size control needed during crystallization
  - Prior knowledge/first principles shows that other unit operations (Coupling reaction, aqueous workup, filtration and drying) have low risk of affecting purity or PSD
    - Knowledge from prior filings (data/reference)
    - Knowledge from lab / piloting data, including data from other compounds using similar technologies
    - First principles knowledge from texts/papers/other respected sources
  - Thus only distillation (i.e., crystallizer feed) and crystallization itself are high risk (red)

API: The Story



Illustrative Examples of Unit Operations:

API Crystallization Hydrolysis Degradation

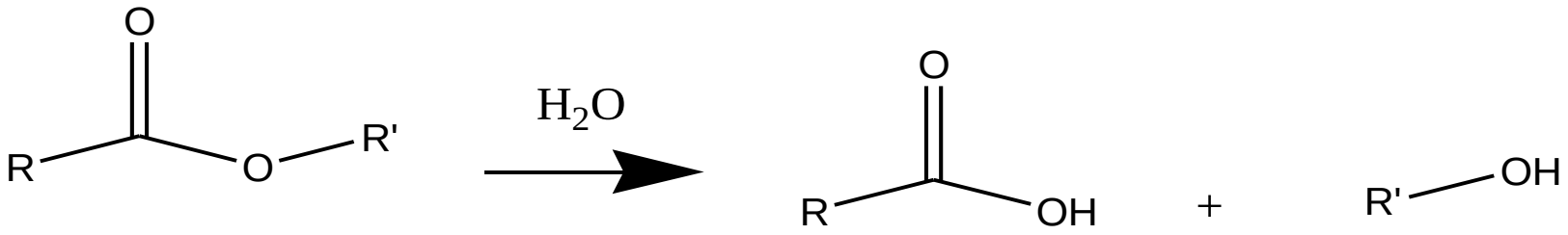
API Crystallization Particle size

API Crystallization Example

- Designed to control hydrolysis degradate
  - Qualified in safety trials at 0.3%
- Designed to control particle size
  - D90 between 5 and 20 microns
    - 'D90' means that 90% of particles are less than that value
  - Qualified in formulation Design of Experiments (DOE) and dissolution studies

Case Study

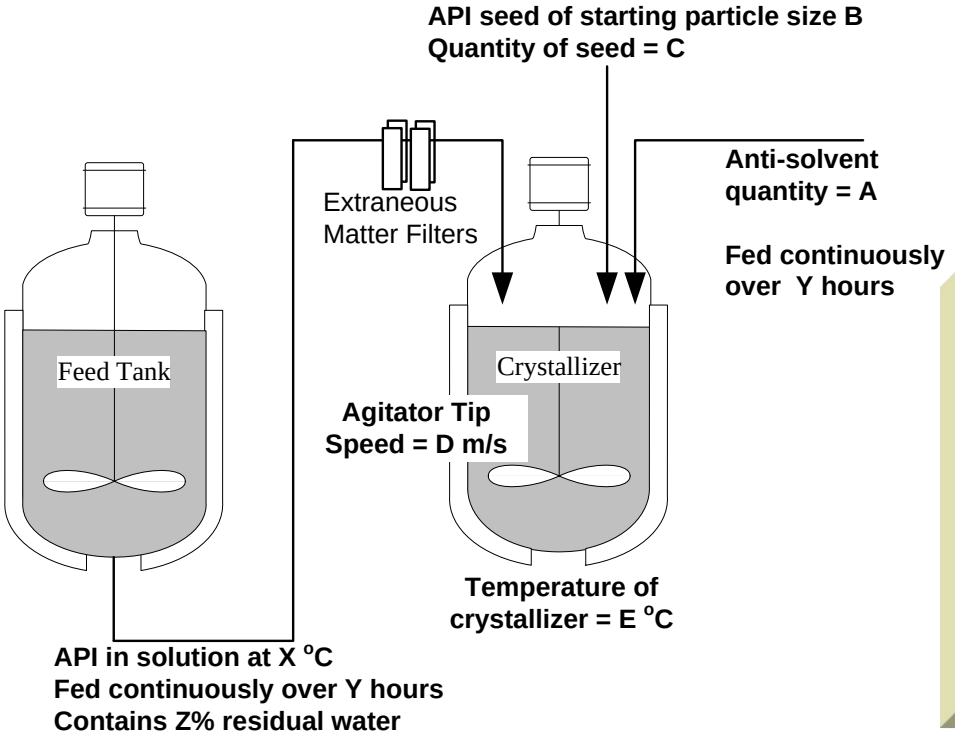
Hydrolysis Degradation



- Ester bond is sensitive to hydrolysis
- More sensitive at higher levels of water and at elevated temperatures
- Prior knowledge/experience indicates that no degradation occurs during the distillative solvent switch due to the lower temperature (40ºC) used for this step
- Degradates are water soluble, so degradation prior to aqueous workup does not impact API Purity
- After Distillative Solvent Switch, batch is heated to 70ºC to dissolve (in preparation for crystallization). Residual water in this hot feed solution can cause degradation and higher impurities in API.

Crystallization Process

Semi-continuous Crystallization Process
1) Create slurry of seed and pure solvents in "Crystallizer"
2) Continuously feed both API in solution (from "Feed Tank") and anti-solvent over Y hours



- **For Risk Assessment (FMEA)**
  - Only crystallization parameters considered, per scientific rationale in risk assessment
  - All relevant parameters considered based on first principles

- Temperature / time / water content have potential to affect formation of hydrolysis degradate
- Charge ratios / agitation / temperature / seed characteristics have potential to affect particle size distribution (PSD)

Case Study

Risk Assessment (FMEA): Purity Control

What is the **Impact** that ---------- will have on purity? 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
Distillative Solvent Switch	Temperature / Time, etc.	1	5	1	5	Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)	9	5	1	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	9	5	1	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	9	1	5	45	Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Antisolvent percentage (charge ratio)	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Crystallization temperature	1	5	1	5	Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters	1	1	1	1	These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.

Case Study

Experimental Setup - Hydrolysis Degradation

- **Crystallization Process Requirements**
  - API feed solution held at 60ºC, to maintain solubility of product, allows for passage through extraneous matter filters.
  - Batch fed to crystallizer slowly (to ensure particle size control). If fed too slowly (over too much time), hydrolysis degradate can form in crystallizer feed.
  - Batch will contain some level of residual water (thermodynamics)
  - No rejection of hydrolysis degradate seen in crystallization (prior knowledge/experience)

- **Process Constraints**
  - Factory process can control well within +/- 10ºC. 70ºC is easily the worst case temperature
  - The batch must be held hot during the entire feed time (~ 10 hours), including time for batch heat up and time for operators to safely start up the crystallization. A total hold time of 24 hours at temperature is the worst case.

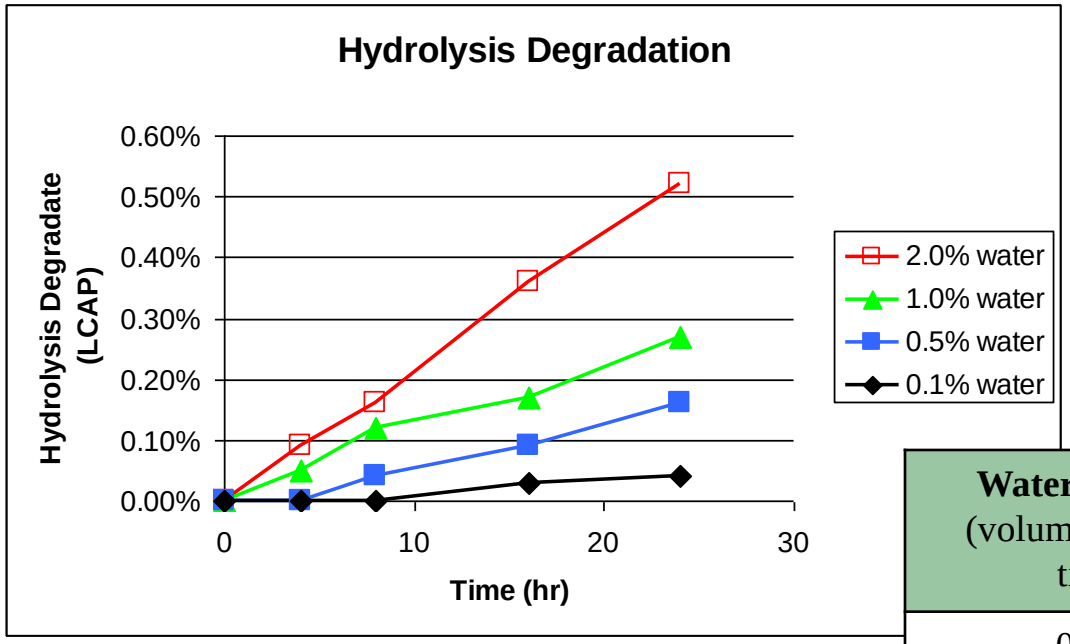
Case Study

Experimental Plan – Hydrolysis Degradation (contd.)

- Univariate experiments justified
  - Only upper end of ranges need to be tested, as first principles dictates this is worst case for degradation rate
    - Lower water content, temperature and hold times will not increase hydrolytic degradation
  - Upper end of range for batch temperature and hold time can be set based on capabilities of a typical factory
  - Therefore, only the water content of the batch needs to be varied to establish the design space
- Experimental Setup
  - Set maximum batch temperature (70ºC)
  - Set maximum batch feed time (include heat up time, hold time, etc.) = 24 hours
  - Vary residual water level
  - Monitor degradation rate with criteria for success = max 0.3% degradate (qualified limit)

Case Study

Experimental Data



Design Space Defined

Max Temp: 70ºC

Max Feed Time = 24 hr

Max Water content = 1.0%

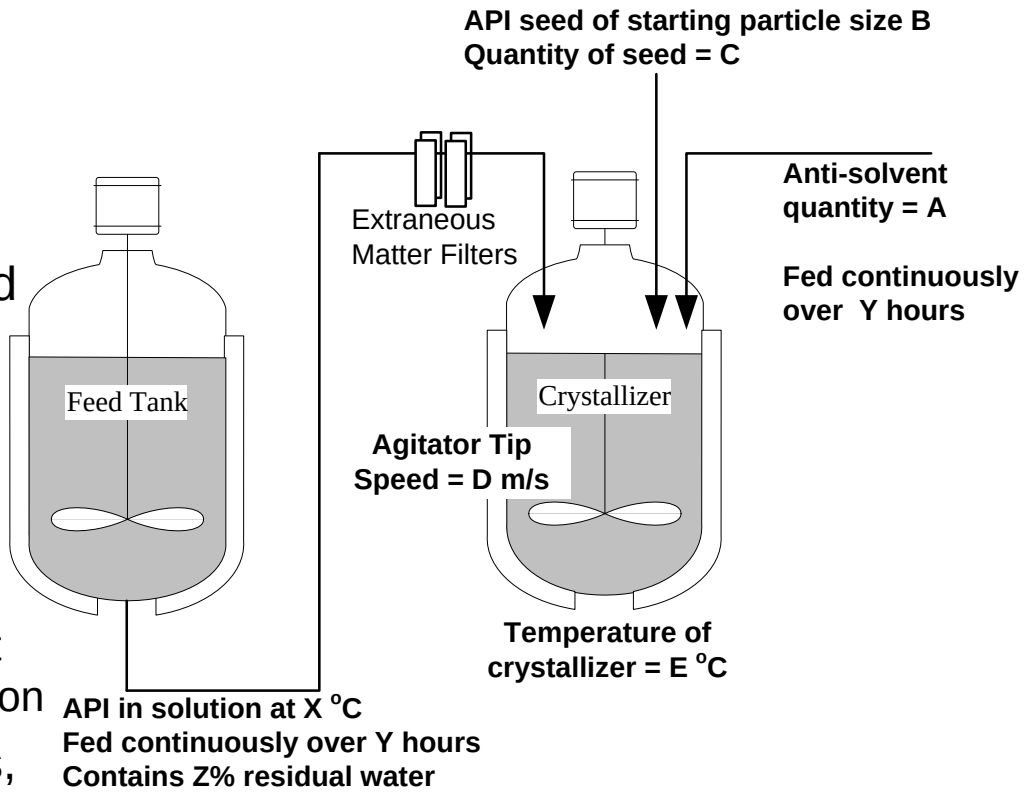
At these conditions, degradate level remains below qualified limit of 0.3%

Water Content (volume% by KF titration)	**Degradate Level at 24 hrs** (LC area%)
0.1%	0.04%
0.5%	0.16%
1.0%	0.27%
2.0%	0.52%

Case Study

Particle Size Distribution Control - Process History

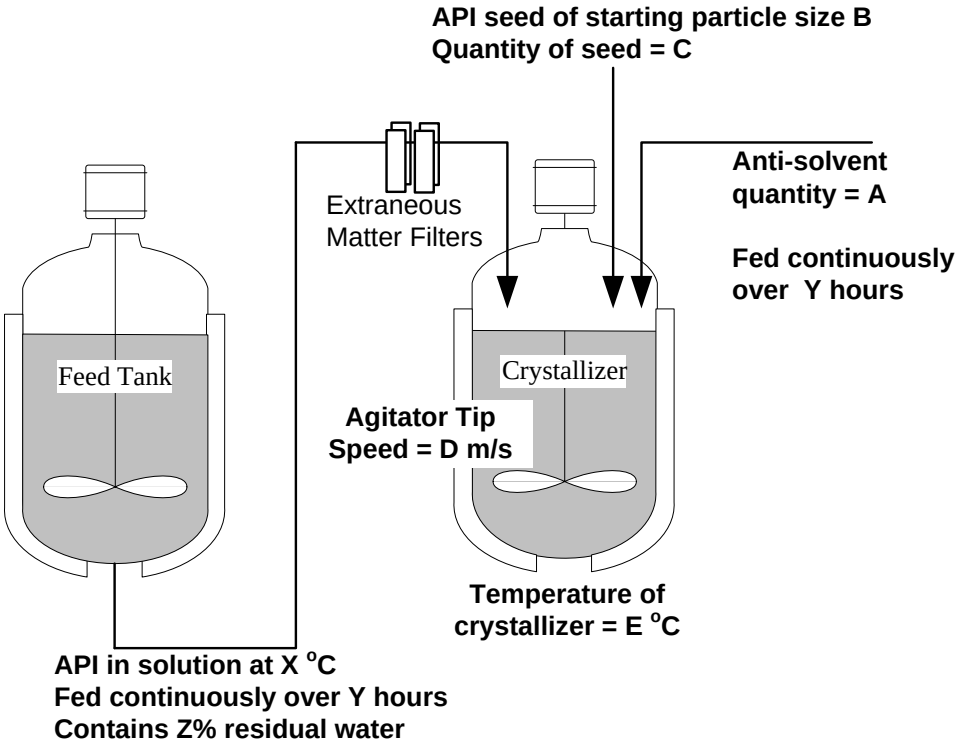
- *Changes in formulation drive changes in API process*
- Ph I and II trials performed with API-excipient mixture filled in hard gelatin capsules (liquid filled capsules = LFC)
- First API Deliveries
  - Simpler Crystallization Process
    - No PSD control; crystal agglomeration observed, but acceptable for LFC formulation
- Ph III trials performed with tablets, requiring small PSD for processing and dissolution



Case Study

Particle Size Distribution Control - Process History (contd.)

- Changes to crystallization process
  - Develop semi-continuous crystallization to better control PSD (narrow the distribution) and control agglomeration
  - Add air attrition milling of seed to lower the final API PSD
  - API Particle Size Distribution Specification: 5 to 20 micron D90
- Risk Assessment
  - Charge ratios/agitation/temperature/ seed characteristics have potential to affect PSD
    - Based on data in a previous filing and experience with this technology.
    - Per prior knowledge, other unit operations (including filtration and drying) do not affect PSD.
    - Lab data and piloting experience demonstrate that growing crystals are sensitive to shear (agitation) in the crystallizer, but not during drying.



Case Study

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 dispersed and thermally equilibrated before crystallizing. Hence no impact of feed temp variation on crystal size.
Crystallization	Water content of Feed	1	5	5	25	Prior knowledge (solubility data) shows that small variations in water 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 during crystallization, 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

Case Study

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 cryst… the hot crystallizer feed will be well… equilibrated before crystallizing. H… variation on crystal size.
Crystallization	Water content of Feed	1	5	5	25	Prior knowledge (solubility data) shows that small variations in water 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 during crystallization, 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

Experimental Design, PSD Control

Half Fraction Factorial

- Test: feed addition time
  amount API seed (wt%)
  agitation tip speed
  crystallization temperature
- Experimental ranges based on QTPP and chosen by:
  - Prior knowledge: estimates of what ranges would be successful
  - Operational flexibility: ensure that ranges are suitable for factory control strategy

Study Factors				Response
Feed Rate (hrs)	Seed (wt%)	Temp °C	Tip Speed m/s	D90 (microns)
15	1	10	0.44	13.5
5	5	10	0.44	14.5
5	1	10	2.67	5.5
15	5	10	2.67	2.2
5	1	30	0.44	21.4
15	5	30	0.44	13.5
15	1	30	2.67	12.4
5	5	30	2.67	7.4
10	3	20	1.56	7.8
10	3	20	1.56	8.3
10	3	20	1.56	6.1

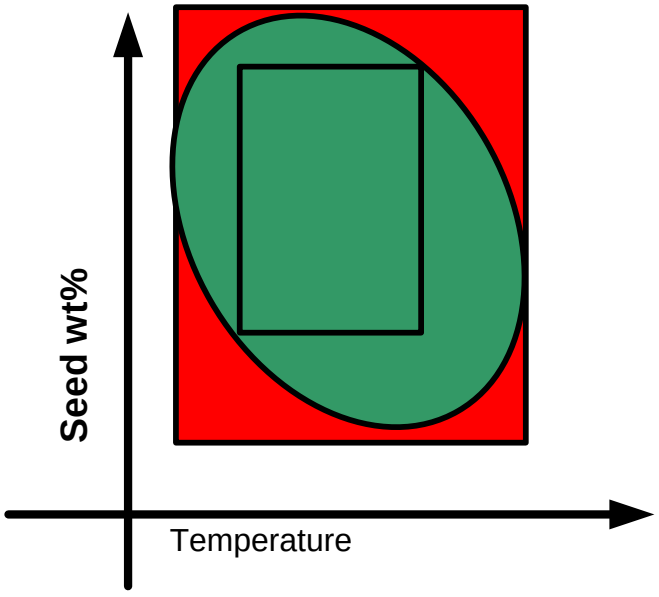
•Experimental Results: D90 minimum = 2.2 microns; maximum = 21.4 microns
- Extremes are outside of the desired range of 5 to 20 microns for D90

Case Study

PSD Control -- Design Space

- Statistical Analysis of crystallization data allows for determination of the design space
- Analysis of DOE data generates a predictive model
  - PSD D90 =
    19.3 - 2.51*A - 8.63*B + 0.447*C - 0.0656*A*C + 0.473*A^2 + 1.55*B^2
    - where A = seed wt%, B = agitator tip speed (m/s) and C = temperature (ºC)
    - Statistical analysis shows that crystallization feed time does not impact PSD across the tested range
- Model range across DOE space = 2.2 to 21.4 microns
  - Model error is ±1 micron
- Model can be used to create a design space using narrower ranges than used in the DOE
  - Adjust ranges until model predicts acceptable D90 value for PSD

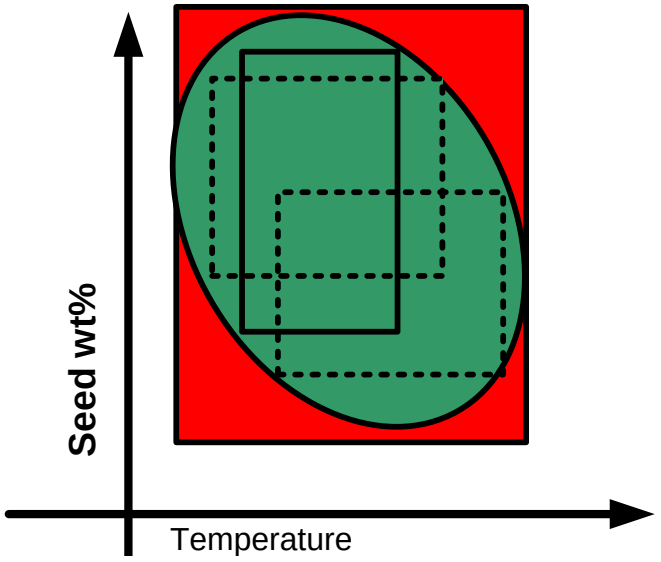
Options for Depicting a Design Space



- In the idealized example at left, the oval represents the full design space. It would need to be represented by an equation.
- Alternatively, the design space can be represented as the green rectangle by using ranges
  - a portion of the design space is not utilized, but the benefit is in the simplicity of the representation

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

Options for Depicting a Design Space



- Other rectangles can be drawn within the oval at top left, based on multiple combinations of ranges that could be chosen as the design space
- Exact choice from above options can be driven by business factors
  - e.g., keep seed charge narrow, maximizing temperature range, since temperature control is less precise than a seed charge

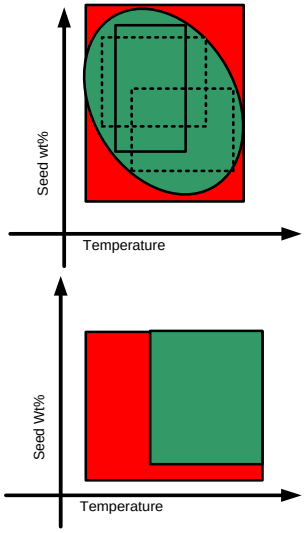
For purposes of this case study, an acceptable “squared off” design space can be chosen

Temperature = 20 to 30ºC
Seed charge = 1 to 2 wt%
Agitation = 1.1 to 2.5 m/s
Feed Rate = 5 to 15 hr (limit of knowledge space)
Monte Carlo analysis ensures that model uncertainty will be effectively managed throughout the range
Since the important variables affecting PSD are scale independent, model can be confirmed at scale with “center point” (optimum) runs

Options for Expanding a Design Space

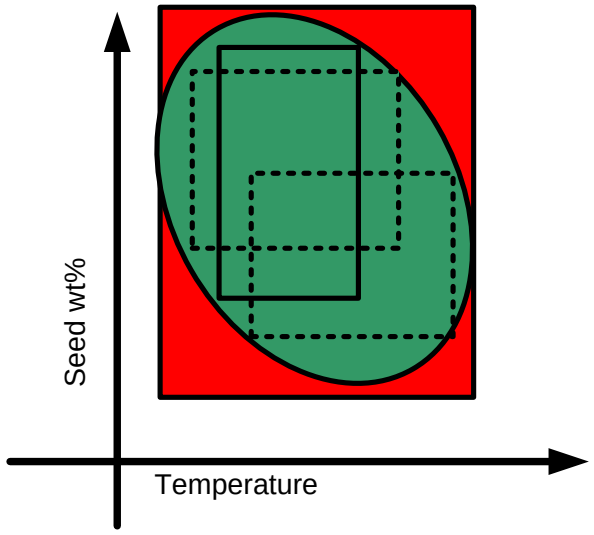
- **Why expand a Design Space?**
  - Business drivers can change, resulting in a different optimum operating space

- **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



Case Study

Options for Expanding a Design Space Case A

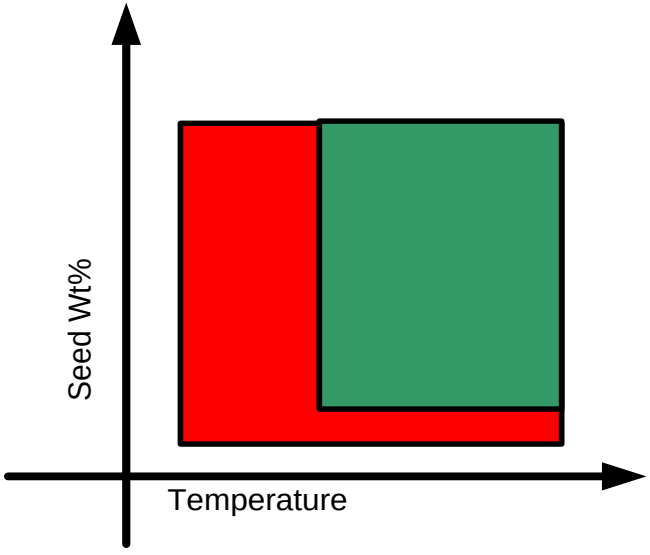


- When the original design space was artificially constrained for simplicity
  - Alternate combinations of ranges could be chosen as the new design space, based on original data.
    - e.g. the range for seed wt% could be constrained, allowing widening of the temperature range

The large square represents the ranges tested in the DOE. The red area represents points of failure. The green area represents points of success.

The boxes represent simplified design spaces within the points of success

Options for Expanding a Design Space Case B



- When some edges of the design space are the same as edges of the knowledge space
  - Additional experiments could be performed to expand the upper limits of seed wt% and temperature

The large square represents the ranges tested in the DOE. The red area represents points of failure. The green area represents points of success.

Case Study

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
- Quality systems
    - Should be capable of managing changes within and to the design space
    - Product lifecycle can result in future design space changes

Case Study

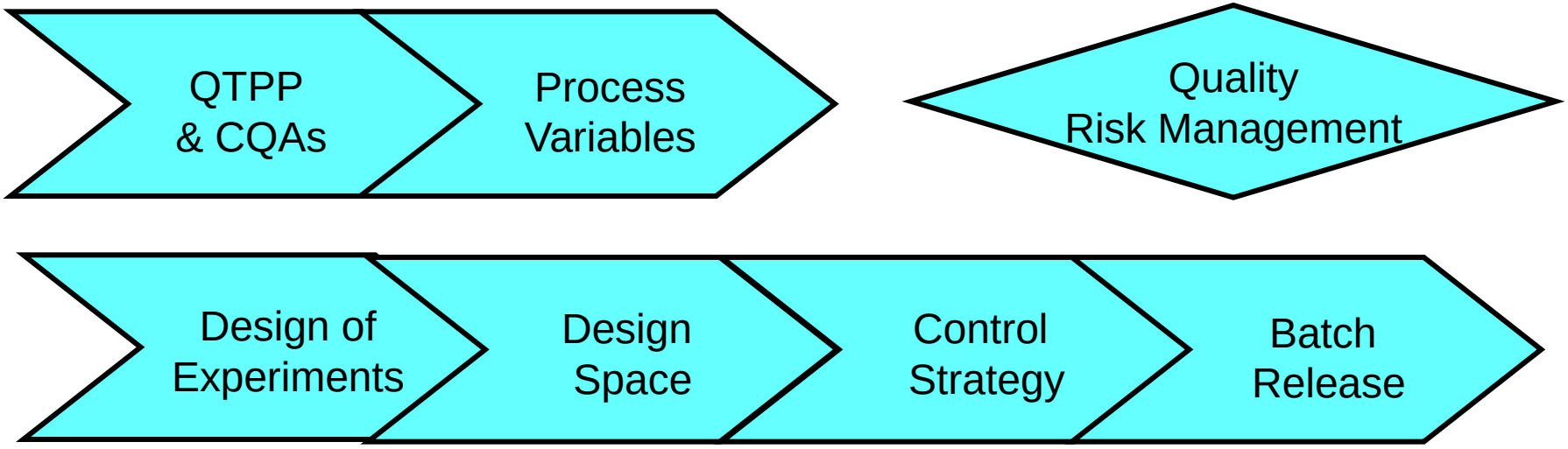
API Crystallization: Design Space & Control Strategy

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 wt%	Control via in process assay

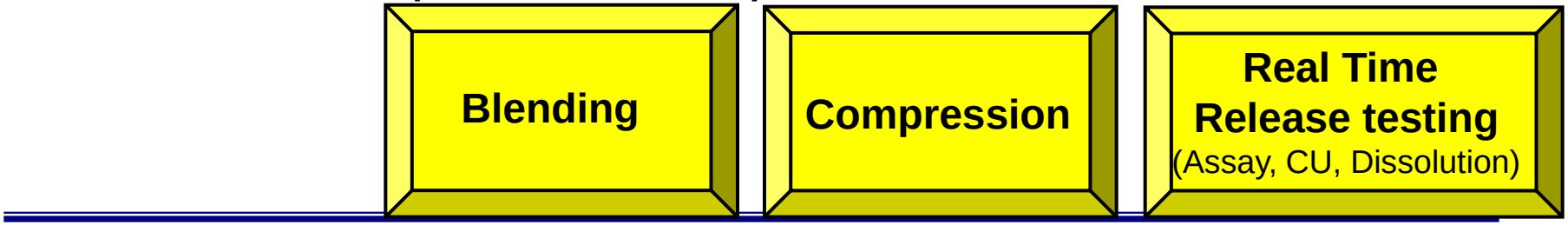
Batch Release for API

- **Testing conducted on the final API**
  - Hydrolysis degradate levels are tested by HPLC
  - Particle size distribution does not need to be tested, if the design space and associated model are applied
    - In this case study, PSD is tested since the actual PSD result is used in a mathematical model applied for predicting dissolution in the following drug product control strategy
  - Additional quality tests not covered in this case study
- **Verify that the crystallization parameters are within the design space**
  - Temperature = 20 to 30º C
  - Seed charge = 1 to 2 wt%
  - Agitation = 1.1 to 2.5 m/s
  - Feed time = 5 to 15 hr
  - API feed solution water content < 1 wt%

QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



Case Study

QTPP and CQAs

QTPP

Dosage form and strength	Immediate release tablet containing 30 mg of active ingredient.
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution.
Description and hardness	Robust tablet able to withstand transport and handling.
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance. Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm.

CQAs derived using Prior Knowledge
(e.g. previous experience of developing tablets)

CQAs may be ranked using quality risk assessment.

Drug Product CQAs

- Assay
- Content Uniformity
- Dissolution
- Tablet Mechanical Strength

CQAs to Focus on for this Story

- **Drug Product CQAs**
  - Assay & Content Uniformity
  - Dissolution

Rationale for Formulation & Process Selection

- Amokinol characteristics
  - BCS class II (low solubility, high permeability)
  - Susceptible to hydrolysis
  - 30 mg per tablet (relatively high drug loading)
- Direct compression process selected
  - Wet granulation increases risk of hydrolysis of Amokinol
  - High drug loading enables content uniformity to be achieved without dry granulation operation
  - Direct compression is a simple, cost-effective process
- Formulation Design
  - Excipient compatibility studies exclude lactose due to API degradation
    - Consider particle size aspects of API and excipients
  - Dual filler system selected and proportions optimised to give good dissolution and compression (balance of brittle fracture and plastic deformation consolidation mechanisms)
  - Conventional non-functional film coat selected based on prior knowledge

Tablet Formulation

2.3.P.1 Description and Composition of the Drug Product (Sakura Tablet, Film-coated Tablet)

Function	Specification	Excipient	Sakura Tablet 30 mg
Active ingredient	Separate specification	Amokinol	30 mg / tablet (100 mg)
Excipient	Pharmacopoeial or other compendial specification. May have additional requirements for Functionality Related Characteristics	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

Case Study

Direct Compression Process

2.3.P.3.3 Manufacturing Process

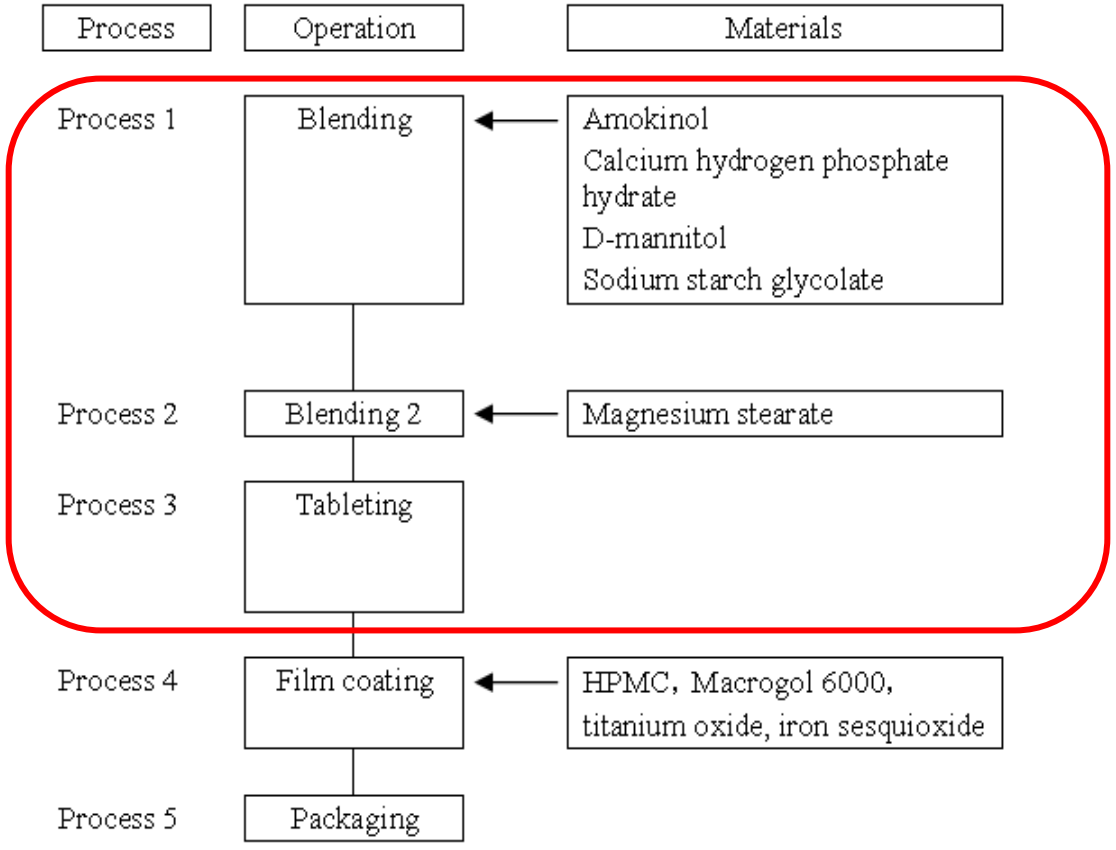


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

Focus of Story

Case Study

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

Example 1:
Real Time Release Testing (RTRT) for Dissolution

Case Study

Developing Product and Process Understanding

Investigation of the effect of API particle size on Bioavailability and Dissolution

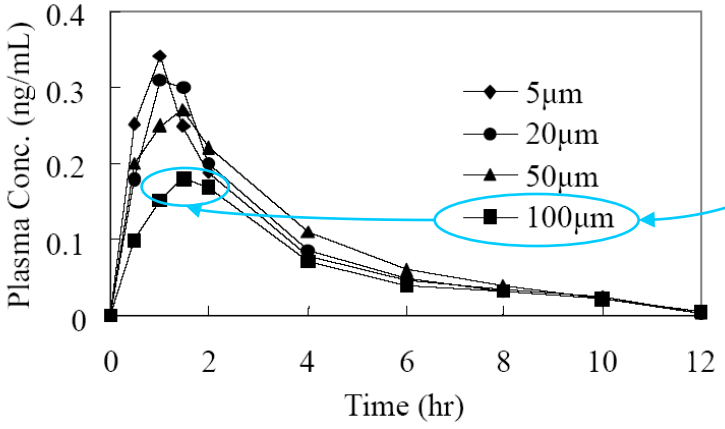


Figure 2.3.P.2.3-3 Blood Concentration Profiles

Drug Substance with particle size D90 of 100 microns has slower dissolution and lower Cmax and AUC

In Vivo In Vitro correlation (IVIVC) established at 20 minute timepoint

Early time points in the dissolution profile are not as critical due to PK results

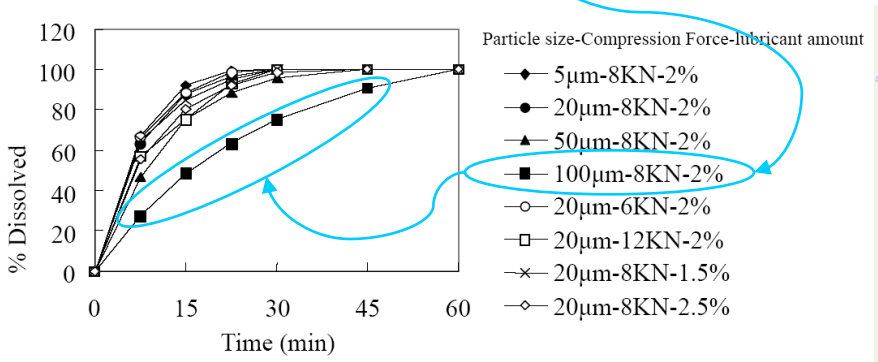


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Particle Size (D90%), Compression Force and/or Lubricant Amount

Case Study

Developing Product and Process Understanding: DOE Investigation of factors affecting Dissolution

Multifactorial DOE study of variables affecting dissolution

- **Factors:**
  - API particle size [API] unit: log D90, microns
  - Mg-Stearate Specific Surface Area [MgSt] unit: cm^2/g
  - Lubrication time [LubT] unit: min
  - Tablet hardness [Hard] unit: N
- **Response:**
  - % API dissolved at 20 min [Diss]
- **DOE design:**
  - RSM design
  - Reduced CCF (quadratic model)
  - 20+3 center point runs

Exp No	Run Order	API	MgSt	LubT	Hard	Diss
1	1	0.5	3000	1	60	101.24
2	14	1.5	3000	1	60	87.99
3	22	0.5	12000	1	60	99.13
4	8	1.5	3000	10	60	86.03
5	18	0.5	12000	10	60	94.73
6	9	1.5	12000	10	60	83.04
7	15	0.5	3000	1	110	98.07
8	2	0.5	12000	1	110	97.68
9	6	1.5	12000	1	110	85.47
10	16	0.5	3000	10	110	95.81
11	20	1.5	3000	10	110	84.38
12	3	1.5	12000	10	110	81
13	10	0.5	7500	5.5	85	96.85
14	17	1.5	7500	5.5	85	85.13
15	19	1	3000	5.5	85	91.87
16	21	1	12000	5.5	85	90.72
17	7	1	7500	1	85	91.95
18	4	1	7500	10	85	88.9
19	5	1	7500	5.5	60	92.37
20	11	1	7500	5.5	110	90.95
21	12	1	7500	5.5	85	91.95
22	13	1	7500	5.5	85	90.86
23	23	1	7500	5.5	85	89

Note: A screening DoE may be used first to identify which of the many variables have the greatest effect

Factors affecting Dissolution

- Key factors influencing in-vitro dissolution:
  - API particle size is the dominating factor (= CQA of API)
  - Lubrication time has a small influence (= low risk parameter)

Acknowledgement: adapted from Paul Stott (AZ) – ISPE PQLI Team

Predictive Model for Dissolution

- Prediction algorithm
  - A mathematical representation of the design space for dissolution
  - *Factors include: API PSD D90, magnesium stearate specific surface area, lubrication time and tablet hardness (linked to compression pressure)*

Prediction algorithm:

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

Case Study

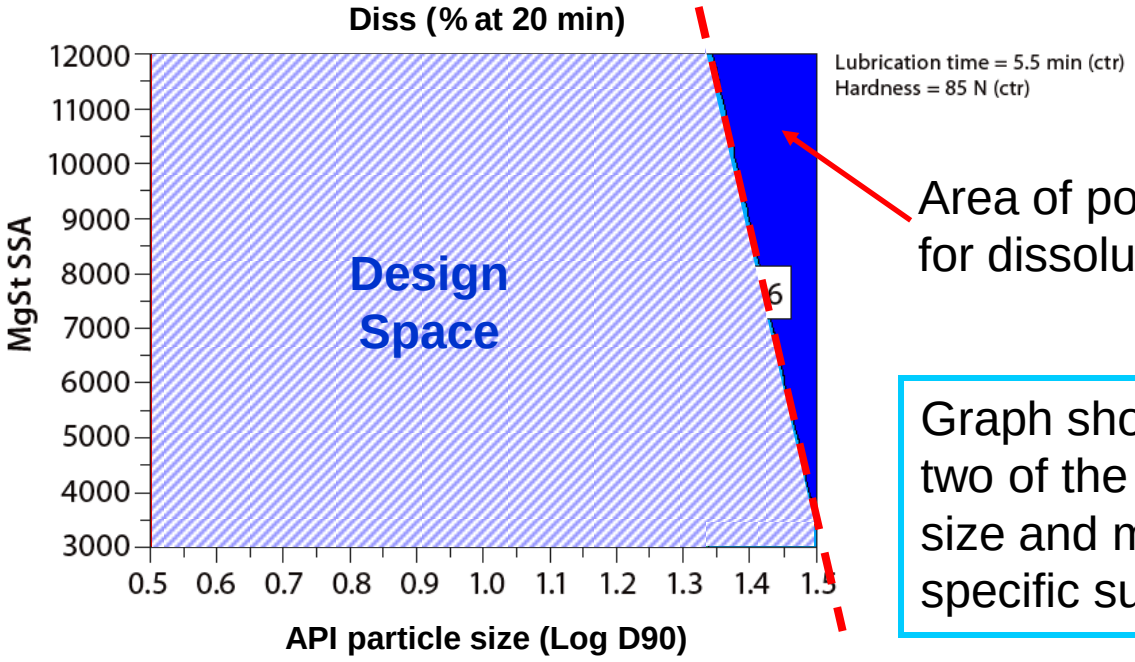
Predictive Model for Dissolution

- Account for uncertainty
  - Sources of variability (predictability, measurements)
- Confirmation of model
  - compare model results vs. actual dissolution results for batches
  - continue model verification with dissolution testing of production material, as needed

	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)

Dissolution: Design Space

- Response surface plot for effect of API particle size and magnesium stearate specific surface area (SSA) on dissolution



Area of potential risk for dissolution failure

Graph shows interaction between two of the variables: API particle size and magnesium stearate specific surface area

Acknowledgement: adapted from Paul Stott (AZ)

Dissolution: Control Strategy

- **Controls of input material CQAs**
  - API particle size distribution
    - Control of crystallisation step
  - Magnesium stearate specific surface area
    - Specification for incoming material
- **Controls of process parameter CPPs**
  - Lubrication step blending time
  - Compression pressure (set for target tablet hardness)
    - 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 in API particle size, for example, and assure dissolution performance

Example 2:
Real Time Release Testing (RTRT) for Assay and Content Uniformity

Case Study

Quality Risk Assessment

Impact on Assay and Content Uniformity CQAs

- QRA shows API particle size, moisture control, blending and lubrication steps have potential to affect Assay and Content Uniformity CQAs
  - Moisture is controlled during manufacturing by facility HVAC control of humidity (GMP control)

	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

Blending Process Control Options

Decision on conventional vs. RTR testing

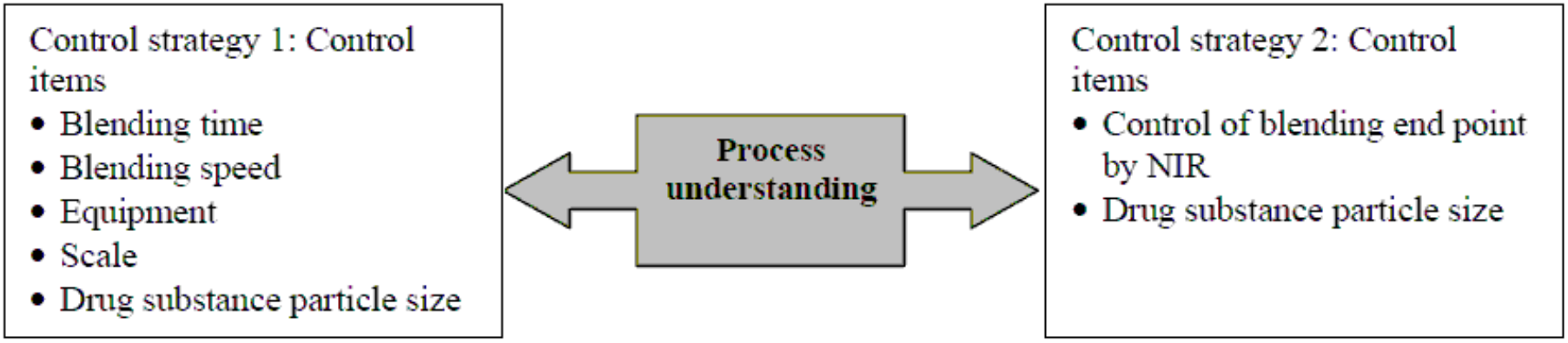


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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.

Case Study

Process Control Option 1

DOE for the Blending Process Parameter Assessment to develop a Design Space

- Factors Investigated:
  Blender type, Rotation speed, Blending time, API Particle size

DOE design

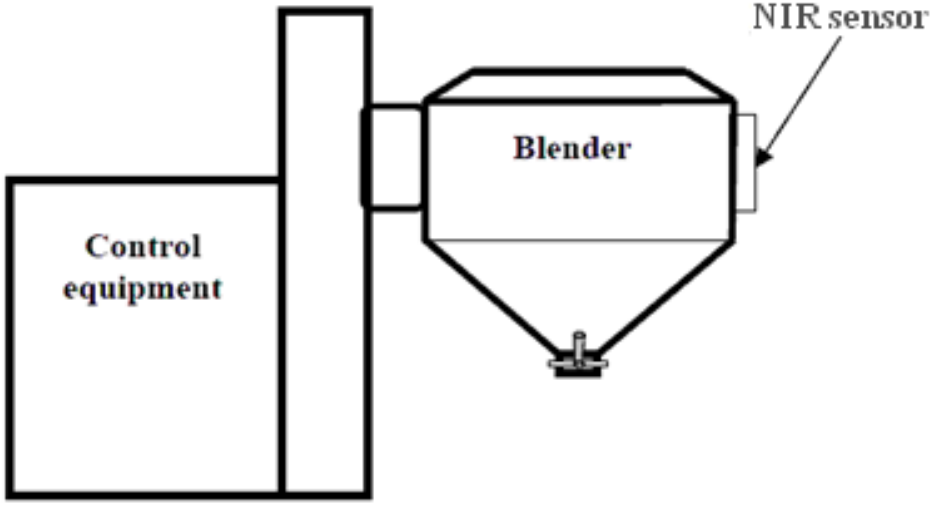
Experiment No.	Run	Condition	Blending time (minutes)	Rotation speed (rpm)	Blender	Particle size D90 (μm)
1	2	varied	2	10	V type	5
2	7	varied	16	10	V type	40
3	10	varied	2	30	V type	40
4	5	varied	16	30	V type	5
5	6	varied	2	10	Drum type	40
6	1	varied	16	10	Drum type	5
7	8	varied	2	30	Drum type	5
8	11	varied	16	30	Drum type	40
9	3	standard	9	20	V type	20
10	12	standard	9	20	Drum type	20
11	9	standard	9	20	V type	20
12	4	standard	9	20	Drum type	20

Process Control Option 2

Blend uniformity monitored using a process analyser

- Control Strategy to assure homogeneity of the blend
  - Control of blending end-point by NIR and feedback control of blender
  - API particle size

Equipment: XXXXX
Location of sensor attachment: Side position of the blender
Wavelength: XXXX cm^{-1} (Range of wave number: XXX to XXX cm^{-1})
Spectral Acquisition mode: diffuse reflectance

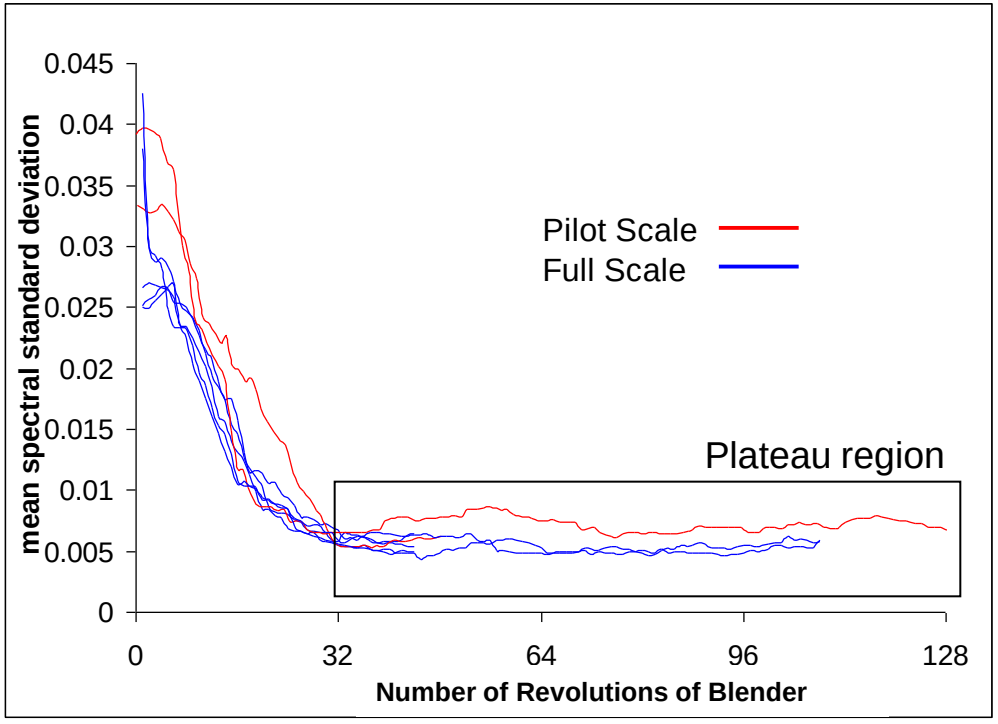


In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility

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



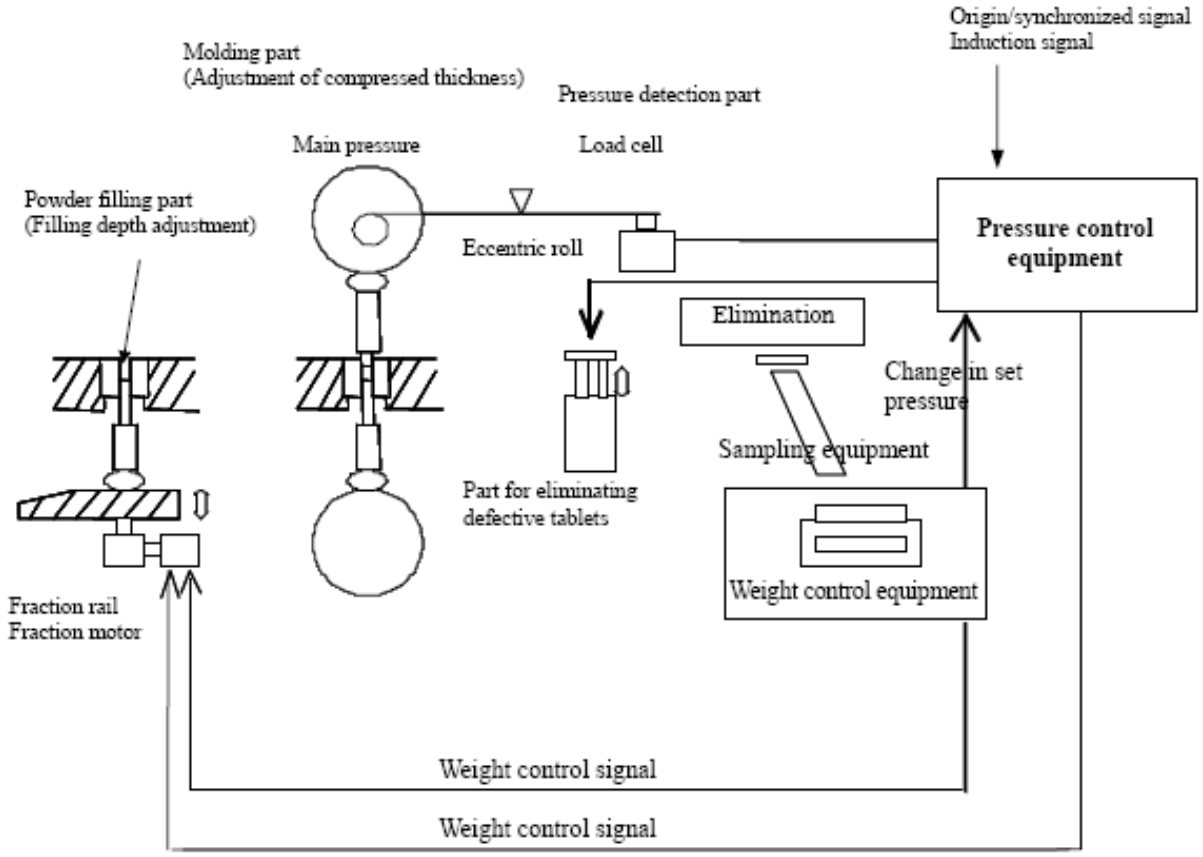
Data analysis model will be provided

Plan for updating of model available

Acknowledgement: adapted from ISPE PQLI Team

Case Study

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.

RTRT of Assay and Content Uniformity

- Real Time Release Testing Controls
  - Blend uniformity assured in blending step (on-line NIR spectrometer for blending end-point)
  - API assay is analyzed in blend by HPLC
    - API content could be determined by on-line NIR, if stated in filing
  - Tablet weight control with feedback loop in compression step
- No end product testing for Assay and Content Uniformity (CU)
  - Would pass finished product specification for Assay and Uniformity of Dosage Units if tested because assay assured by combination of blend uniformity assurance, API assay in blend and tablet weight control (if blend is homogeneous then tablet weight will determine content of API)

Case Study

Control Strategy

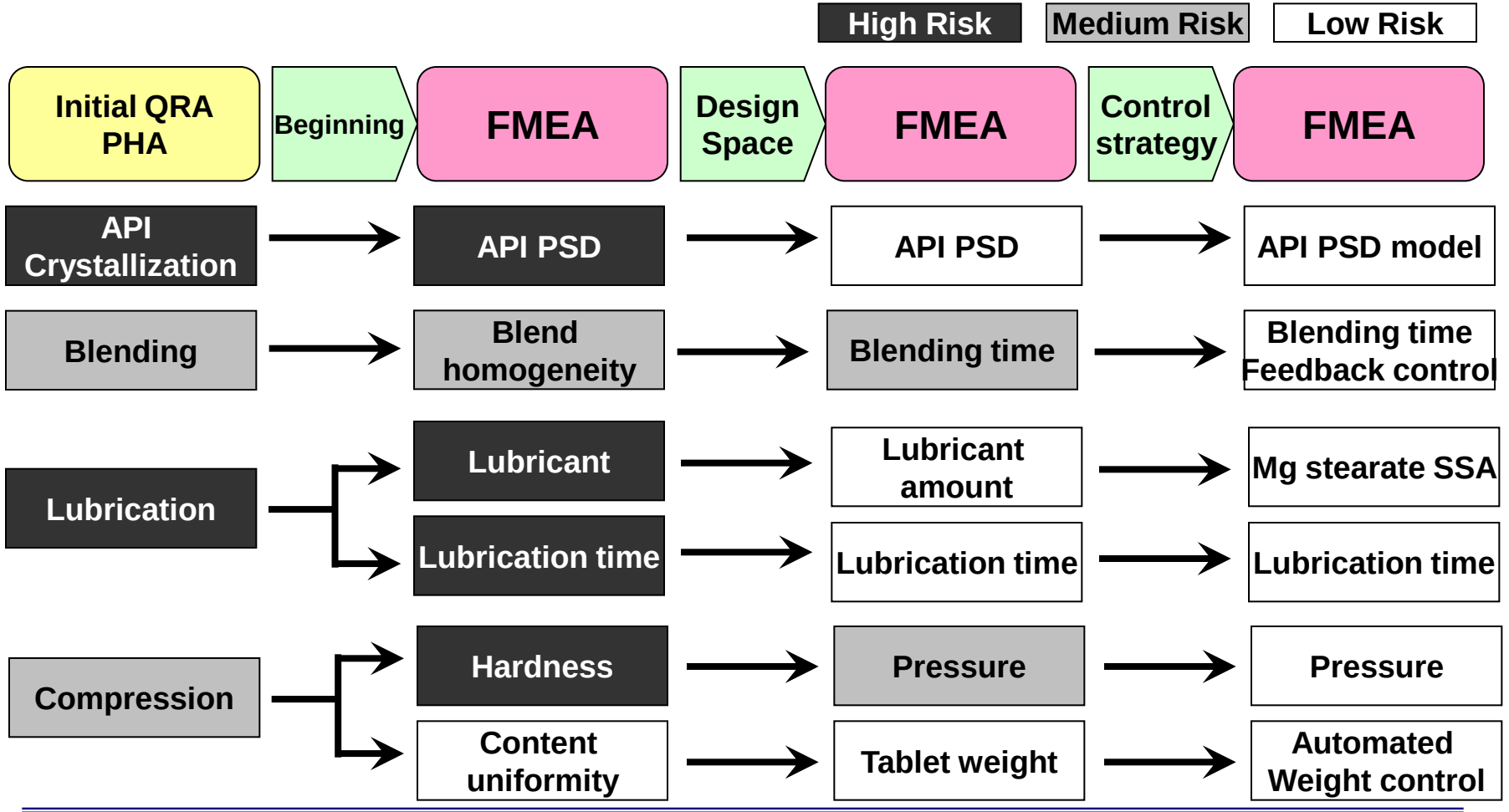
- **Input materials meet specifications and are tested**
  - API PSD
  - Magnesium stearate specific surface area
- **Assay calculation**
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop)
    - For 10 tablets per sampling point, <2% RSD for weights
- **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 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

Case Study

Drug Product Specifications

- **Use for stability, regulatory testing, site change, whenever RTR testing is not possible**
  - Assay acceptance criteria: 95-105% of nominal amount (30mg)
  - Uniformity of Dosage Unit acceptance criteria
  - Test method: HPLC
- **Input materials meet specifications and are tested**
  - API PSD
  - Magnesium stearate specific surface area
- **Assay calculation** (drug product acceptance criteria 95-105%)
  - 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%)
  - Not covered in this case study

Iterative risk assessments



Batch Release Approach

QA / Qualified Person assures

- Batch records are audited under the PQS
  - Parameters are within the filed design space
  - Proper process controls and RTRT were performed and meet approved criteria
- Appropriate model available for handling process variation which is subject to GMP inspection
- Predictive models are further confirmed and maintained at the production site

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

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