Implementation of ICH Q8, Q9, Q10

Case Study

Development → Assessment → Implementation → Inspection

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

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Content

- ***Case Study***
- ***Development***
- ***Assessment***
- ***Manufacturing Implementation and PQS***
- ***Inspection***

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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.

Acknowledgement

This presentation has been developed by members of the ICH Quality Implementation Working Group (Q-IWG)

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Implementation of ICH Q8, Q9, Q10

Case Study

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

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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*

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Basis for Development Information

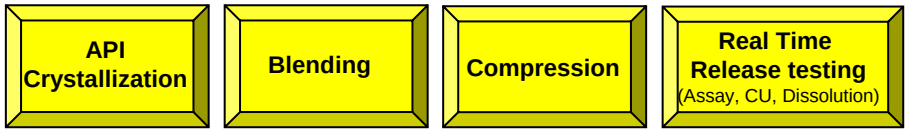
- Fictional active pharmaceutical ingredient (API)
- Drug product information is based on the 'Sakura' Tablet case study
  - Full Sakura case study can be found at http://www.nihs.go.jp/drug/DrugDiv-E.html
- Alignment between API and drug product
  - API Particle size and drug product dissolution
  -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

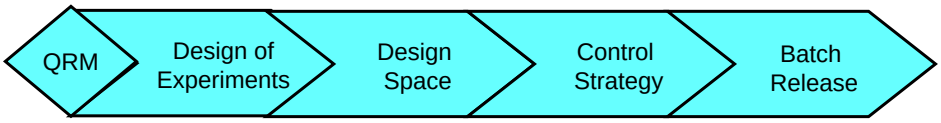
Technical Examples

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

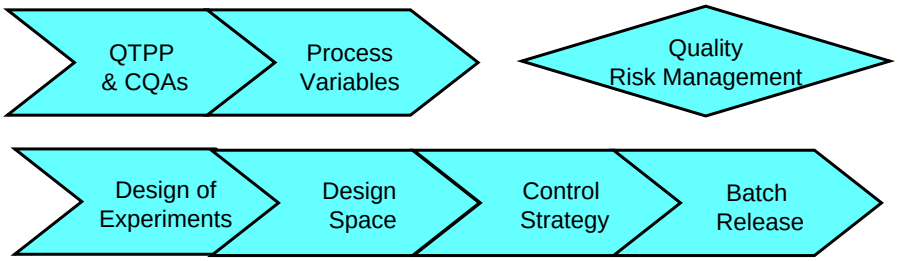


Process Step Analysis

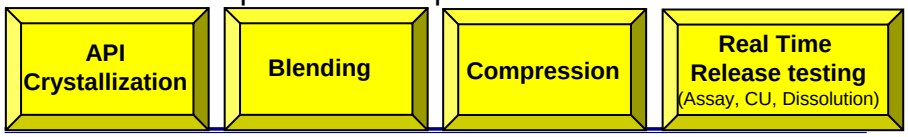
- For each example
  - Risk assessment
  - Design of experiments
  - Design space definition
  - Control strategy
  - Batch release



QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



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 = 30ºC)	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.

Case Study

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

Case Study

Drug Product Process

API and Excipients

Amokinol
D-mannitol
Calcium hydrogen phosphate hydrate
Sodium starch glycolate

→ **Blending**

Lubricant

Magnesium Stearate

→ **Lubrication**

→ **Compression**

Coating

HPMC, Macrogol 6000
titanium oxide
iron sesquioxide

→ **Film coating**

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)

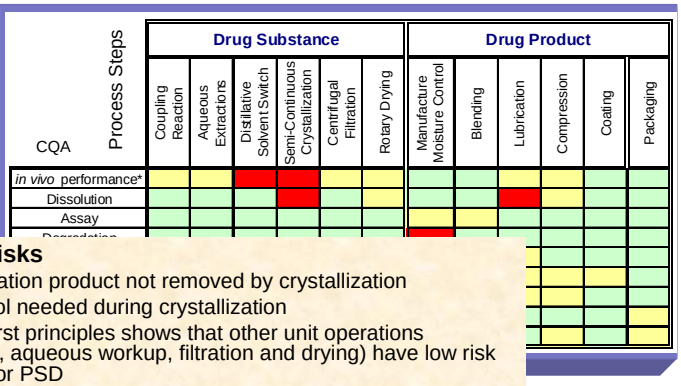
Process Steps

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)

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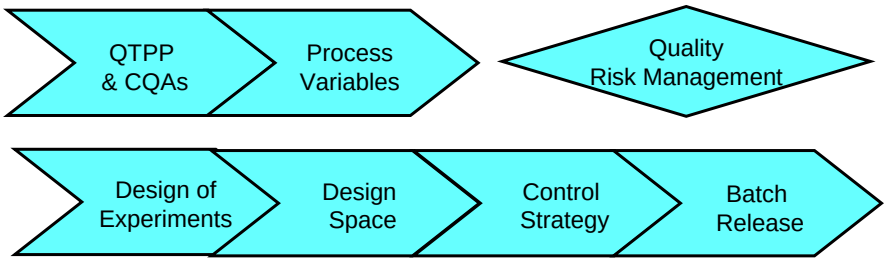
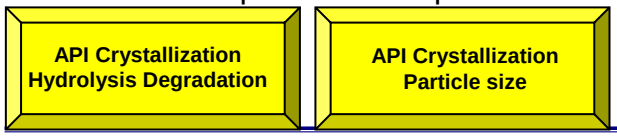
Case Study

API: The Story



Illustrative Examples of Unit Operations:



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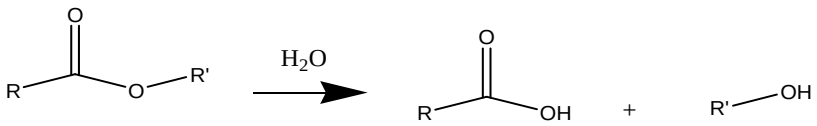
API Crystallization Example

- 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

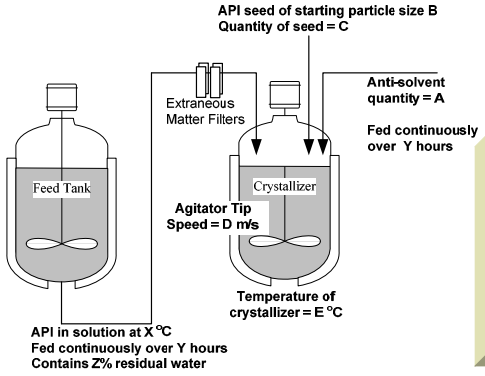
Hydrolysis Degradation



- 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)

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

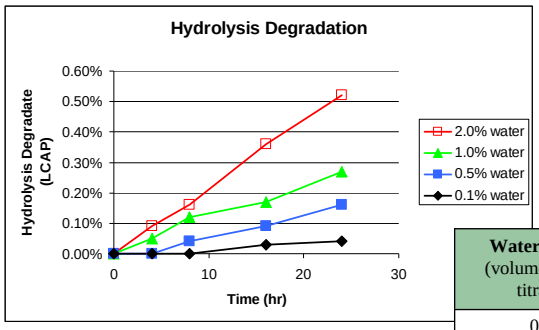
- **Crystallization Process Requirements**
  - API feed solution held at 60ºC, to maintain solubility of product, allows for passage through extraneous matter filters.
  - Batch fed to crystallizer slowly (to ensure particle size control). If fed too slowly (over too much time), hydrolysis degradate 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)

Experimental Data



Design Space Defined

Max Temp: 70ºC

Max Feed Time = 24 hr

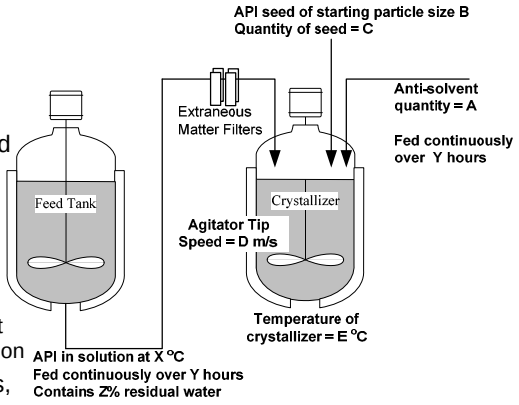
Max Water content = 1.0%

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%

Particle Size Distribution Control - Process History

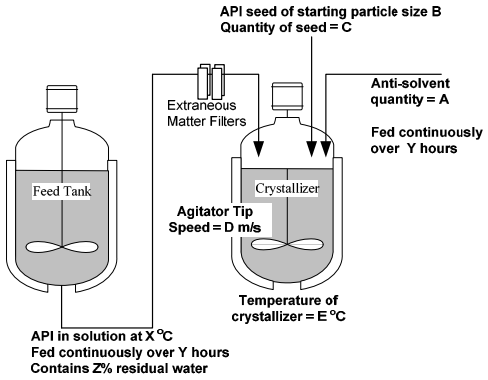
- *Changes in formulation drive changes in API process*
- Ph I and II trials performed with API-excipient mixture filled in hard gelatin capsules (liquid filled capsules = LFC)
- First API Deliveries
  - Simpler Crystallization Process
    - No PSD control; crystal agglomeration observed, but acceptable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

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Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

To be investigated in DOE

Case Study

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

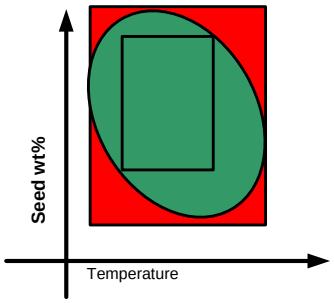
Case Study

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

Case Study

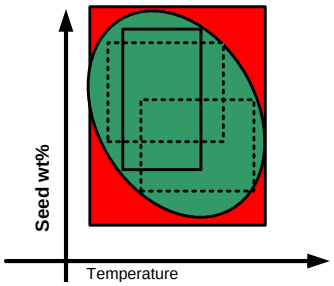
Options for Depicting a Design Space



- 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

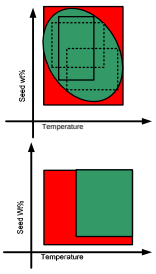


- Other rectangles can be drawn within the oval at top left, based on multiple combinations of ranges that could be chosen as the design space
- Exact choice from above options can be driven by business factors
  - e.g., keep seed charge narrow, maximizing temperature range, since temperature control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

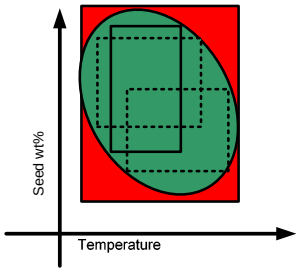
Options for Expanding a Design Space

- **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



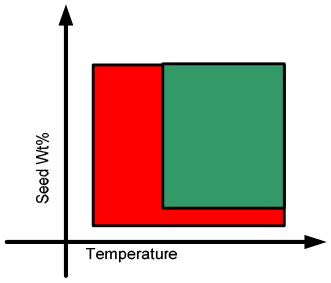
- When the original design space was artificially constrained for simplicity
  - Alternate combinations of ranges could be chosen as the new design space, based on original data.
    - e.g. the range for seed wt% could be constrained, allowing widening of the temperature range

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

Case Study

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

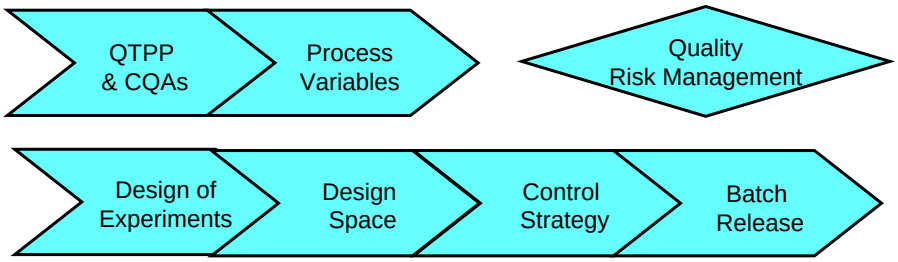
API Crystallization: Design Space & Control Strategy

Particle Size	Crystallization	Temperature	20 to 30°C	Control between 23 and 27°C
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

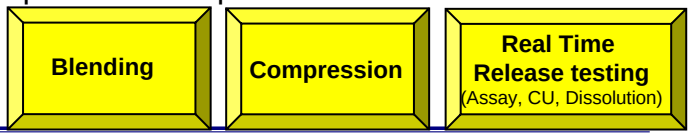
Batch Release for API

- **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:



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

Process	Operation	Materials
Process 1	Blending	Amokinol Calcium hydrogen phosphate hydrate D-mannitol Sodium starch glycolate
Process 2	Blending 2	Magnesium stearate
Process 3	Tableting	
Process 4	Film coating	HPMC, Macrogol 6000, titanium oxide, iron sesquioxide
Process 5	Packaging	

Focus of Story

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

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

Developing Product and Process Understanding

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

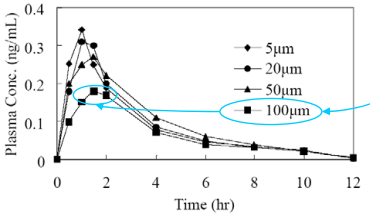


Figure 2.3.P.2.3-3 Blood Concentration Profiles

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

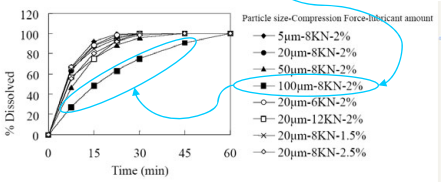


Figure 2.3.P.2.3-2 Dissolution Profiles from Tablets with Varied Drug Substance Particle Size (D90%), Compression Force and/or Lubricant Amount

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

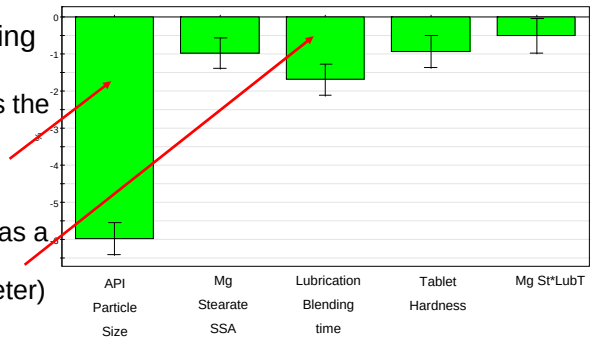
Exp No	Run Order	API	MgSt	LubT	Hard	Diss
1	1	0.5	3000	1	60	101.24
2	14	1.5	3000	1	60	87.99
3	22	0.5	12000	1	60	99.13
4	8	1.5	3000	10	60	86.03
5	18	0.5	12000	10	60	94.73
6	9	1.5	12000	10	60	83.04
7	15	0.5	3000	1	110	98.07
8	2	0.5	12000	1	110	97.68
9	6	1.5	12000	1	110	85.47
10	16	0.5	3000	10	110	95.81
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

Case Study

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

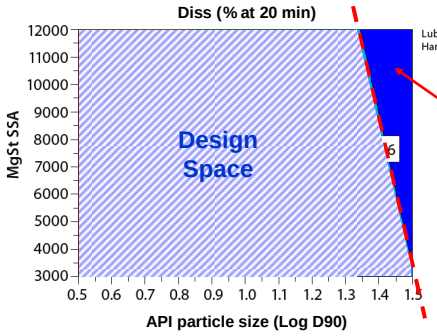
Predictive Model for Dissolution

- 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

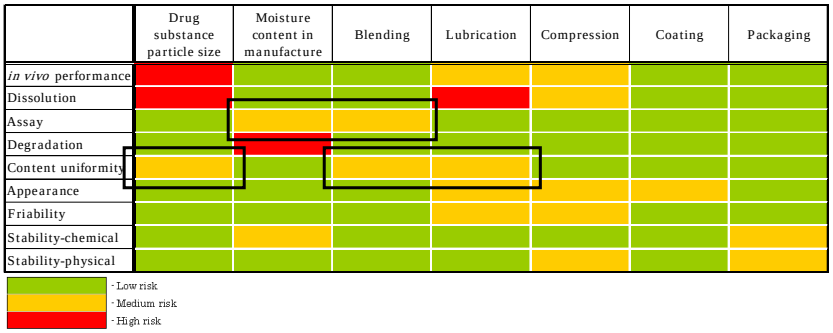
- **Controls of input material CQAs**
  - API particle size distribution
    - Control of crystallisation step
  - Magnesium stearate specific surface area
    - Specification for incoming material
- **Controls of process parameter CPPs**
  - Lubrication step blending time
  - Compression pressure (set 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

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)



Blending Process Control Options

Decision on conventional vs. RTR testing

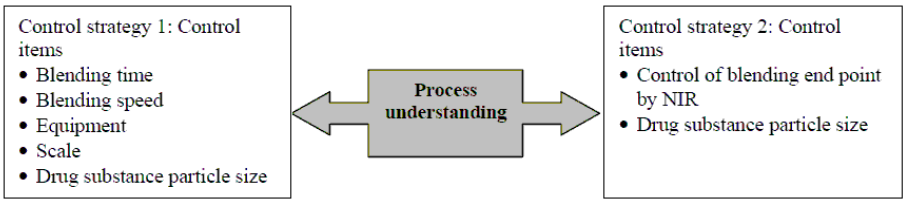


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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 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

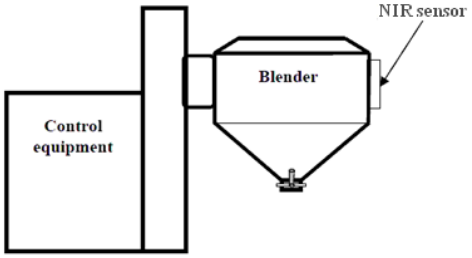
Case Study

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



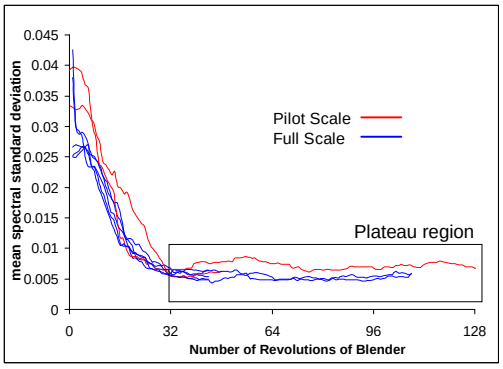
In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility

Case Study

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

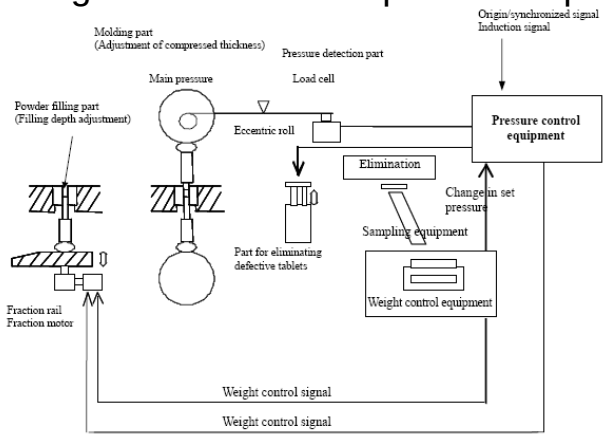


Data analysis model will be provided
Plan for updating of model available

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.

Case Study

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

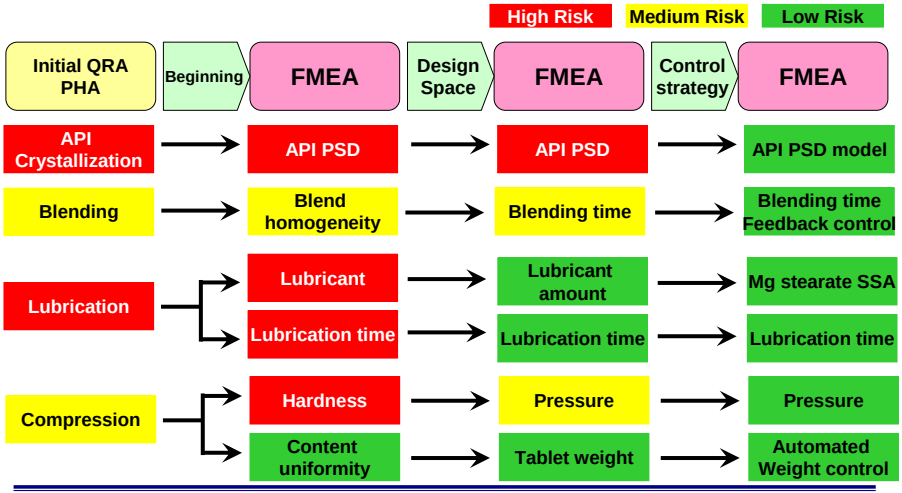
- **Input materials meet specifications and are tested**
  - API PSD
  - Magnesium stearate specific surface area
- **Assay calculation**
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop)
    - For 10 tablets per sampling point, <2%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

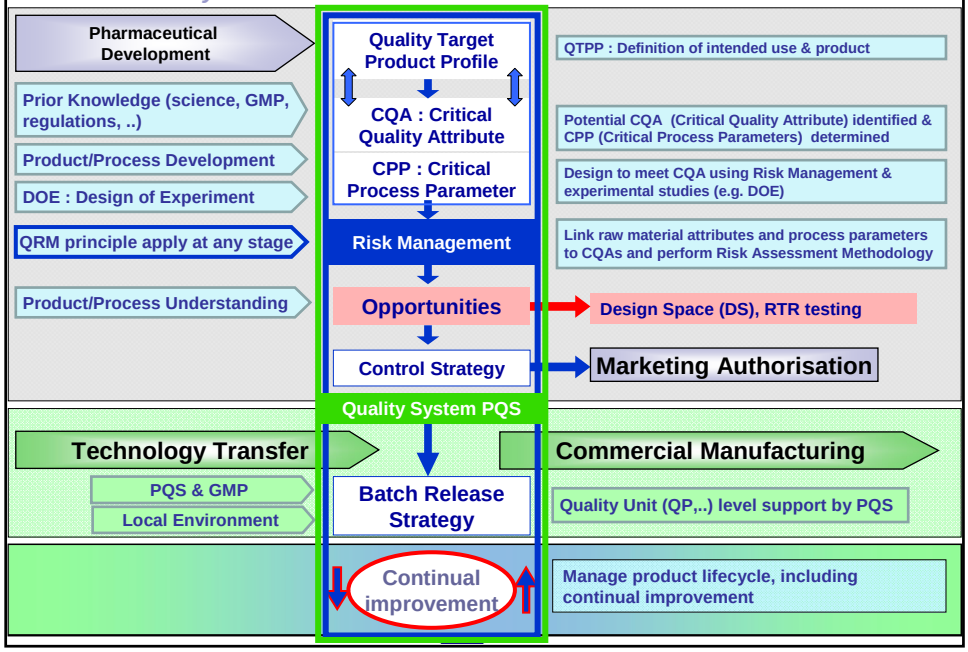
QA / Qualified Person assures

- 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)



Implementation of ICH Q8, Q9, Q10

Product Development: Case Study Overview

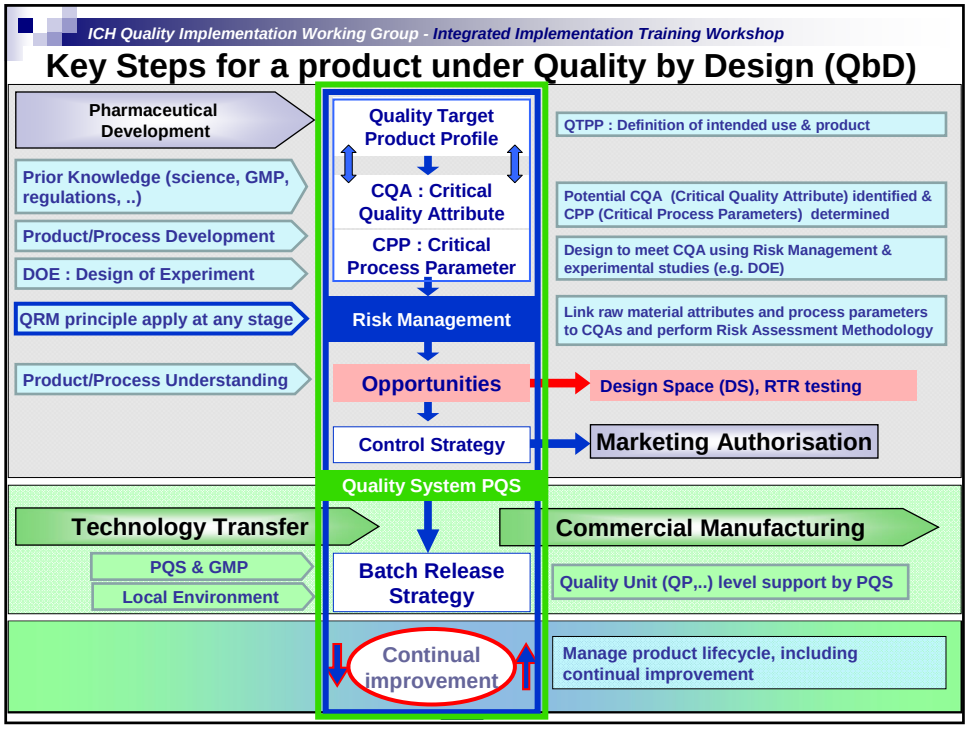
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH

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

ICH



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

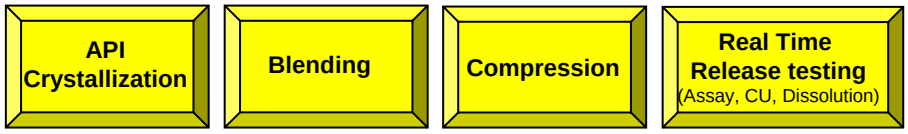
- Fictional active pharmaceutical ingredient (API)
- Drug product information is based on the ‘Sakura’ Tablet case study
  - Full Sakura case study can be found at http://www.nihs.go.jp/drug/DrugDiv-E.html
- Alignment between API and drug product
  - API Particle size and drug product dissolution
  -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

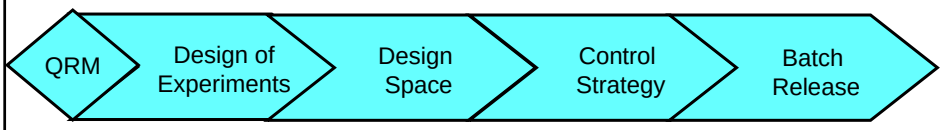
Technical Examples

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

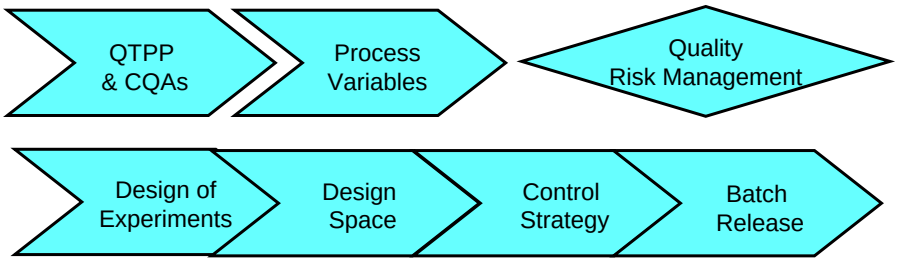


Process Step Analysis

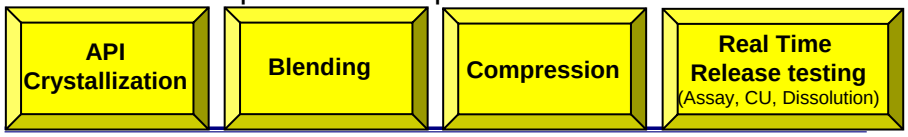
- For each example
  - Risk assessment
  - Design of experiments
    - *Experimental planning, execution & data analysis*
  - Design space definition
  - Control strategy
  - Batch release



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 = 30ºC)	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.

Example from Case Study

API Unit Operations

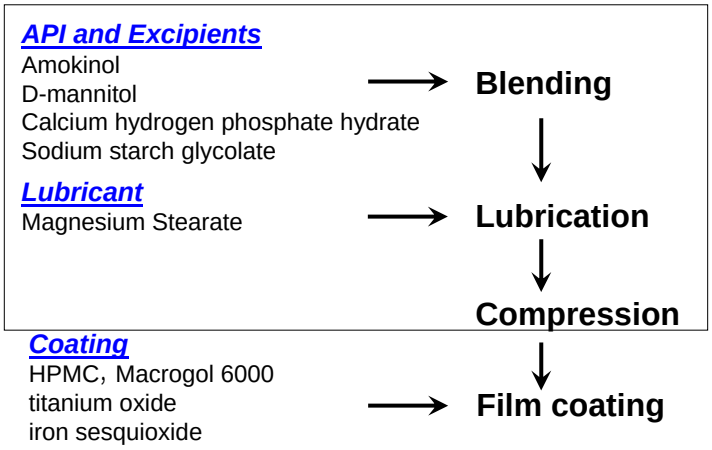
Understand formation & removal of impurities

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

Example from Case Study

Overall Risk Assessment for Process

Process Steps

- 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	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												

Overall Risk Assessment for Process

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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

Risk Assessment:

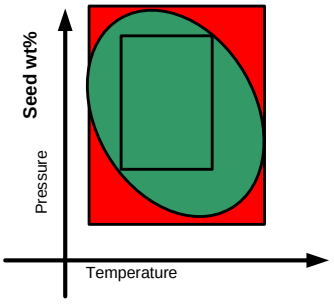
Particle Size Distribution (PSD) Control

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 im crystal size.
Crystallization	Water content of Feed	1	5	5	25	Prior knowledge (solubility data) do not affect crystallization 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



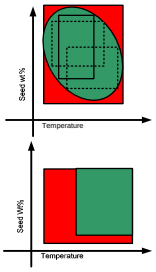
- Oval = full design space represented by equation
- Rectangle represent ranges
  - Simple, but a portion of the design space is not utilized
  - Could use other rectangles within oval
- Exact choice of above options can be driven by business factors

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

Example from Case Study

Design Space / Control Strategy Parameter controls & Testing

Particle Size	Crystallization	Temperature	20 to 30°C	Control between 23 and 27°C
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

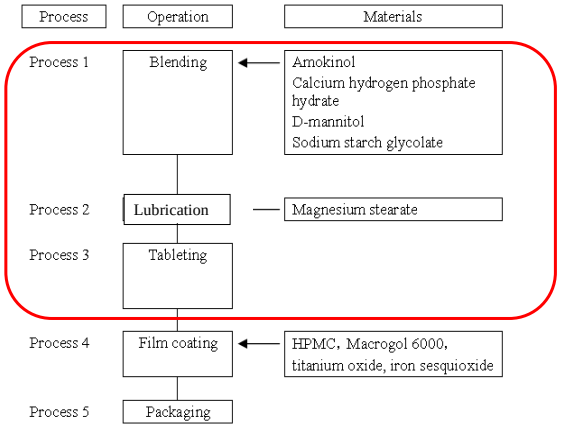
Particle size will be tested in this example, since the result is included in the mathematical model used for dissolution.

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

Drug Product Direct Compression

3.2.P.3.3 Manufacturing Process



Focus of Story

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

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

Example from Case Study

Predictive Model for Dissolution

A mathematical representation of the design space

Prediction algorithm:

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

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

Control strategy 1: Control items	Process understanding	Control strategy 2: Control items
• Blending time • Blending speed • Equipment • Scale • Drug substance particle size		• Control of blending end point by NIR • Drug substance particle size

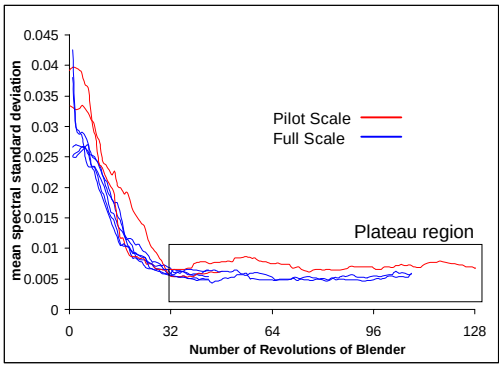
Figure 2.3.P.2.3-7 Control Strategy for Blending Process

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

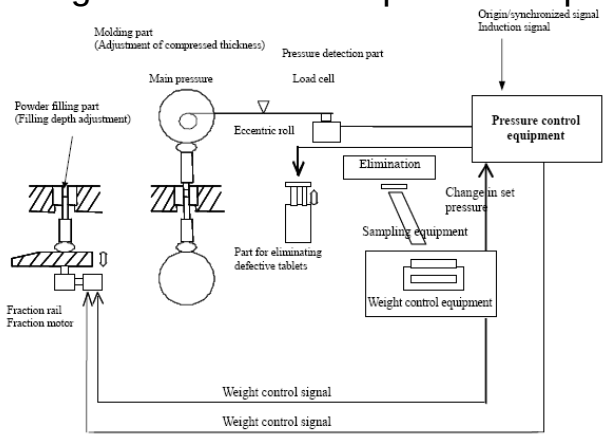
- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
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

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.

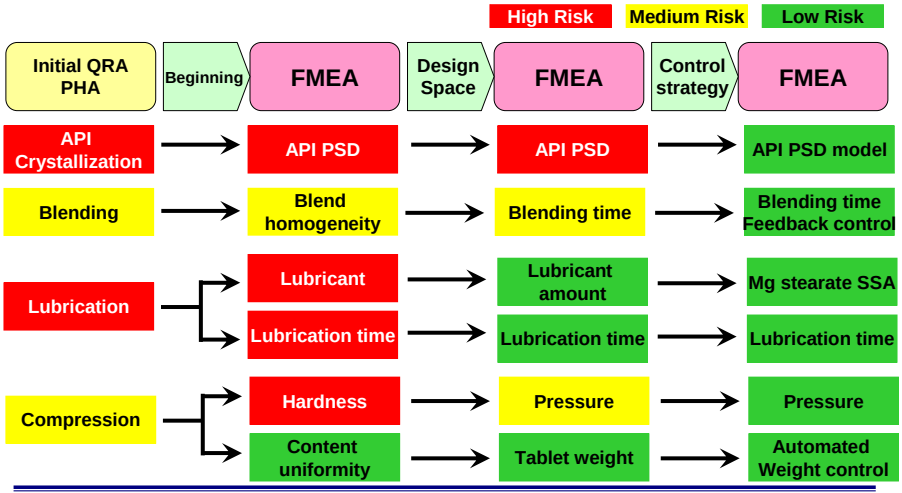
Batch Release Strategy

- **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)

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

Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

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

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Presentation Overview

- Goal of Regulatory Quality Assessment
- Review of the case study
  - Considerations during regulatory evaluation
    - Areas of consideration by assessors will be presented in the form of questions for the assessor
    - The questions presented here are not necessarily the ones which are finally communicated in regulatory deficiency letters
  - API and Formulation
  - Manufacturing Process Development
    - Quality Risk Management
    - Design Space
  - Proposed Control Strategy and Real Time Release Testing
  - Assessors - Inspector Interaction

Goal of Regulatory Quality Assessment

- **Assess**
  - That the product is capable of consistently meeting the required quality
  - That the manufacturing process is capable of producing quality product
  - That throughout product shelf life and life cycle commercial batches will link to clinical batches in all relevant aspects
- **These can be accomplished by**
  - Process development and control strategy according to traditional standards
  - Process development and control strategy according to new paradigm

Principles of Assessment

- Assessment principles are the same regardless of the development approach
- Meet Quality Target Product Profiles (QTPPs)
- Areas of assessment:
  - API
  - Formulation
  - Manufacturing process
  - Control strategy
  - Analytical Procedures
  - Stability

Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

API and Formulation

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API General Considerations

- QbD principles apply to APIs
- QbD principles can guide manufacturing process design and control strategy development
- Design space can be developed for API processes

ICH

API- Assessors' Evaluation

- Have starting materials and process been adequately described?
- Are there toxicity concerns with degradants and/or related substances?
- Have adequate specifications and methods been proposed?
- Have adequate process controls been described?
- Was the design space adequately developed and data provided to support it?

Formulation - General Considerations

- **Design space – formulation aspects**
  - Variable composition or component attributes
  - Based on input raw material attributes
    - Lot to lot variability
  - Justified by data (Prior knowledge, DoE, etc)
- **API attributes**
  - To be considered in the development of formulation and choice of dosage form to meet QTPP
  - Additional information may be needed for the development of the formulation e.g. BCS, PK, stability, excipient compatibility

Assessors' Evaluation of the Formulation

- Is dosage form designed to meet QTPP?
- Are the roles of ingredients identified?
- Have the safety and compatibility of ingredients been adequately addressed?
- Is the formulation adequately understood and specified?
- Does the proposed formulation differ from the formulation used in the pivotal clinical trials?

Assessors' Evaluation of the Case Study Formulation

- Why was Calcium Hydrogen Phosphate Hydrate chosen with a water sensitive API?
  - Concern about compatibility and stability
- Has material variability effects been understood?
  - Adequacy of NIR testing
  - Adequacy of dissolution model and method
- What is the function of D-mannitol in the formulation?
  - Described only as excipient in the case study
  - Needs to be further explained

Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

Manufacturing Process Development

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

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Assessment of Manufacturing Process Development

- Production process description needs to have sufficient detail to enable assessment
- Assessment should evaluate
  - Process design
  - Use of risk management processes including risk assessments
  - Design space
  - Robustness

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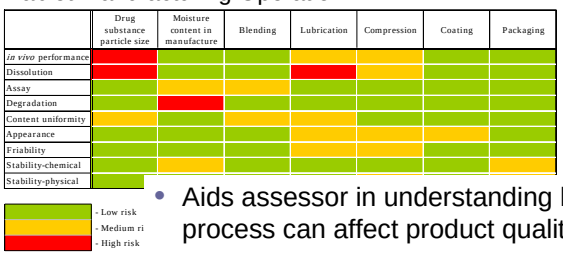
Initial Quality Risk Assessment

Tablet Manufacturing Operation



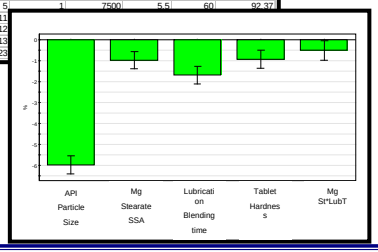
- Aids assessor in understanding how different aspects of the process can affect product quality
- Incorporates known risk factors of drug product – degradation pathways (e.g., moisture sensitivity), solubility factors, etc.
- Includes effects of unit operations and starting materials (including excipient properties)
- Atypical or unusual findings should be explained in greater detail

Assessors' Evaluation of the Risk Assessment

- Assessors to evaluate methodologies and outcome
  - Explanation of risk ranking and score
  - Setting of risk threshold
  - Assurance that relevant factors have been considered
- Are results consistent with scientific principles and prior knowledge?
- Was there a linkage of results to the development of design space and control strategy?

DoE to Support Design Space

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					
21	12					
22	13					
23	23					



- Multifactorial DoE study of variables affecting dissolution
  - Use an appropriate experimental design (e.g., some screening designs cannot determine interactions)
  - Provide more relevant experimental data and statistical analysis for critical unit operations
    - Address what parameters were not varied in the design space experiments

Assessors' Evaluation of Design Space

- Was a clear description of design space and its intended use provided?
- Has the proposed design space been appropriately established?
  - Demonstrated by data, supporting models and statistical evaluation
  - Understanding of interactions of variables
    - Multivariate vs univariate studies
  - Justified for the intended scale
  - Prior knowledge adequately summarised and/or referenced
- How could a design space built around one CQA (e.g particle size), affect other CQAs?
- Is the design space consistent with the control strategy?

Example from the Case Study: Crystallization Design Space

- **Goals of Crystallization Process**
  - D90 between 5 – 20 microns
    - Target set by dissolution and formulation DoE
  - Degradant < 0.3% (qualified)
- **Developmental knowledge**
  - Water during crystallization causes degradation
  - Multiple parameters likely to influence PSD during crystallization

Example from the Case Study: Crystallization Design Space – Cont.

- Univariate studies explored water content of solvent at max addition time and max temp
- DoE of 4 parameters established model for PSD:
  - 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 (C)
    - Statistical analysis shows that crystallization feed time does not impact PSD across the tested range.

Assessors' Evaluation of the Crystallization Design Space

- Was the use of risk management processes acceptable?
  - Was adequate information provided?
  - Was there an appropriate use of prior knowledge?
  - Did the application include the risk assessments for the most important CQA/process parameter pairs e.g. Degradation/Crystallization?
- Was it appropriate to do separate studies on formation of degradant and PSD?
- Are the process parameters 'scale independent'?
- How can the proposed model be confirmed?
  - Case study relied on center point runs at scale

Assessors' Evaluation of the Crystallization Design Space – Continued

- Is it appropriate to split out API PSD and impurity profile in risk assessment (Overall Risk Assessment for Process) ?
  - Presented in the case study combined as "In Vivo Performance"
- Should crystallization have been classified as high risk in the risk assessment for degradation?
- How was process and/or method uncertainty accounted for in the model?
- Did the design space presented illustrate the interaction of parameters?
  - Case study showed two separate response surfaces for the two CQAs evaluated

Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

Proposed Control Strategy and Real Time Release Testing

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

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Regulatory Assessment

Assessors' Evaluation Of the Control Strategy

- Do the CQAs provide assurance that the QTPP will be met?
- Is the control strategy based on appropriate risk management?
- Is the placement of proposed controls maximally effective?
- Does the description of control strategy include down stream tests?
- Are the Specifications adequate?
- What functional tests for excipients are needed? Were these included?
- Assessing some elements of control strategy such as RTRT, PAT, etc. may require assessors and inspectors with specialized training

ICH

Blending Process Control Options

- Purpose – to assure that the blend is uniform
- Conventional control (option 1)
- RTRT (PAT based) control (option 2)

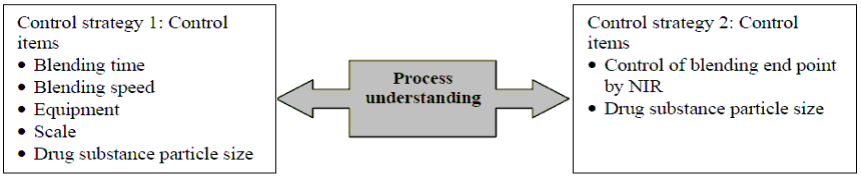


Figure 2.3.P.2.3-7 Control Strategy for Blending Process

Blending Control Option 1

- Perform DoE to develop the design space
- CPPs involved – blender type, blending speed, blending time, API particle size
- **Assessors' evaluation**
  - Were all CPPs properly identified during QRA?
  - Are the reference method and sampling procedure used to assess the blend uniformity adequate?
  - Is the design space developed from the DoE applicable at commercial scale?

Blending Control Option 2

- Control of blending end-point by NIR
- Includes a chemometric model to predict the end-point of the process
- **Assessors' evaluation**
  - Is the model properly developed and validated?
  - Do the model predictions correlate with standard blend uniformity measurements?
  - Are all sources of variation (e.g., excipients) included in the model?
  - Is the probe location adequate?

Real Time Release Testing – Assessors' Evaluation General Considerations

- Have tests been verified at full scale?
- Have analytical procedures been validated? If the procedure contains a model, has it been validated and has an adequate maintenance plan been proposed?
- Have alternate traditional testing procedures been provided for any RTRT? To be used for
  - Stability testing
  - Regulatory testing
  - Break down of equipment when specified in dossier

Example from Case Study: RTRT for Dissolution

- Quality Risk Assessment shows that API particle size, lubrication and compression have potential to impact dissolution
- Analysis of in-vivo data also shows that API particle size impacts bioavailability
  - Larger particles have lower Cmax and AUC
- Multi factorial DoE carried out to estimate impact of factors on dissolution
  - Factors investigated: API particle size, magnesium stearate specific surface area, lubrication time and tablet hardness
  - Response measured: % dissolved at 20 min
  - DoE data analyzed to identify statistically significant factors affecting dissolution

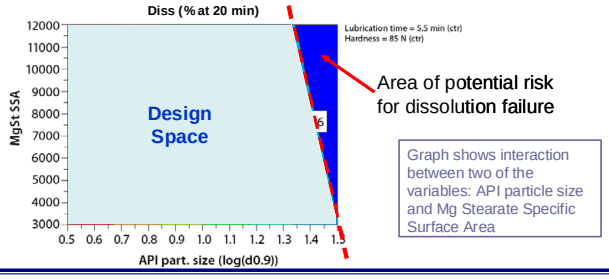
Example: RTRT for Dissolution

- Predictive model for dissolution defined from DOE data

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

- Model verified by comparing predicted data with measured dissolution data for 3 batches

Graphical Representation of Dissolution Design Space



Graph shows interaction between two of the variables: API particle size and Mg Stearate Specific Surface Area

Dissolution Model Based on RTRT – Assessors' Evaluation

- Has a robust and discriminatory reference procedure (e.g. dissolution by HPLC) been provided?
- Has the dissolution model been validated with an independent data set (i.e. not just the DoE data)?
- Has model applicability been demonstrated across all variability proposed in the design space (e.g. change in scale, change in equipment type etc)
- Has process and/or method uncertainty been incorporated in the model?
  - Has a process been described for revision of design space on basis of prediction intervals?
- Has the applicant considered multivariate trend monitoring for the CQA and/or CPP that impact dissolution (e.g. API particle size, compression parameters etc)?
- Have plans been provided for model maintenance throughout the product life cycle?
  - Plans to revise the model (e.g. with change in API PSD outside the range that was evaluated via the DoE)
  - To be done under the company's quality system and subject to GMP inspection

Dissolution Model based on RTRT - Assessors' Evaluation Continued

- Is the model prediction compared with the reference method for a statistically significant number of batches?
- Is the proposed acceptance criteria for dissolution appropriate?
- Given that there are more than 2 parameters that impact dissolution, should the dissolution design space be represented graphically as an interaction of more than one response surfaces?
- How capable is the model:
  - For taking into account variation in tablet hardness throughout the run?
  - For predicting failed batches?

Dissolution Model based on RTRT - Assessors' Evaluation Continued

- Have details been provided on how the model would be used as a feed forward control, to adjust process parameters (e.g. compression parameters) depending on API particle size and/or magnesium stearate specific surface area?
- Could a routine in process disintegration test lower the risk of implementing this RTRT?

Example from the Case Study: RTRT for Tablet Assay and CU

- Based on in-process tablet weight control
  - Part of compression operation
- Fill volume during compression adjusted by a feedback loop from the tablet weight measurement

Example from Case Study: RTRT for Assay and Content Uniformity

- Risk Assessments as part of the QRM process shows four factors have potential to affect Assay and CU:
  - API Particle Size
  - Environmental moisture control
  - Blending and Lubrication
  - Absence of segregation before and during compression
- API Particle Size controlled by incoming materials testing and release
- Blend uniformity and absence of down stream segregation are key elements of control strategy

RTRT for Tablet Assay and CU: Assessors' Evaluation

- Are adequate data presented to demonstrate absence of segregation?
  - During compression, especially at beginning and end of run
  - When blend is held prior to compression
- Does the NIR method predict % active content of the blend (vs. indicating uniformity by variance change)?
- How is the use of the RTRT described in the specification?
- Is the information provided (e.g. data points, number of batches, comparison of individual tablets) adequate, to compare the assay calculated by weight to assay measured by HPLC?

Implementation of ICH Q8, Q9, Q10

Regulatory Assessment

Assessor – Inspector Interactions

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Assessor - Inspector Interaction

- Certain aspects of the application may need to be verified at site, such as
  - Has a statistically based criterion for release (e.g. acceptance limits, sample size, confidence intervals, outliers) been defined and addressed by the PQS?
  - Does the company's quality system have procedures to trend tablet weight during routine production and to accept/reject batches on the basis of RTRT?

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Assessor - Inspector Interaction Continued

- Certain aspects of the application may need to be verified at site, such as
  - Implementation of commercial manufacturing process
  - Implementation of design space, RTRT, control strategy.
  - Management of design space and models
  - Confirmation of data
  - Input for batch release strategy
    - Sampling plan especially for RTRT
- Communication between inspector and assesor is important

Case Study Example of Interaction Between Assessors and Inspectors

Points to Consider

- For Crystallization Design Space
  - Conducting the inspection during the review period
  - Communication between Inspector and assessor prior to inspection
  - Including assessors and inspectors on inspection
    - May require specialized training for things like models and RTRT
  - Reviewing procedures for design space management within the company's quality system
- For future inspections after commercialization
  - Did verification of design space for crystallization at commercial scale support conclusion that the design space was scale independent?

Conclusions

- Use of ICH Q8, Q9, Q10 will facilitate regulatory assessment
  - Knowledge rich applications provide transparency and facilitate assessment
    - Systematic development described in regulatory submissions will improve the regulatory assessment
    - Improve the efficiency of the review / assessment
  - Enable science and risk based regulatory decisions
  - Improve communication
    - Between Regulators and Industry
    - Between Assessors and Inspectors

Implementation of ICH Q8, Q9, Q10

Manufacturing Implementation and the Pharmaceutical Quality System

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Introduction

- Moving through the product lifecycle
  - Development into Commercial Manufacturing site
  - 'smooth transition' – continuation of product and process learning
- Manufacturing role will be simplified by a well developed product
  - More product and process knowledge

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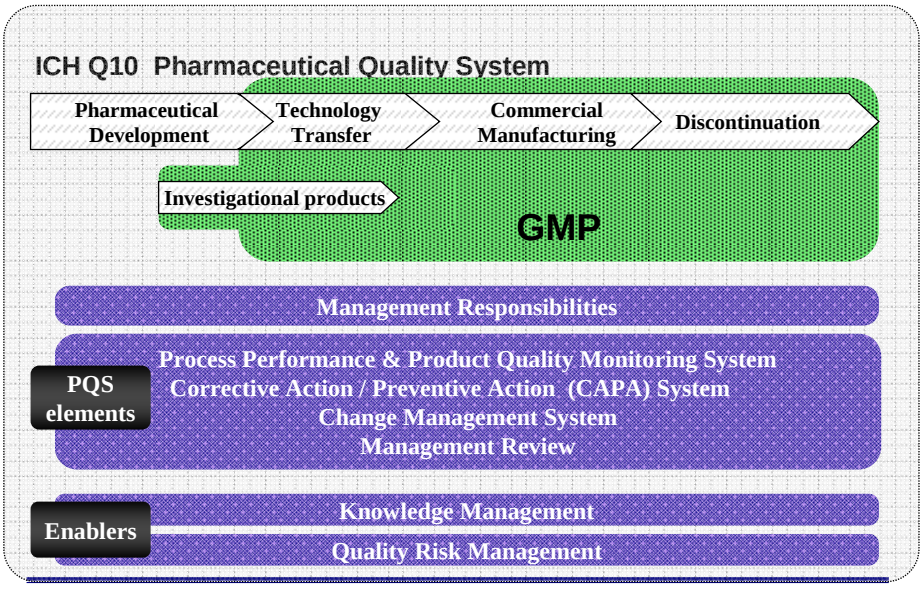
Introduction

- Manufacturing still have a key role to play
  - Using that knowledge gained during development
  - Using current site knowledge (e.g. similar products)
  - Building on that knowledge through transfer, validation, and commercial manufacturing activities
  - Feedback of that knowledge to Development
- Will consider the PQS in this presentation
  - And how it can help 'drive' the product through the lifecycle

- **Pharmaceutical Quality System**
- Scale-up and Technology Transfer
- Process Validation
- Change Management and Continual Improvement
- Quality Unit (QA/QC) and Batch Release



- Pharmaceutical Quality System
- **Scale-up and Technology Transfer**
- Process Validation
- Change Management and Continual Improvement
- Quality Unit (QA/QC) and Batch Release

Scale up and Technology Transfer

- Creates a unique opportunity to jointly learn more about product and process (development/manufacturing)
  - Needs to be properly planned
    - Use development knowledge
    - Involve the correct people (knowledge and training)
    - Ensure enough time
    - Use QRM to identify risks of next scale up
    - Tests the documentation (master batch record, SOP's)
- Technology Transfer must ensure that the
  - Process works in practice (facility, equipment)
  - Control strategy works in practice
    - Proving Predictive models work at increased scale
    - Real Time Release Testing data can be used with confidence

Case Study: Drug Product Manufacturing Process

2.3.P.3.3 Manufacturing Process

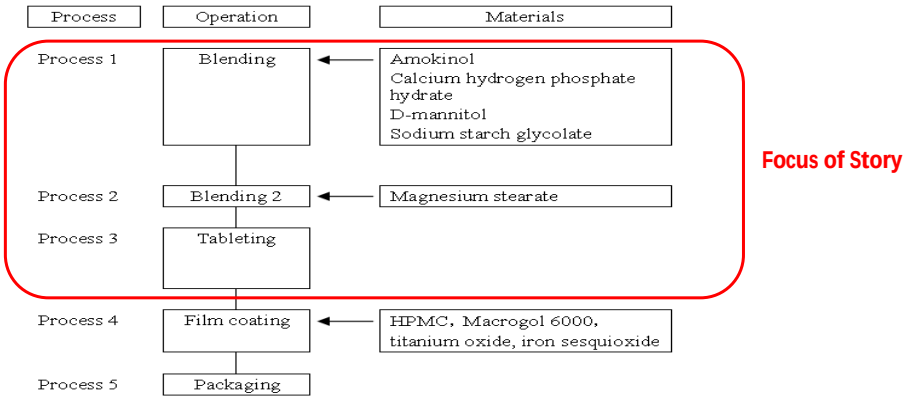


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

Drug Product Process Scale-up

Case Study Focal Steps – Blending and Tabletting

- Early Clinical Development – Liquid-filled capsules
- Phase 3 Scale – 50,000 units (made in Development)
  - Technology Transfer to Production Begins
- Verification of Predictive Model
- Scale at time of Submission 200,000 units (made in Manufacturing plant)
- QRM Evaluation for next scale-up (?)
- Desired Commercial scale – 1,000,000 units (Planned for Commercial Plant(s)

Predictive Model Verification

- Predictive Models proposed and utilized during Development phase
- Laboratory testing for dissolution and compressed tablet CU is performed:
  - During Tech Transfer to evaluate and confirm predictive Model at pilot and commercial scale at site of manufacture
  - Confirmatory Laboratory testing for dissolution and compressed tablet CU compared to values calculated by model for initial commercial batches (e.g. the first 10 batches)
- Review Development, Process Validation, and Commercial scale batch data to analyze and refine predictive model
- Periodic confirmatory testing of commercial batches

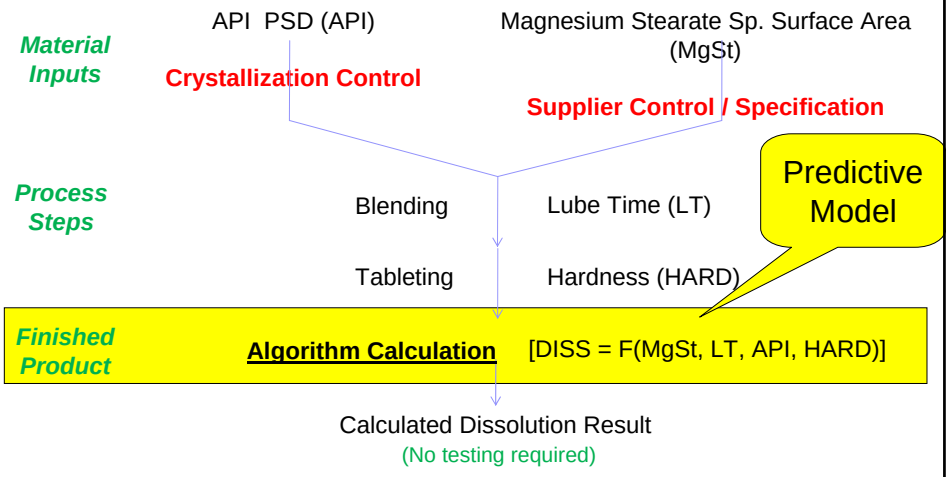
Control Strategy

Finished product is not tested by QC lab for assay, CU and dissolution

- **Input materials** meet specifications and are routinely tested for their critical attributes
  - 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)
    - 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
  - Compression force monitored and in range

- **Dissolution (See next slide)**
  - Predictive model using input and process parameters for each batch calculates dissolution meeting acceptance criteria
  - Input and process parameters used are within the filed design space

Dissolution: Control Strategy



Note: Use of algorithm potentially allows process to be adjusted for variation in API particle size, for example, and ensure dissolution performance.

Example

Predictive Model for Dissolution

Prediction algorithm:
Diss = 108.9 – 11.96 × API – 7.556×10^{-5} × MgSt – 0.1849 × LubT – 3.783×10^{-2} × Hard – 2.557×10^{-5} × MgSt × LubT

Factors include: API PSD, magnesium stearate specific surface area, lubrication time, tablet hardness

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)

No failures. Verify model in production scale to determine if it provides suitable and sufficient surrogate to replace direct measurement of the critical product attribute (dissolution). **The model will be maintained within the PQS**

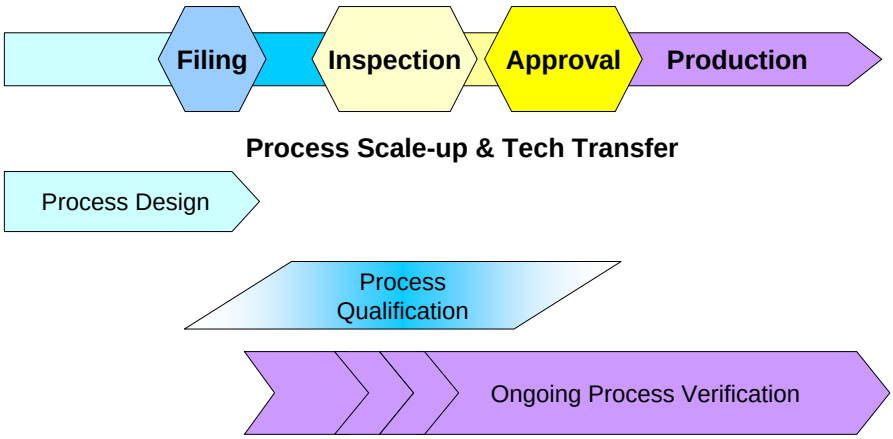
- Pharmaceutical Quality System
- Scale-up and Technology Transfer
- **Process Validation**
- Change Management and Continual Improvement
- Quality Unit (QA/QC) and Batch Release

Process Validation

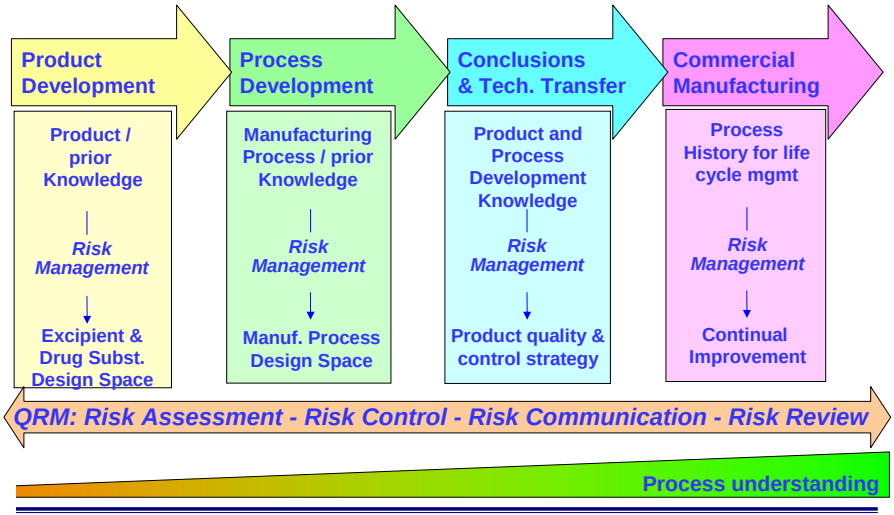
- Helps to build confidence in the product and process

- Consider new approach to process validation
  - No longer a one-off exercise (i.e. 3 validation batch approach)
  - Process Validation starts earlier in the product lifecycle
  - Continues throughout the remainder of the product lifecycle
  - Focus more on the critical parts of the process
    - Use of Development knowledge
    - Use of Process monitoring data
    - Use of QRM tools (e.g. FMEA)
    - Use of statistical process capability and control analysis

Process Validation Lifecycle



Role of Quality Risk Management in Process Validation



Ongoing Process Verification

Continual process verification

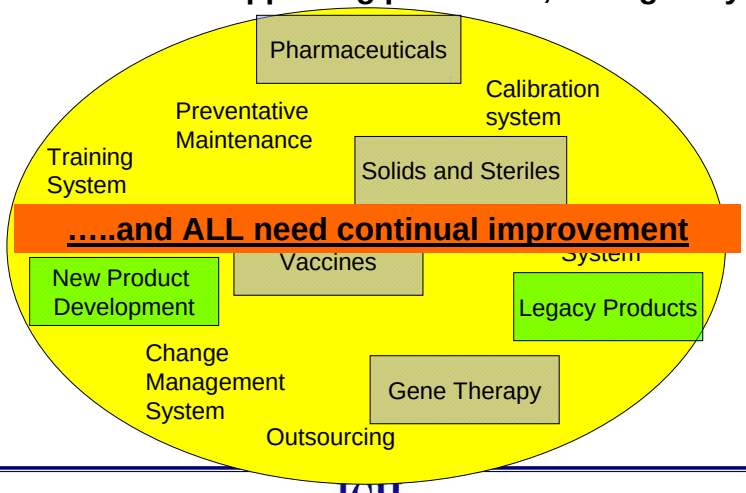
- Can be established by placing process monitor/evaluation tools at appropriate manufacturing steps based upon thorough product and process understanding
- Can be built in process validation protocols for the
  - initial commercial production
  - manufacturing process changes
  - continual improvement throughout the product lifecycle.

- Pharmaceutical Quality System
- Scale-up and Technology Transfer
- Process Validation
- **Change Management and Continual Improvement**
- Quality Unit (QA/QC) and Batch Release

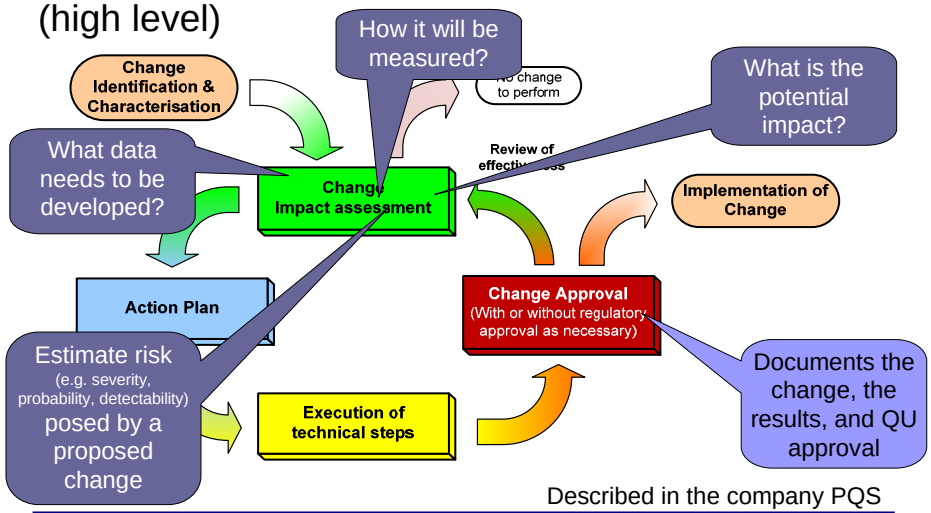
Change Management and Continual Improvement

- Changes *WILL* happen throughout the product lifecycle
  - **Proactively** due to business or technical reasons
    - Part of continual improvement initiatives
      - > e.g. new supplier, batch size change, new equipment
  - **Reactively** driven as part of CAPA
    - Due to deviations, OOS, batch rejections
- The PQS must include a *robust* change management system
  - Use of knowledge and Quality Risk Management
- Continual Improvement must be part of our daily working lives
  - Helped by data (e.g. trend data, Statistical Process Control)
  - Driven by people - as part of the culture!

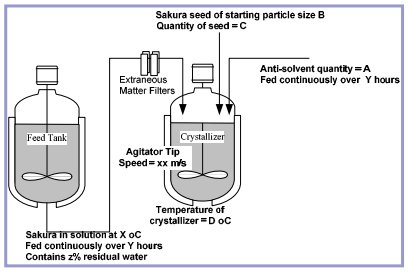
Different Types of Products, at Different Stages of Lifecycle All need 'relevant' supporting processes, managed by PQS



Typical Change Management Process Map (high level)



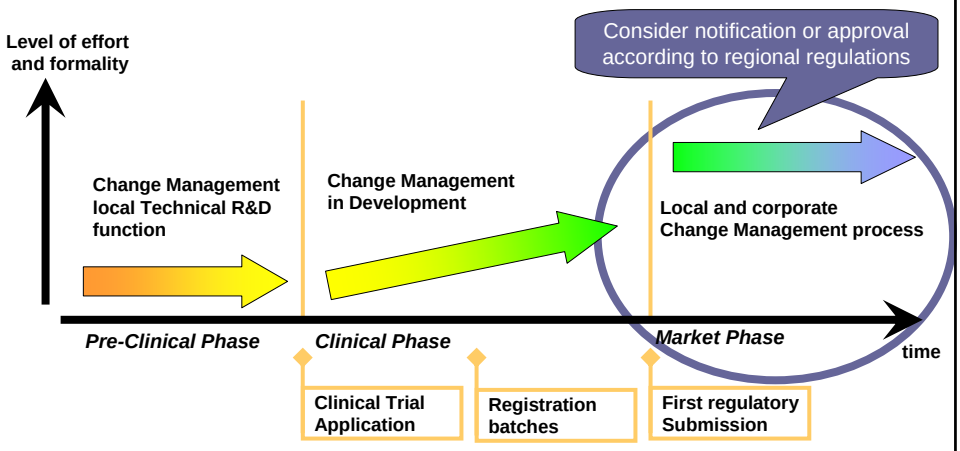
Change Management



- **What happened?**
  - Over time the seed characteristics changed
- **Available knowledge**
  - Seed characteristics has an influence on the Particle Size distribution
  - The Control Strategy provides guidance:

CQA	Unit Operation	Parameter	Design Space	Comments
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

Different Change Management approaches over the Life Cycle



Change Management Process

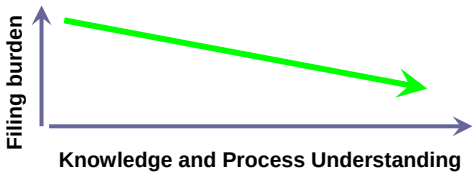
- **Verification by Quality Management**
  - Consider Technical Regulatory Filing
  - Link to Knowledge Management
    - Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components.
    - Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; deviations, customer complaint, returns, CAPA and OOS's assessments; continual improvement; and *change management* activities.

Based on ICH Q10, Pharmaceutical Quality Systems

Change Management Process

Quality Management will:

- Verify if proposed change to operating range is within design space
- Utilise Knowledge and Process Understanding



- Ensure Manufacturing can perform the change without prior notification of health authorities
  - Critical process parameters within design space
  - Non-critical process parameters

Change Management process

- **Confirmation of successful change: e.g.**
- **Process Validation**
  - Can be operated as a lifecycle monitoring i.e. 'Continuous Process Verification'
- **Annual Product Review (APR)**
  - The effectiveness of the change is demonstrated

Further elements of the PQS

Continual Improvement of the Product

Inputs
- Manufacturing Experience
- Deviations / CAPA
- Performance Monitoring
- Customer Complaints
- Management Reviews
- Material Variance

Continual Improvement

Lifecycle Adjustment
- Readily achieved as part of routine feedback
- Require permanent & substantial process/facility design to improve original concept

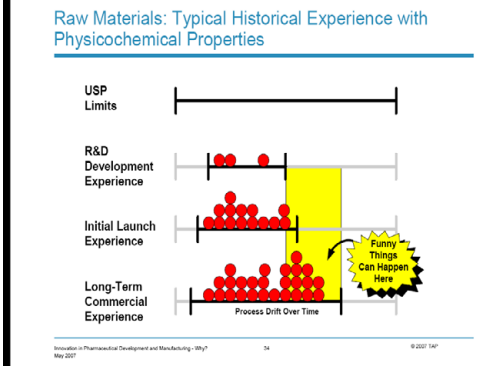
Expanded Body of Knowledge

Feed Forward

Feedback

Lifecycle Management

Change Management and Continual Improvement of the Product



[Jean-Marie Geoffroy, May, 2007]

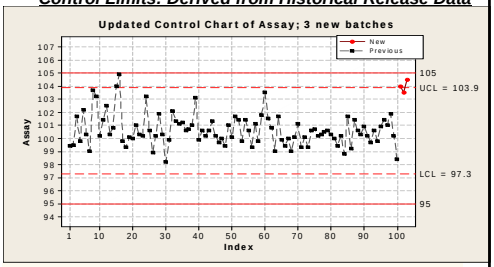
Raw Materials

- Can be one major source of process variation – even if within the agreed specification limits
- Commercial manufacturing experience will increase our understanding of such raw material batch to batch variation over time
- Case study example:
  - Magnesium Stearate Specific Surface Area

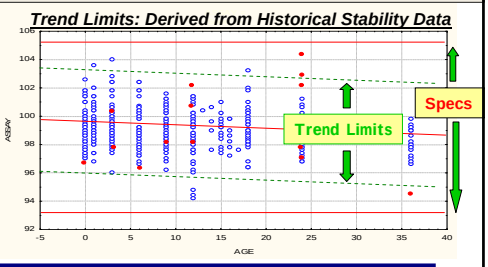
Continual Monitoring

- Process Tracking and Trending
  - Statistical Process Control
  - Address trends before they become problems
- Product Quality Monitoring
  - Analyze parameters & attributes in the control strategy
  - Reduce sources of variation

Control Limits: Derived from Historical Release Data



Trend Limits: Derived from Historical Stability Data



- Pharmaceutical Quality System
- Scale-up and Technology Transfer
- Process Validation
- Change Management and Continual Improvement
- **Quality Unit (QA/QC) and Batch Release**

Quality Unit (QA/QC) and Batch Release

- The role of the Quality Unit does not change generally with respect to Batch Release just because of Design Space, Real Time Release Testing, etc.
- Will consider some specific aspects that the Quality Unit may need to consider as part of their role
  - e.g. Real Time Release Testing

Manufacturing Quality Unit Oversight

- Lifecycle Responsibility - Cross functional with commercial/R&D
- Modifications of site PQS to ensure alignment with enhanced development approach (e.g. design space, RTR testing)
- Key development information (knowledge) must be available to manufacturing sites (e.g. predictive models, design space)
- Continual Improvement in the Commercial part of the Lifecycle
- Maintenance and use of the Design Space and Control Strategy
- Use of Risk Management within the Quality System
- Clear traceability between CQA's, CPP's, specifications
  - Development → Production

Supplier and Outsourced Manufacturing Activities

- Increasing trend for industry to use outsourcing
  - Industry may outsource

……but they can never outsource their responsibilities and and accountability!

- Company PQS must ensure appropriate control of:
  - Suppliers
    - Active Pharmaceutical Ingredients, Excipients
    - Other GxP related materials (e.g. cleaning materials)
  - Third party contractors
    - Manufacturing, Packaging, Distribution, Transportation
- PQS must consider selection and assessment, responsibilities, communication, ongoing monitoring, reviewing performance, and verifying supply chain

Real Time Release Testing versus QC Testing

- Need to ensure the same degree of confidence in the Real Time release testing as 'traditional' Quality Control laboratory testing, for example:
  - Responsibilities clearly defined
    - Routine maintenance and calibration (e.g. NIR)
    - Reporting deviations
  - Qualification and Validation
    - Qualification of test equipment (e.g. NIR)
    - Validation of analytical testing method
    - Validation of any data handling software and summary reporting (e.g. statistical software)

RTR Testing: Batch Release Considerations

- In line with marketing authorisation requirements?
- Sample sizes?
- Samples taken how frequently?
- Samples representative of the process? (e.g. tablet weight from each compression head)
- Data statistically analysed and reported correctly?
- What constitutes an RTR testing deviation (e.g. testing equipment failure), and how will it be handled under the quality system?

Conclusions

- **Scale up and Technology Transfer**
  - Scale-up of manufacturing processes and controls must confirm and support final design space
  - Proof of concept and adaptation of Control Strategy for commercial applicability
- **Process validation**
  - Over the lifecycle rather than a one time event
  - Confirms predictive models at full scale
  - Incorporates QRM Principles and Knowledge Management
  - Part of PQS at commercial manufacturing site

Conclusions (continued)

- **Change Management**
  - Need to consider development information
  - Changes within the design space can be managed internally without prior regulatory notification
  - Changes to Non-Critical process parameters can be managed internally without prior regulatory notification
- **Continual Improvement of the product**
  - Proactive use of trended data
  - Feed expanded knowledge back to Development

Conclusions (continued)

- **Quality Unit and Batch Release**
  - Use of Risk Management within the Quality System
  - Lifecycle responsibility with Cross functional alignment with commercial/R&D
  - Ensure alignment of the site PQS with enhanced development approach (continual improvement of the PQS itself)
  - Maintenance and use of the Design Space and Control Strategy, and predictive models

Key elements for manufacturing

Implementation of an enhanced development approach in a PQS should consider especially

- Scale up and Technology Transfer
- Process validation
- Change Management
- Continual Improvement
- Quality Unit and Batch Release

Implementation of ICH Q8, Q9, Q10

Inspection

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Outline

- Aim of Inspection
  - Inspection as a key part of the regulatory process
- Types of inspection
- What is and is not different in the Q8,9,10 paradigm
- PAI based on the case study
- Concluding Messages

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Aim of the inspection

Inspections of a firm's manufacturing operation are essential to evaluate commercial manufacturing capability, adequacy of production and control procedures, suitability of equipment and facilities, and effectiveness of the quality system in assuring the overall state of control. Notably, pre-approval inspections include the added evaluation of authenticity of submitted data and link to dossier.

Types of inspection

- System based (including general statements)
  - Routine GMP inspection
- Product oriented
  - Pre Approval Inspections (PAI)
  - Post approval
    (often combined with system inspections)
  - For Cause Inspections e.g. handling suspected quality defects or, in the EU and Japan, the assessment for licensing manufacturing sites

What is or is not different under Q8,9,10?

What is or is not different under Q8,9,10?

Assessment provides essential input on product/process design, and feeds into the inspection to evaluate commercial process implementation (please see concluding messages for the other quotes)

> Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale-up activities can be useful in further developing the control strategy.
>
> ICH Q10

What is or is not different under Q8,9,10?

- The inspection methodology and scope is the same
- The inspection is more focused e.g.
  - What about implementing the process parameters (both CPPs and non-critical)?
  - How to perform change control in the design space?
  - Are you inside / outside Design Space?
    - How to manage an event 'out of design space'?
- Is the manufacturing site capable of implementing the control strategy (e.g. RTRT)?
- Is the manufacturing site capable of developing and implementing an appropriate batch release strategy based on GMP and control strategy ?

What is or is not different under Q8,9,10?

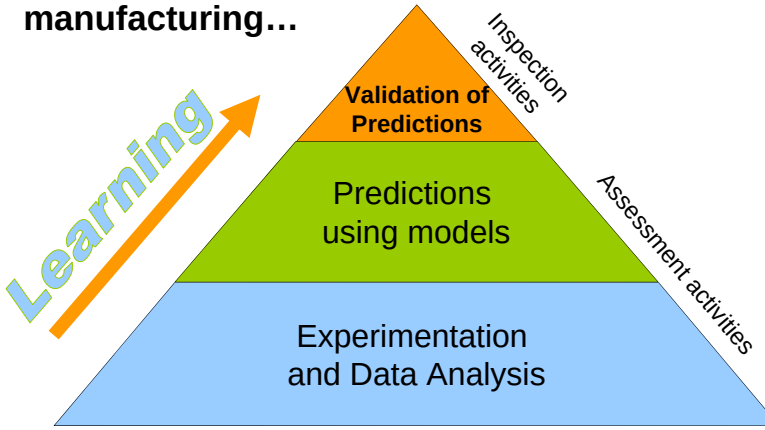
- **RTRT is an option BUT once it is granted in the Marketing Authorisation it should be appropriately applied**
  - To assure acceptable implementation of RTRT and models
  - Reverting to conventional testing of finished product is not allowed unless justified e.g. for investigational purposes, equipment failure (see Q&A)
  - Post-approval plan for monitoring of the models

What is or is not different under Q8,9,10?

- **Drug Product Development predictions based on predictive mathematical models**
  - Protocols for change control
  - Flexible change management under quality system
  - Protocols for monitoring
  - Protocols for management of out of trends, deviations, and specifications
  - These predictive models will be verified/ validated at commercial site and throughout lifecycle. Subsequent adaptation under PQS will be monitored by inspection oversight

What is or is not different under Q8,9,10?

- **Process development, scale-up/ validation, manufacturing…**



What is or is not different under Q8,9,10?

Focus of post approval inspection

- Maintain a State of Control via the PQS using e.g.:
  - Management review of process performance and product quality
  - Process performance and product quality monitoring system
  - Corrective action and preventive action (CAPA) system
  - Change management system
- Contributing to the continual improvement of the product

PAI based on the case study

Pre Approval Inspections (PAI)

- General issues on API
  - Outsourcing of API
  - Supplier management of Starting Materials, intermediates, etc. under PQS
- General issues on Drug Product
  - Supplier management of API and excipients under PQS

General considerations on inspections

- How is PQS operating?
  - Reminder: the goal of the PQS is to have systems in place to support new product and to detect any potentially non-compliant product to prevent its distribution on the market
- Clarify if PQS is product or site specific or global
- How PQS is integrating “outsourced” activities ?
- It is also important to look at the continual improvement of the PQS itself
- Manufacturing process improvements
  - Is process knowledge used for product quality improvement? How? When?
- Evaluate the site’s operations, with personnel interviews throughout (production, quality…)

General on Pre Approval Inspections (PAI)

- **Based on information in the application**
  - The inspection will incorporate process understanding from DOE experiments and the filed Design Space
  - As well as learning from development experience (could include, if available, technology transfer activities)
  - discussion with the reviewer
- **Based on information at the site**
  - Feasibility of the process
  - Personnel
  - Facilities
  - Equipment
  - Raw material controls
  - Risk management
  - Etc.

General on Pre Approval Inspections (PAI)

- Technology transfer from development site to manufacturing site: protocols and acceptance criteria
  - Are DOE predictions scalable?
- Provide the possibility to review batches in addition to those submitted in the application (e.g. Process Qualification batches)
- Review Process Validation plan and Master Validation plan (or equivalent)

General on PAI - API

- API process would be reviewed (DMF, batch records, receipt/handling/storage of starting materials, any holding during the process, as well as storage of the API). Some of which is included in submitted dossiers
- Equipment/ facility capability, production SOPs, scale-up
- Control of starting materials and intermediates
- Control for potential degradation
- Control of particle size during crystallization
- Focus is on critical parameters e.g. degradation and crystallization. Are there parameters other than those described in the application file impacting product quality?

General on PAI - Drug Product

- Inspectors will look at
  - Process feasibility
  - Equipment capability
  - Scale up, including learning
- Review the pivotal clinical batch (IMP) for deviations and process comparison of bio-batch to scale up
- Review other development batches beyond those submitted in the application (e.g. scale up batch, demo batches)

General on PAI - Drug Product

- Potential variables and associated risk (e.g. raw materials, sites, equipment, personnel…) as described in the following slide
- What parts of the process require control and why?
- Review the development report, if one has been prepared

General on PAI Drug Product

Evaluation of potential variables and associated risk

- Does the operation support the intended volume of production?
- Resources
- Equipment (including support equipment e.g HVAC)
- Documentation including written procedures
- Personnel training
- Environmental control
- IT support/validation/control
- Is there a process for acquiring and managing knowledge?

Elements from the case study

Assessment of the implementation of marketing authorisation at the manufacturing site through current GMP and PQS

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

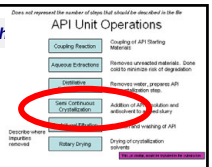
CQA	Drug Substance						Drug Product					
	Coupling Reaction	Aqueous Extractions	Distillative Solvent Switch	Semi-Continuous Crystallization	Centrifugal Filtration	Rotary Drying	Manufacture Moisture Control	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance*												
Dissolution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

PAI - API

- Related to the case study slide as presented Information in the application assists the focus on the inspection e.g.
  - Concentrate on the ‘red’ and ‘yellow’ boxes in the application
  - Evaluation of assessment of impact on e.g. Critical Quality Attributes (CQA) and whether current controls are of sufficient support
  - Due to potential hydrolysis degradation - testing by HPLC would be reviewed - any batch rejections, quality issues, processing issues, reprocessing…in accordance with current GMPs

API Unit Operations

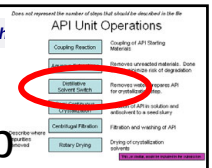
Coupling Reaction	Coupling of API Starting Materials
Aqueous Extractions	Removes unreacted materials Done cold to minimize risk of degradation
Distillative Solvent Switch	Removes water, prepares API for crystallization step
Semi Continuous Crystallization	Addition of API in solution and anti-solvent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



PAI - API

Questions which could be raised during the inspection

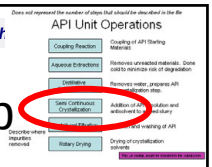
- Water level in the vessel is a critical parameter for the crystallization step: is it related to the vessel fill volume? Is the vessel size a critical parameter?
- Does the crystallization step concern sub-batches or full batch? Determine precise batch size versus vessel fill volume and evaluate other factors that influence particle size.



PAI - API: evaluation of Scale-Up impact during API-PAI

Questions which could be raised during the inspection

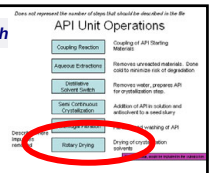
- **Distillative Solvent Switch**
  - Distillation time
  - Decompression level
  - Distillation temperature



PAI - API: evaluation of Scale-Up impact during API-PAI

Questions which could be raised during the inspection

- **Semi Continuous Crystallization**
  - Preparation stage of feed solution
    - Control water content
    - Dissolution temperature
    - Dissolution time
  - Crystallization stage
    - Program of temperature descent
    - Stir speed
    - Concentration
    - Timing of seed crystal



PAI – API

Questions which could be raised during the inspection

- The assessor will evaluate the proposed control strategy of the API for identified CQA(s), hydrolytic degradation and Particle Size Distribution (PSD).
- The inspector will evaluate the proposed plans for implementation of the control strategy (linked to submitted dossier), audit data, and evaluate cGMP (e.g. facility, equipment, production and QC)
- The inspector will evaluate the site's capability to ensure appropriate storage and shipment conditions for API to ensure:
  - Temperature and Humidity control; any dessicant used
  - May look at studies to assure storage/shipment stability

Drug Product Direct Compression Manufacturing Process

2.3.P.3.3 Manufacturing Process

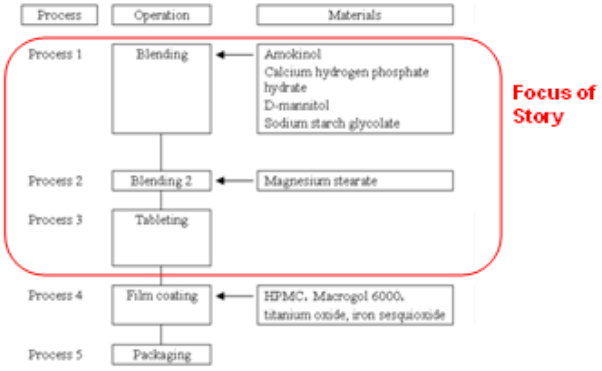


Figure 3.2.P.3.3-1 Summary of the Manufacturing Process

PAI - Drug Product

- Inspectors will look at aspects of the raw Material Controls Program e.g.
  - Supplier selection and qualification program
  - Incoming raw material testing program
- Example of the Case study
  - Mg Stearate
    - Focus on critical quality attribute (CQA) including specific surface area (SSA)
    - Is the sampling plan and testing adequate?
  - Sodium Starch Glycolate
    - Similar focus if sampling plan and testing is adequate as it is a disintegrant

PAI - Drug Product

- Evaluation of manual aspects of unit operations with focus on manual or semi-automated aspects in the enhanced approach such as
  - Blender loading and discharge
  - Transport and storage of blends
  - Charging of the compression machine
  - Training adequacy (risk based training?)
- Evaluate mechanical aspects of unit operations e.g.
  - Special equipment performance and capability to deliver the desired output

PAI - Drug Product

Can the test method as named in the application be implemented?

- **Evaluate the viability of blend homogeneity**
  - Looking at e.g. IQ, OQ, PQ and check e.g. type of transmittance probe or window
  - Scientific justification to determine the precise hold time after blending which could include studying the demonstration of absence of segregation / aggregation during discharge, transport, charging and hold time
  - API assay in blend: sampling tool, number of samples, sampling plan
  - Stability to moisture risks

PAI - Drug Product

Control of Compression operation e.g.

- Evaluate details of the control strategy for tablet hardness established within quality system
  - How is this parameter controlled on line, at line or in line?
  - Provide sampling plan
  - Total number of tablets tested
  - Acceptance criteria
  - SOPs for handling deviations

PAI - Drug Product

Check the basis for replacing the end-product testing & how to manage deviations under the PQS

- **Tablet weight**
  - Sampling plan
  - Monitoring models
  - Frequency and total number of tablets per batch
  - Management of out of spec in the frame of feedback control system and handling of other deviations
  - Batch Overall RSD

Concluding messages

Concluding messages

- Implementation of Q8, Q9 and Q10 should enhance GMP compliance and could have a positive impact on frequency and duration of inspections.

Concluding messages

- Assessment and inspection are complementary but different activities
  - Encourage collaboration among assessors and inspectors in pre-approval inspections respecting the distinct roles of assessors and inspectors
- Inspection determines manufacturing capability
- Information from technology transfer activities, scale-up, demonstration, and process qualification batches is particularly valuable

Concluding messages

- PQS and QRM are not only considered specifically for product, but as systematic lifecycle approaches
- Ultimate goal for assessors and inspectors is to be sure that the marketed product meets the predefined quality