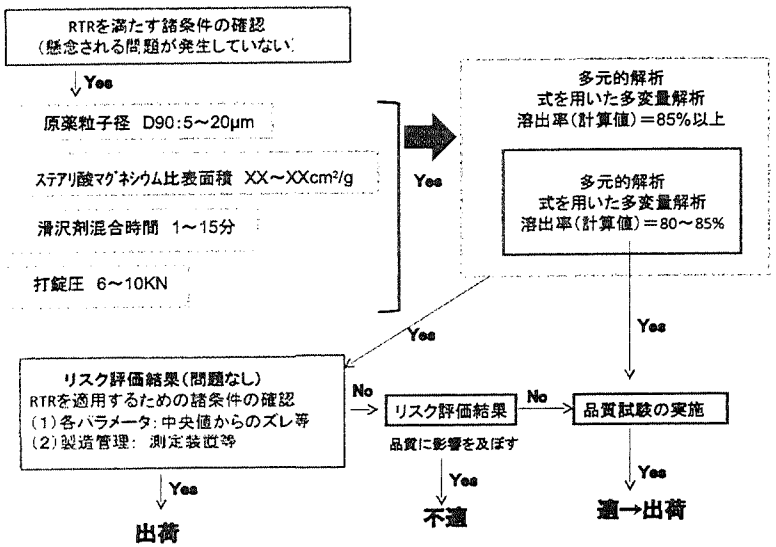
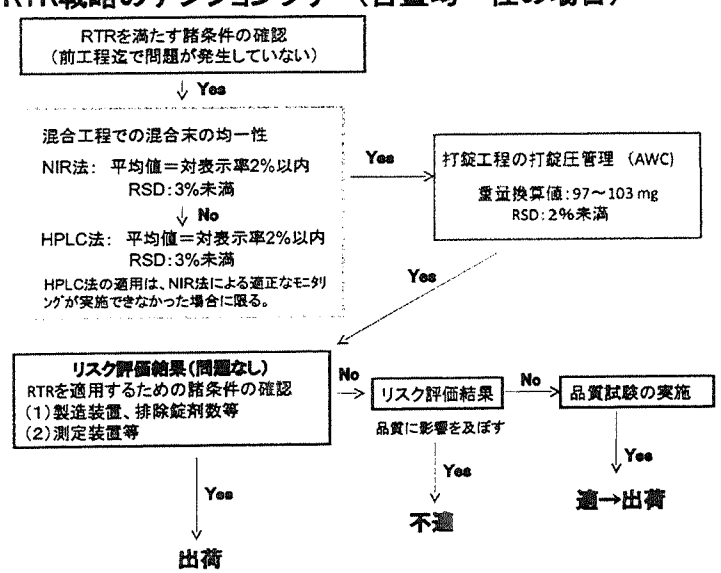
RTR戦略のデシジョンツリー（溶出評価の場合）



RTR戦略のデシジョンツリー（含量均一性の場合）



含量均一性評価に関する品質管理戦略


Tablet

含量均一性を求めるには:
①錠剤を構成する粉末の均一性
②製剤質量
が分かれば求められる。

①錠剤を構成する粉末の均一性 → NIR
インラインNIRで連続モニタリングを行い、連続したサンプリング6時点の結果が判定値以内となった時点で混合工程を終了

②製剤質量 → Auto weight control (AWC)
打錠圧力と製剤質量との間に直線的な相関関係が成立することを利用。
打錠圧力を測定することで錠剤質量を算出し管理。
打錠圧力の管理範囲に入らない錠剤は排除する。

表 2.3.P.3.4.1.1-1 混合末の均一性の管理値

サンプリング時点数	n=10
判定値	平均値＝対表示率 2%以内
	RSD：3%未満

表 2.3.P.3.4.1.1-2 打錠圧の管理

制御範囲(重量換算値)	97～103 mg
RSD	2%未満

品質管理戦略
各パラメータ毎の管理（通常の工程管理レベルを想定し設定）

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含量評価に関する品質管理戦略


Tablet

含量を求めるには:
①錠剤を構成する粉末中の主薬含量
②製剤質量
が分かれば求められる。

含量(%) ＝混合末含量×製剤質量+理論錠剤質量

表 2.3.P.3.4.1.3-1 工程管理項目と管理幅

工程管理項目	管理幅
混合末含量(混合工程)	98～102%
錠剤質量(打錠工程)	97～103mg

品質管理戦略
1. 各パラメータ毎の管理
2. 計算値（含量%）での管理（通常の規格よりも厳しく運用）

パラメータ選定のうえで重要なポイント
重量値について、①打錠圧力からの計算値を使う、②錠剤質量の測定値（実測値）

⟹ 真値が要求される項目については、実測値を使う方が望ましいと判断

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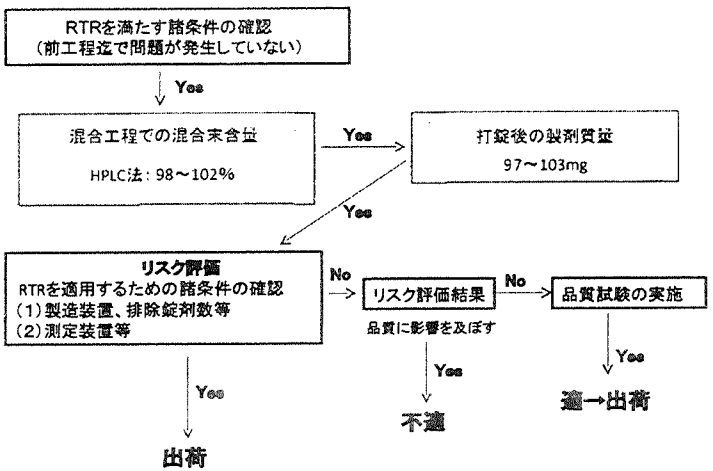
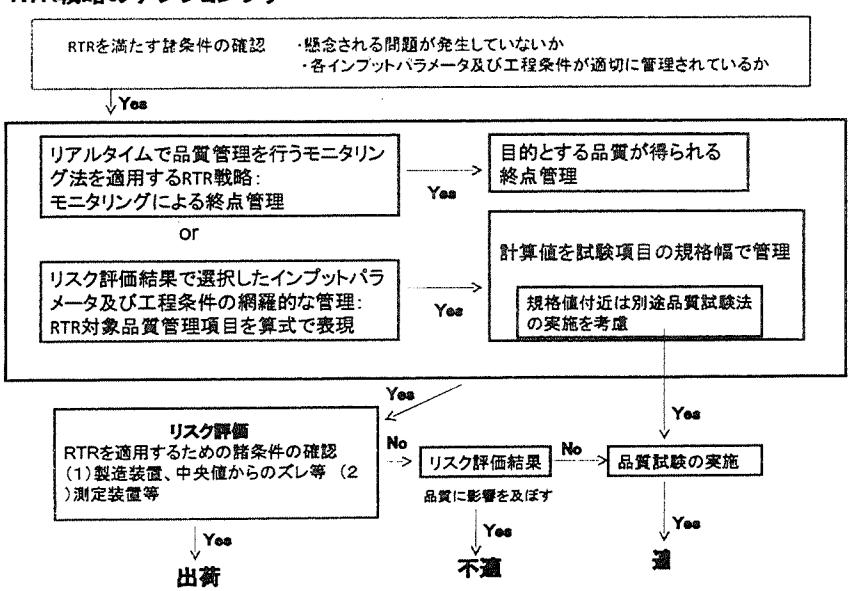
RTR戦略のデシジョンツリー（含量の場合）



RTR戦略のデシジョンツリー



まとめ：

1. **パラメータの設定：**
製造工程の検討結果やリスク評価結果から、出荷試験項目の品質特性に影響を及ぼすパラメータを選択する（複数の工程にまたがるケースが多い）

2. **パラメータ間の関連性：**
（1）選択したパラメータを品質特性として判定に用いる場合（含量均一性）
（2）選択したパラメータから理論式により品質特性を表現できる場合（含量）
（3）選択したパラメータを組み合わせて品質特性を表現する場合（溶出性）

> 多変量算法を用いて「あてはめ式」を使用する場合、実験値の桁数や各係数の影響度について注意が必要
> $Y = aX + bY + cZ$
> a,b,c(X,Y,Z)の数値の中では、桁数の大きい係数或いは実験値に計算結果が、大きく影響される。

3. **従来の試験法の活用：**
1. 製造行為は問題ないが、特に工程管理試験やモニタリング測定で、不具合が発生した場合
2. 規格値に近い試験結果が得られた場合のリスク管理の位置付けで品質試験を実施する場合

最後に

1. **RTRに関する議論の主な論点：**
①RTRTを設定した場合にも、承認書レベルにおいて、最終製品の規格及び試験法を設定すべきであること。
⟹ **単にモニターするといった内容の記載ではない。**
②最終製品の試験を実施するケースをあらかじめ明確にしておくことである。
⟹ **デシジョンツリー （研究班の案では申請書にデシジョンツリーを記載）**
この論点はICHのIWGのQA案と一致している。

2. **リアルタイム品質管理の条件：**
①製品の規格の項目に対して、どのような（中間製品の）品質特性が寄与しているかの理解が必要。
⟹ **品質特性の理解**
②それらを製造工程中において、実際にリアルタイムに評価できること。
⟹ **リアルタイムな評価法の構築**
③工程条件の調整により品質特性が管理できること。
⟹ **品質特性の管理**

3. リアルタイム品質管理(工程運転中に連続的に評価し続けること)の意義:

(1)品質管理のレベル向上並びに、実績データの積み上げによる将来の変更・改善を容易にすることにあると考えられる。

(2) リアルタイル品質管理の実践は、①「出荷試験の実施の減少につながる」

②「連続的工程モニターは工程バリデーションの代替法である。」

このような内容はQ8本文や用語欄に記述されている。

「Q8,Q9,Q10の実践を通じプロセスバリデーションの革新的アプローチを可能にする(Q10付属書の記載)。」

リアルタイムの品質管理は、従来のバリデーションに対するパラダイムシフト

リアルタイムの品質管理は、**「研究開発データに基づき、工程パラメータを決め、工程が安定していることを仮定し運転をする。」**という従来のアプローチを大きく変えていく可能性を秘めているものである。

Implementation of ICH Q8, Q9, Q10

Case Study

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

ICH

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*

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.

Basis for Development Information

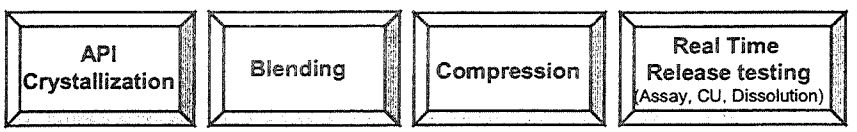
- Fictional active pharmaceutical ingredient (API)
- Drug product information is based on the 'Sakura' Tablet case study
  - Full Sakura case study can be found at http://www.nihs.go.jp/drug/DrugDiv-E.html
- Alignment between API and drug product
  - API Particle size and drug product dissolution
  -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

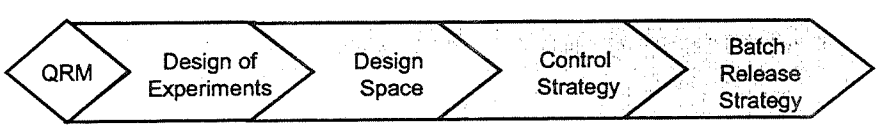
Technical Examples

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

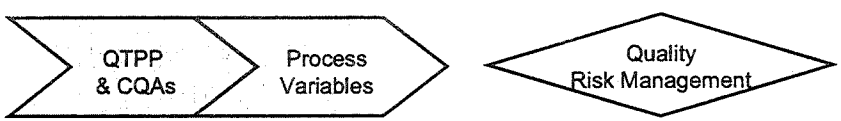


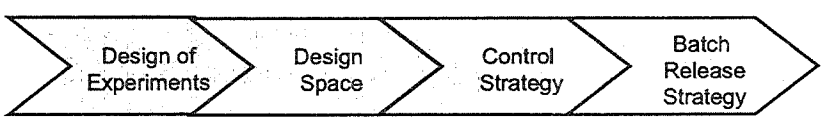
Process Step Analysis

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

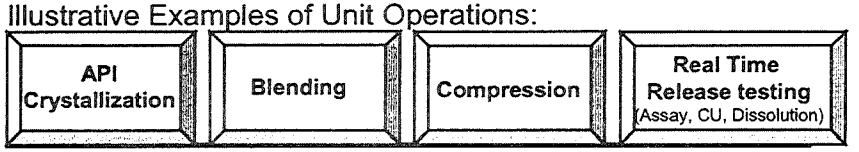


QbD Story per Unit Operation





Illustrative Examples of Unit Operations:



添付資料5

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))

Quality Target Product Profile (QTPP) Safety and Efficacy Requirements

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

Assumptions for the case

- API is designated as Amokinol
  - Single, neutral polymorph
  - Biopharmaceutical Classification System (BCS) class II – low solubility & high permeability
  - Solubility (dissolution) 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
[illegible]	Removes water, prepares API for crystallization step
[illegible]	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)

The composition of Sakura Tablet is shown in Table 2.3.P.1-1.

Table 2.3.P.1-1 Composition of Sakura Table

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

Drug Product Process

API and Excipients
Amokinol
D-mannitol
Calcium hydrogen phosphate hydrate
Sodium starch glycolate
→ **Blending**

Lubricant
Magnesium Stearate
→ **Lubrication**

→ **Compression**

Coating
HPMC, Macrogol 6000
titanium oxide
iron sesquioxide
→ **Film coating**

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

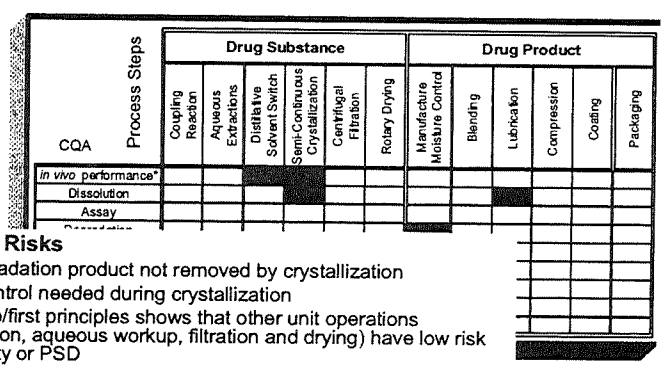
* includes bioperformace of API and safety (API purity)

Process Steps

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

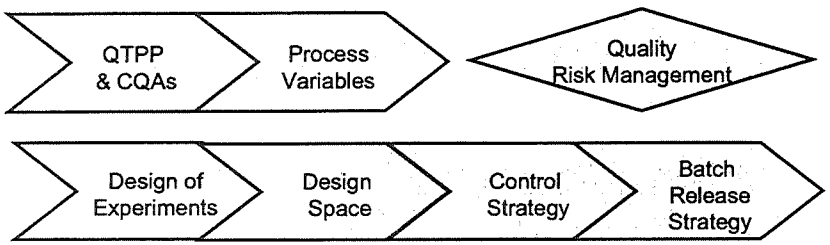
Initial Risk Assessment

- Focus on Impact to CQA's

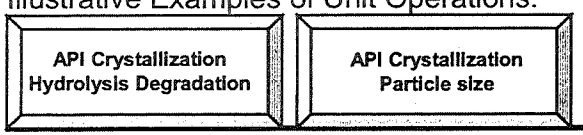


- **Drug Substance Risks**
  - Hydrolysis degradation product not removed by crystallization
  - Particle size control needed during crystallization
  - Prior knowledge/first principles shows that other unit operations (Coupling reaction, aqueous workup, filtration and drying) have low risk of affecting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

API: The Story



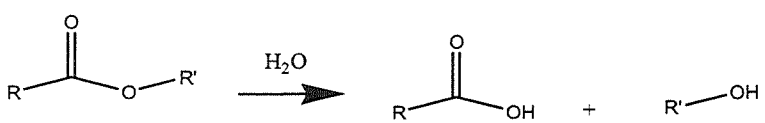
Illustrative Examples of Unit Operations:



API Crystallization Example

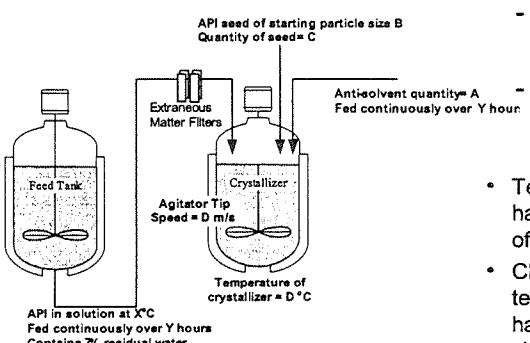
- Designed to control hydrolysis degradate
  - Qualified in safety trials at 0.3%
- Designed to control particle size
  - D90 between 5 and 20 microns
    - 'D90' means that 90% of particles are less than that value
  - Qualified in formulation Design of Experiments (DOE) and dissolution studies

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 (40°C) 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 70°C to dissolve (in preparation for crystallization). Residual water in this hot feed solution can cause degradation and higher impurities in API.

Crystallization Process



- **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 ... 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely ... 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain ... 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)	5	1	9	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	5	1	9	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	1	5	9	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.

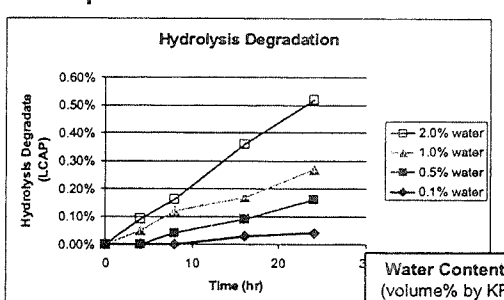
Experimental Setup - Hydrolysis Degradation

- **Crystallization Process Requirements**
  - API feed solution held at 60°C, 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 +/- 10°C. 70°C 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.

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 (70°C)
  - 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



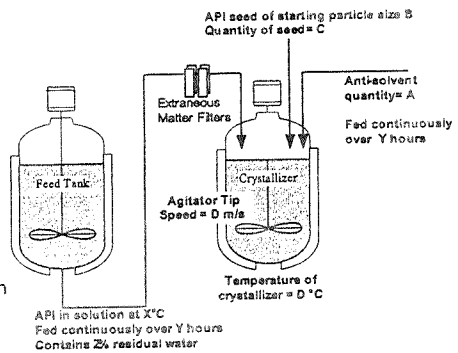
Design Space Defined
Max Temp = 70°C
Max Feed Time = 24 hr
Max Water content = 1.0%
At these conditions, degradate level remains below qualified limit of 0.3%

Water Content (volume% by KF titration)	Degradation Rate (LC area% / hr)	Max Degradate at 24 hrs (LC area%)
0.1%	0.0017%/hr	0.04%
0.5%	0.0067%/hr	0.16%
1.0%	0.011%/hr	0.27%
2.0%	0.022%/hr	0.52%

Case Study

Particle Size Distribution Control - Process History

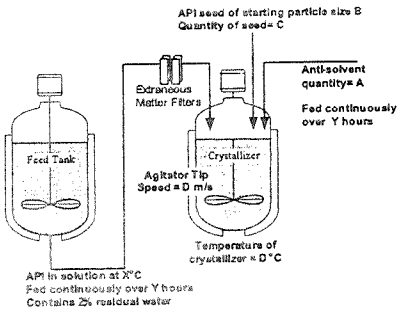
- *Changes in formulation drive changes in API process*
- Ph I and II trials performed with API-excipient mixture filled in hard gelatin capsules (liquid filled capsules = LFC)
- First API Deliveries
  - Simpler Crystallization Process
    - PSD control and agglomeration observed, but acceptable for 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 the particles are not sensitive to shear.



Case Study

Risk Assessment:

Particle Size Distribution (PSD) Control

What is the **Impact** that ——— will have on PSD? 1) minimal 9) significant
What is the **Probability** that variations in ——— will occur? 1) unlikely 9) highly likely
What is our **Ability to Detect** a meaningful variation in ——— at a meaningful control point? 1) certain 9) unlikely

Unit Operation	Parameter	IMPACT	PROBABILITY	DETECT	RPN	Comments
Crystallization	Feed Temperature		5		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		5	5	25	Prior knowledge (solubility data) shows that small variations in water do not affect crystallization kinetics.
Crystallization	Addition Time (Feed Rate)	5			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	5	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	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	5			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)	5	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution				9	Seed PSD controlled by release assay performed after air attrition milling.
Crystallization	Feed Concentration				1	Same logic as for antisolvent percentage

Case Study

Risk Assessment:

Particle Size Distribution (PSD) Control

What is the **Impact** that ——— will have on PSD? 1) minimal 9) significant
What is the **Probability** that variations in ——— will occur? 1) unlikely 9) highly likely
What is our **Ability to Detect** a meaningful variation in ——— at a meaningful control point? 1) certain 9) unlikely

To be investigated in DOE

Unit Operation	Parameter	IMPACT	PROBABILITY	DETECT	RPN	Comments
Crystallization	Addition Time (Feed Rate)	5			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	5	5	5	225	Prior knowledge (Chemical Engineering theory) highlights seed wt percentage variations as a potential source of final PSD variation
Crystallization	Temperature	5			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)	5	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further 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

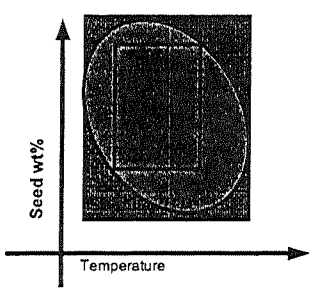
Study Factors				Response
Feed Rate (hrs)	Seed (wt%)	Temp °C	Tip Speed m/s	D90 (microns)
15	1	10	0.44	13.5
5	5	10	0.44	14.5
5	1	10	2.67	5.5
15	5	10	2.67	2.2
5	1	30	0.44	21.4
15	5	30	0.44	13.5
15	1	30	2.67	12.4
5	5	30	2.67	7.4
10	3	20	1.56	7.8
10	3	20	1.56	8.3
10	3	20	1.56	6.1

•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

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 (°C)
    - Statistical analysis shows that crystallization feed time does not impact PSD across the tested range
- Model range across DOE space = 2.2 to 21.4 microns
  - Model error is 1 micron
- Model can be used to create a design space using narrower ranges than used in the DOE
  - Adjust ranges until model predicts acceptable D90 value for PSD

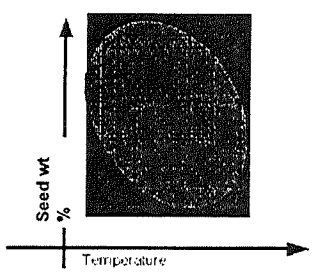
Options for Depicting a Design Space



- In the idealized example at left, the oval represents the full design space. It would need to be represented by an equation.
- Alternatively, the design space can be represented as the green rectangle by using ranges
  - a portion of the design space is "thrown away", 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

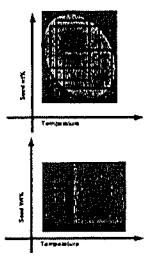


- Other rectangles can be drawn within the oval at top left, based on multiple combinations of ranges that could be chosen as the design space
- Exact choice can be driven by business factors
  - e.g., keep seed charge narrow, maximizing temperature range, since temperature control is less precise than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

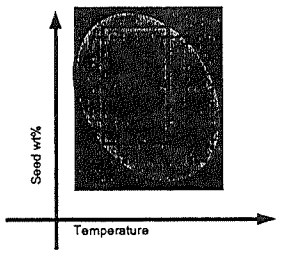
For purposes of this case study, an acceptable "squared off" design space can be chosen
Temperature = 20 to 30°C
Seed charge = 1 to 2 wt%
Agitation = 1.1 to 2.5 m/s
Feed Rate = 5 to 15 hr (limit of knowledge space)
Monte Carlo analysis ensures that model uncertainty will be effectively managed throughout 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



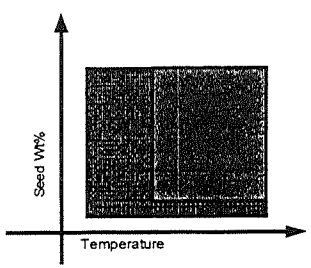
Options for Expanding a Design Space Case A



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

The large square represents the ranges tested in the DOE. The red area represents points of failure. The green area represents points of success.
The boxes represent simplified design spaces within the points of success

Options for Expanding a Design Space Case B



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

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

API Crystallization: Design Space & Control Strategy

- Control Strategy should address:
  - Parameter controls
    - Include control of unstudied "high impact / low probability" parameters from the risk assessment, since the risk assessment implies that the parameter is easily controlled
  - Testing
    - Final API will be tested for hydrolysis degradate with limit of NMT 0.3%
    - 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 the design space
  - Program 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 (e.g. < 0.5%)

Case Study

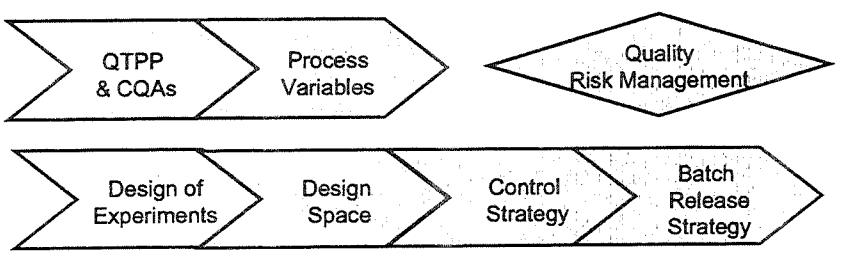
Batch Release for API

- **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 30° C
  - Seed charge = 1 to 2 wt%
  - Agitation = 1.1 to 2.5 m/s
  - Feed Rate = 5 to 15 hr
  - Water content < 1 wt%

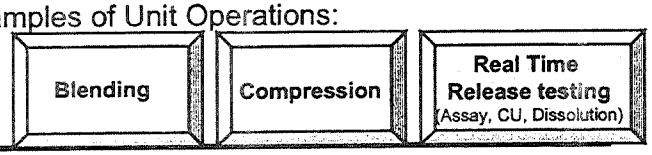
Case Study

Case Study Organization

QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



Case Study

QTPP and CQAs

QTPP

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

Drug Product CQAs

- •Assay
- •Content Uniformity
- •Dissolution
- •Tablet Mechanical Strength

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

CQAs may be ranked using quality risk assessment.

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)

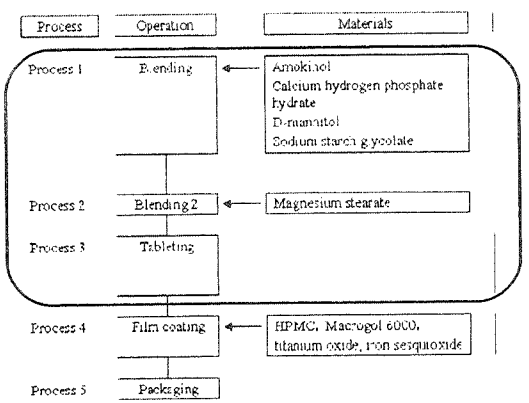
The composition of Sakura Tablet is shown in Table 2.3.P.1-1.

Table 2.3.P.1-1 Composition of Sakura Table

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	May have additional specifications for pharmacopoeial or other compendial grades	HPMC	2.4 mg
Polishing agent		Macrogol 6000	0.3 mg
Coloring agent		Titanium oxide	0.3 mg
Coloring agent		Iron sesquioxide	Trace amount

Direct Compression Process

2.3.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

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

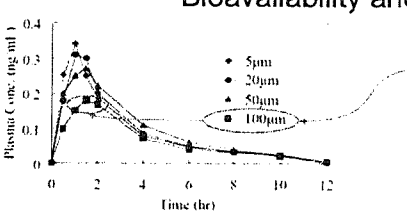
Quality Risk Assessment: Impact on Dissolution CQA

- Quality Risk Assessment shows API Particle Size, Filler, Lubrication and Compression steps have potential to affect dissolution
- Filler: Experimental work established that D-mannitol and calcium hydrogen phosphate hydrate are compatible with Amokinol and give acceptable compression and dissolution characteristics

	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							

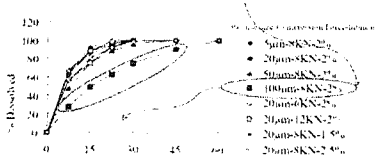
Developing Product and Process Understanding

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



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

In Vivo In Vitro correlation (IVIVC) established



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

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

Multifactorial DOE study of variables affecting dissolution

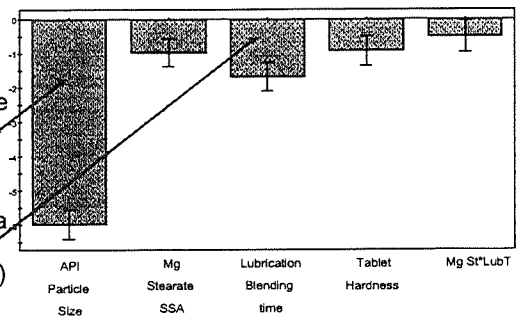
- **Factors:**
  - API particle size [API] unit: log(d(0.9), microns)
  - Mg-Stearate Specific Surface Area [MgSt] unit: cm^2/g
  - Lubrication time [LubT] unit: min
  - Tablet hardness [Hard] unit: N
- **Response:**
  - % API dissolved at 20 min [Diss]
- **DOE design:**
  - RSM design
  - Reduced CCF (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	97.66
9	6	1.5	12000	1	110	85.47
10	16	0.5	3000	10	110	95.81
11	20	1.5	3000	10	110	84.38
12	3	1.5	12000	10	110	81
13	10	0.5	7500	5.5	85	96.85
14	17	1.5	7500	5.5	85	85.13
15	19	1	3000	5.5	85	91.87
16	21	1	12000	5.5	85	90.72
17	7	1	7500	1	85	91.95
18	4	1	7500	10	85	88.9
19	5	1	7500	5.5	60	92.37
20	11	1	7500	5.5	110	90.95
21	12	1	7500	5.5	85	91.95
22	13	1	7500	5.5	85	90.86
23	23	1	7500	5.5	85	89

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

Factors affecting Dissolution

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



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

Predictive Model for Dissolution

- Prediction algorithm
  - A mathematical representation of the design space for dissolution
  - *Factors include: API PSD, magnesium stearate specific surface area, lubrication time, tablet hardness*

Prediction algorithm:

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

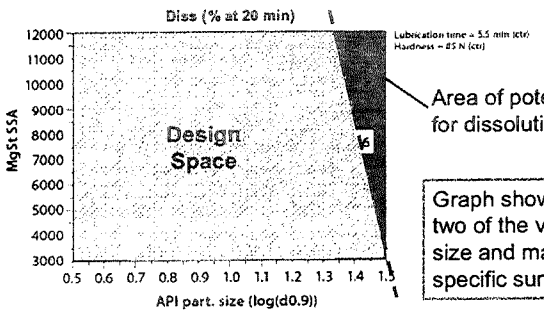
Predictive Model for Dissolution

- 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
    - Control of crystallisation step
  - Magnesium stearate specific surface area
    - Specification for incoming material
- **Controls of process parameter CPPs**
  - Lubrication step blending time
    - Linked to feedback loop from NIR results
  - Compression force (or 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)

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

- Low risk
- Medium risk
- High risk

Blending Process Control Options

Decision on conventional vs. RTR testing

Control strategy 1: Control items		Control strategy 2: Control items
• Blending time • Blending speed • Equipment • Scale • Drug substance particle size	Process understanding	• 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 particle 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 Operation to develop a Design Space

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

DOE design

Table 2.3.P.2.3-1 Experimental Design for Blending Process Parameter Assessment

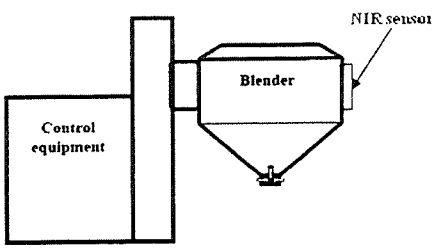
Experiment No.	Run	Condition	Blending time (minutes)	Rotation speed (rpm)	Blender	Particle size D90 (μm)
1	2	varied	2	10	V type	10
2	7	varied	16	10	V type	50
3	10	varied	2	30	V type	50
4	5	varied	16	30	V type	10
5	6	varied	2	10	Drum type	50
6	1	varied	16	10	Drum type	10
7	8	varied	2	30	Drum type	10
8	11	varied	16	30	Drum type	50
9	3	standard	9	20	V type	30
10	12	standard	9	20	Drum type	30
11	9	standard	9	20	V type	30
12	4	standard	9	20	Drum type	30

Process Control Option 2

Blend uniformity monitored using a process analyser

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

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

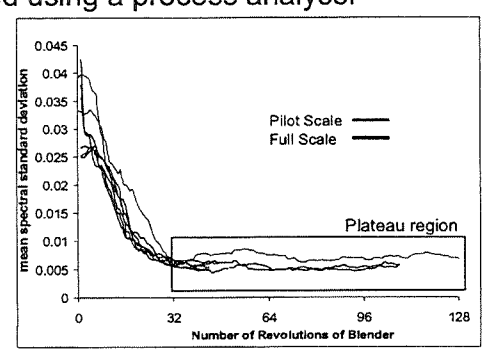


In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility

Process Control Option 2

Blend uniformity monitored using a process analyser

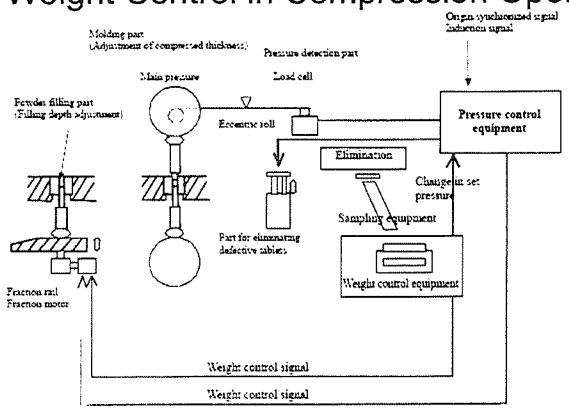
- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
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



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

Acknowledgement: adapted from Paul Stott (AZ) – 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.

RTRT of Assay and Content Uniformity

- Finished Product Specification – *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
- Real Time Release Testing Controls
  - Blend uniformity assured in blending step (online NIR spectrometer for blending end-point)
  - API assay is analyzed in blend by HPLC
  - Tablet weight control 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)

Batch Release Strategy

- **Finished product not tested for assay, CU and dissolution**
- **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 monitored for tablet hardness
- **Water content**
  - NMT 3% in finished product (not covered in this case study)

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

Key Messages

- 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

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