Control Strategy Case Studies

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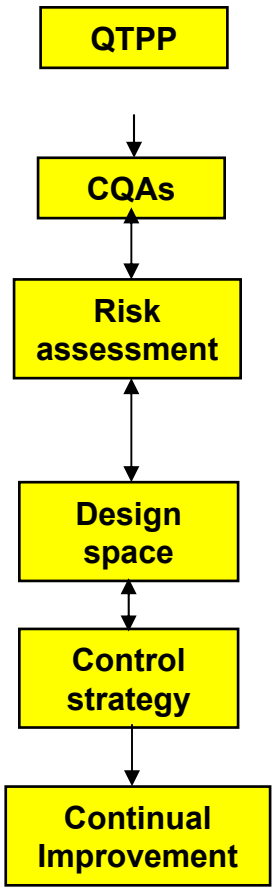
Control Strategy Case Studies

"The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls." [from ICH Q8]

This talk will present 2 case studies.

Example QbD Approach (ICH Q8R)



- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

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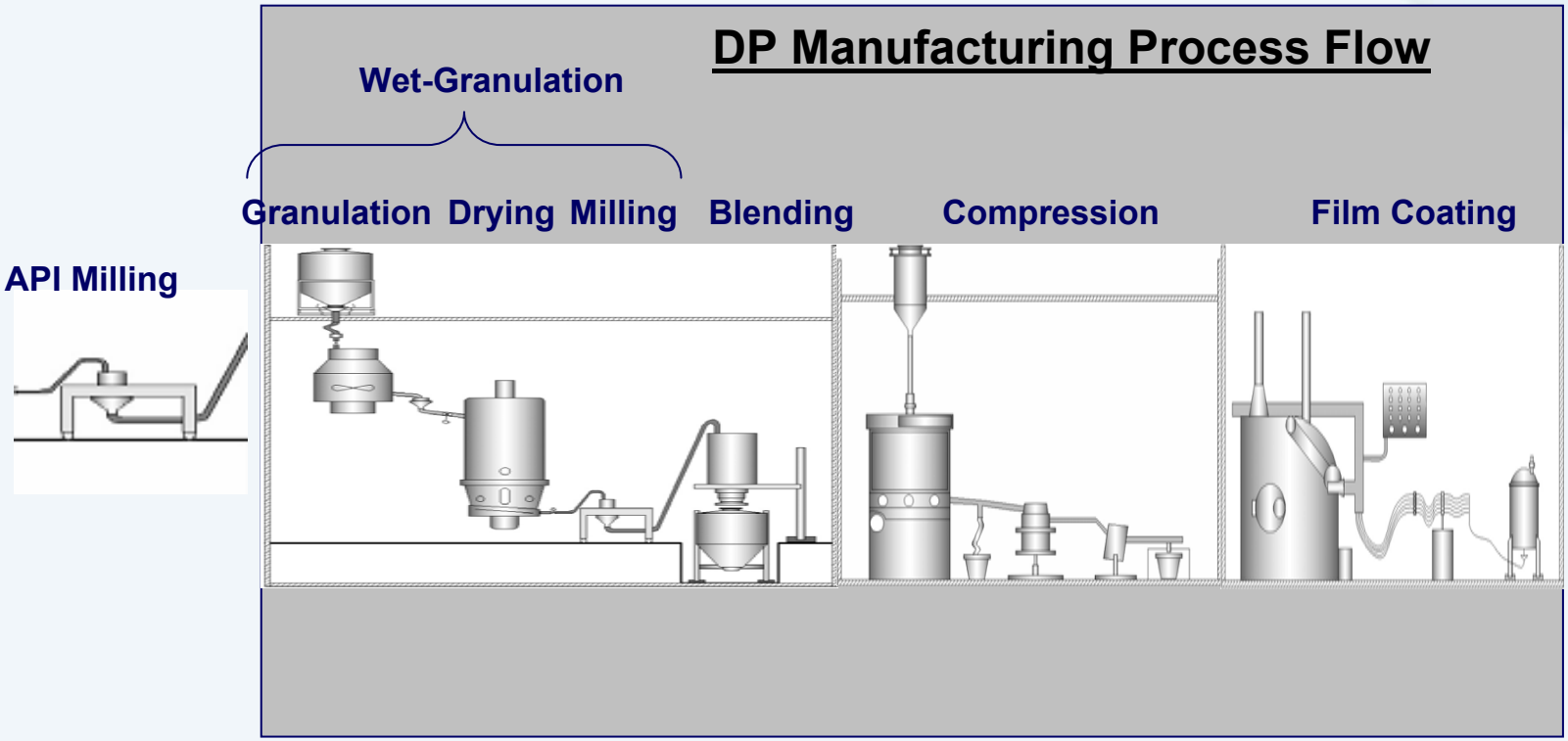
Case Study #1:
Development of a Drug Product (DP) Control Strategy



- Drug Product Manufacturing Process involves:
  1. High-shear wet-granulation process encompassing granulation, drying and milling in order to produce a granule
  2. Blending to produce a compression mix
  3. Compression to produce tablet cores
  4. Film coating to produce final drug product – Film-coated Tablet

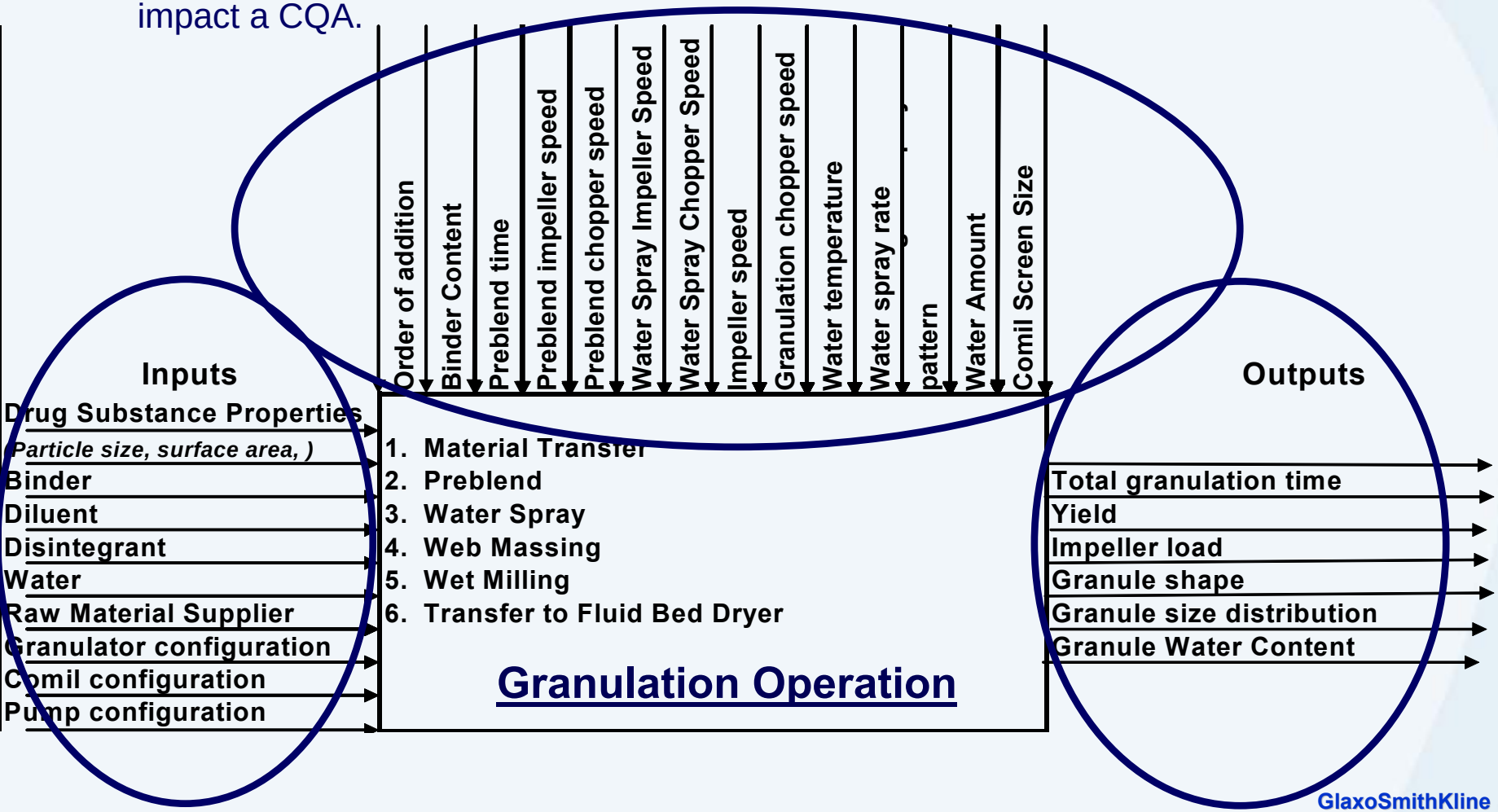
Case Study #1: The Initial Risk Assessment

DP CQAs	Potential Impact of Unit Operations					
	Wet-Granulation	Drying	Milling	Blending	Compression	Coating
Appearance	Low	Low	Low	Low	High	High
Assay	High	High	Low	High	Low	Low
Content Uniformit	High	Low	High	High	High	Low
Impurities	High	High	Low	High	Low	High
Dissolution	High	High	High	High	High	Low

- Based on prior knowledge, each unit operation is assessed to determine the potential to impact the CQAs of the Drug Product.
- For this case study, let's focus on dissolution.
  - Drug dissolution from drug product is a critical quality attribute (CQA) that significantly impacts the efficacy of the drug product.
    - target is 80% dissolution at 45 minutes
  - The wet-granulation operation has high potential to impact dissolution.

Case Study #1: Use of IPO Diagrams

- An IPO (Input-Process-Output) diagram can be used to help identify all input attributes, process parameters and output attributes for each unit operation that might possibly impact a CQA.



Case Study #1:
Use of Critical Relationship Matrices

- The attributes and parameters identified in the IPO diagram can be input into a Critical Relationship Matrix to identify potential links between Drug Product CQAs and the attributes & parameters in the unit operation.

Material Attributes

Parameters

VARIABLE	Granule Size Distribution	Homogeniety	Bulk Density	Porosity	Flow	Yield	Dissolution
API Size Distribution							X
Addition Order	No Effect						
Water Amount							X
Water Addition Rate							X
Water Temperature	No Effect						
Mixing Time							X

- In this example, it can be seen that the amount of water used in the granulation operation and the mixing time have a high potential to impact granule bulk density, which can then impact dissolution.

Case Study #1:
Use of Failure Mode and Effects Analysis (FMEA)

- The attributes and parameters with highest potential to impact Drug Product CQAs can be determined using an FMEA.

STEP	POTENTIAL FAILURE MODE	DP or API CQAs Affected	POTENTIAL EFFECT(S) OF FAILURE	SEV	POTENTIAL CAUSE(S) OF FAILURE	OCC	CURRENT CONTROLS	DET	Risk Priority Number
Granulation Water Addition	Change of lance location	Granule Size, Bulk Density, Flow	Failed dissolution	10	Incorrect granule formation	4	Batch documentation sign-off	4	160
Granulation Wet Mixing	Increase in mixing time	Bulk Density	Failed dissolution	10	Incorrect granule formation	1	DCS controls	1	10
Granulation Wet Mixing	Increase in impeller load	Bulk Density	Failed dissolution	10	Incorrect granule formation	4	No control. See actions.	10	400

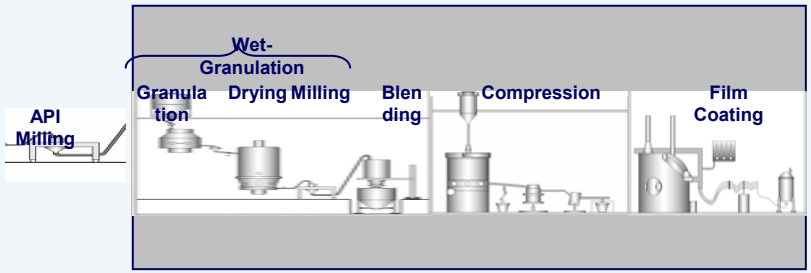
- From this FMEA, it can be concluded that the water addition and wet-mixing processes need to be more thoroughly studied to determine appropriate controls.

Score Severity based on likely impact on Drug Product CQA.

Score Occurrence based on probability of failure.

Score Detection based on probably of detecting failure.

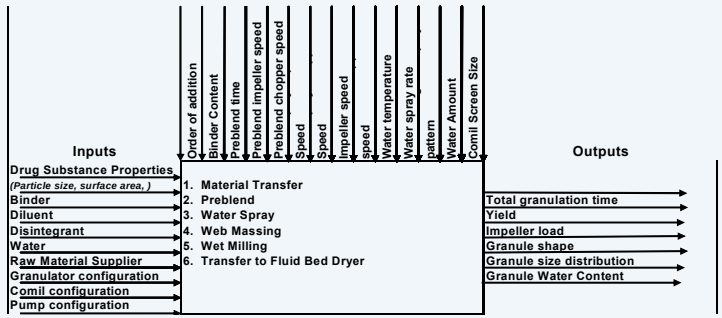
Case Study #1: Conclusions from Prior Knowledge & Risk Assessments



DP Manufacturing Process Flow

	Potential Impact of Unit Operations					
DP CQAs	Wet-Granulation	Drying	Milling	Blending	Compression	Coating
Appearance	Low	Low	Low	Low	High	High
Assay	High	High	Low	High	Low	Low
Content Uniformit	High	Low	High	High	High	Low
Impurities	High	High	Low	High	Low	High
Dissolution	High	High	High	High	High	Low

Initial Risk Assessment



IPO & Relationship matrix

STEP	POTENTIAL FAILURE MODE	DP or API CQAs Affected	POTENTIAL EFFECT(S) OF FAILURE	SEV	POTENTIAL CAUSE(S) OF FAILURE	OCC	CURRENT CONTROLS	DET	RPN
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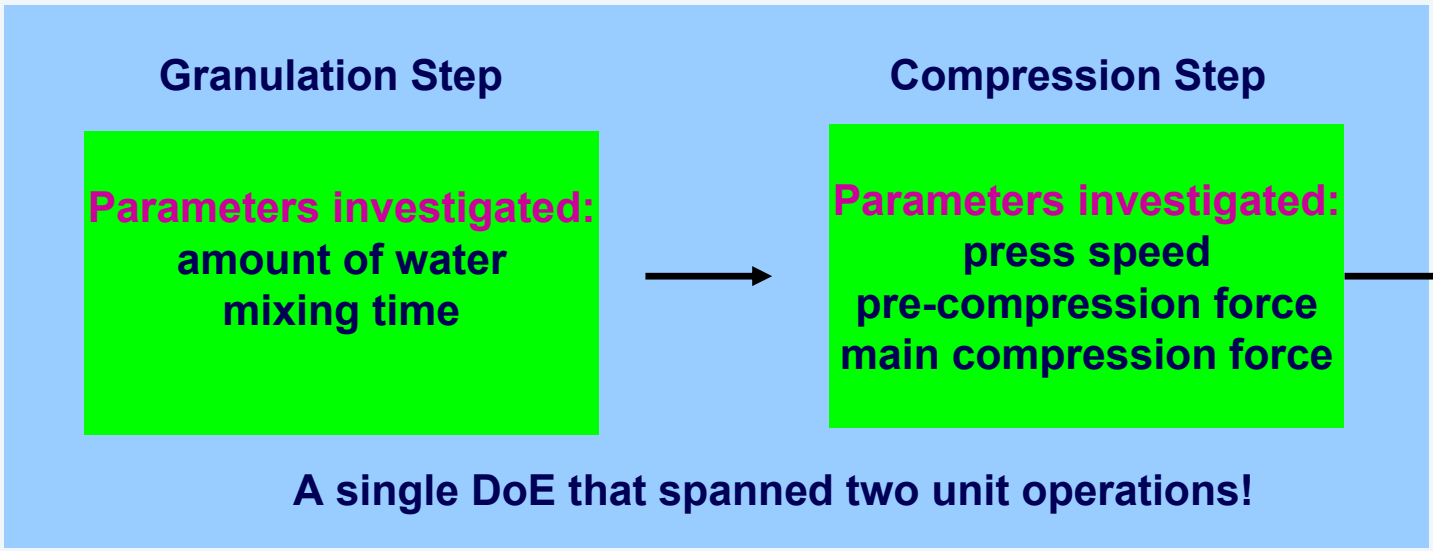
FMEA

- Potential critical quality attributes and process parameters are identified.
- Experiments can be designed to understand these attributes & parameters.

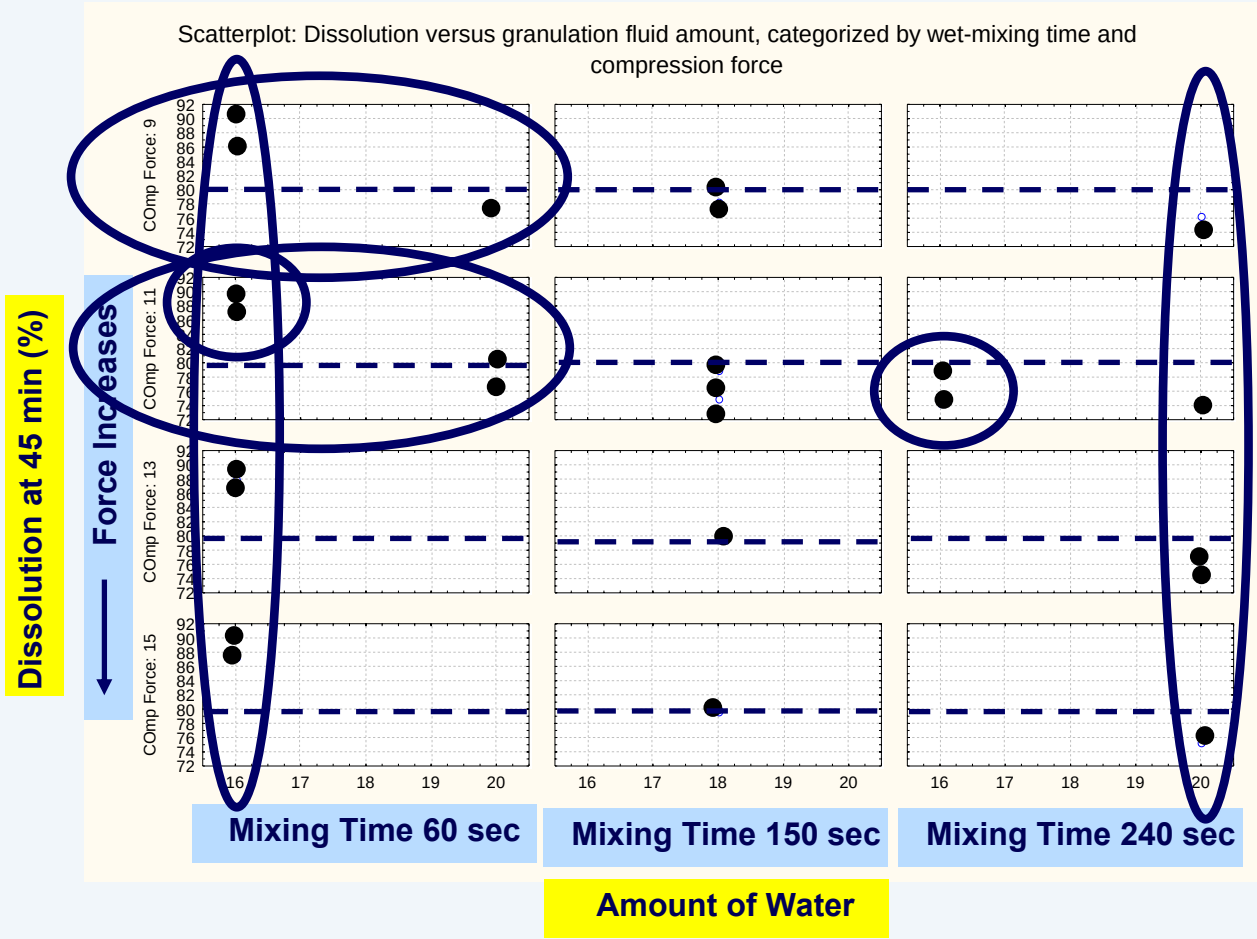
Case Study #1: Granulation & Compression DoE

A DoE (Design of Experiments) was used to assess parameters and attributes in the granulation and compression processes for their impact on Drug Product dissolution and other CQAs.



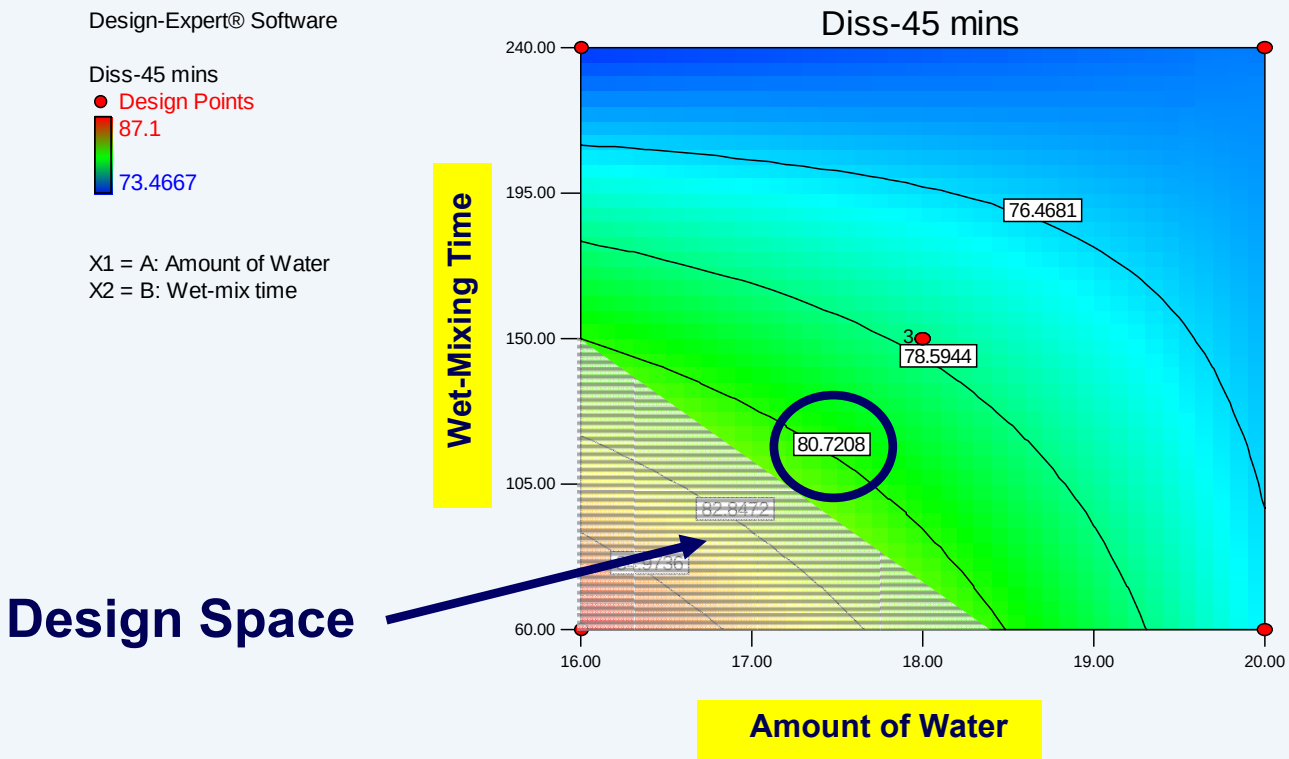
- 9 granulation experiments, followed by 24 compression experiments per granulation experiment (216 experiments in total)
- experiments performed at 1/10th manufacturing scale

Case Study #1: Granulation/Compression DoE outputs



- Compression Force has little impact on Dissolution.
- Increasing the amount of water added results in a decrease in Dissolution.
- Increasing Wet-Mixing Time results in a decrease in Dissolution.

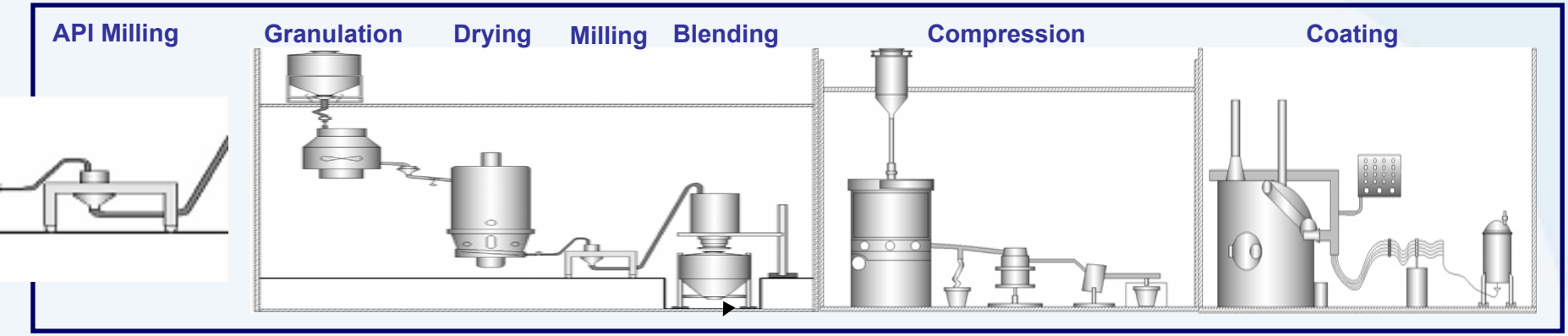
Case Study #1:
DoE outputs … a Design Space



Design Space

- Water amount can range from 16-18%. The required wet-mixing time is linked to the water amount and can range from 60-150 sec.
- This defines a Design Space that has been demonstrated to provide assurance of 80% dissolution in 45 minutes.

Case Study #1:
Control Strategy for Drug Product Dissolution



Attributes that influence dissolution

API Particle size

Granule Properties

Parameters that affect these attributes

Mill Speed
Feeder Rate

Amount of Water
Wet-Mixing Time

Experimental Data

Operating Ranges for parameters

Operating Design Space for amount of water and wet-mixing time.

Controls

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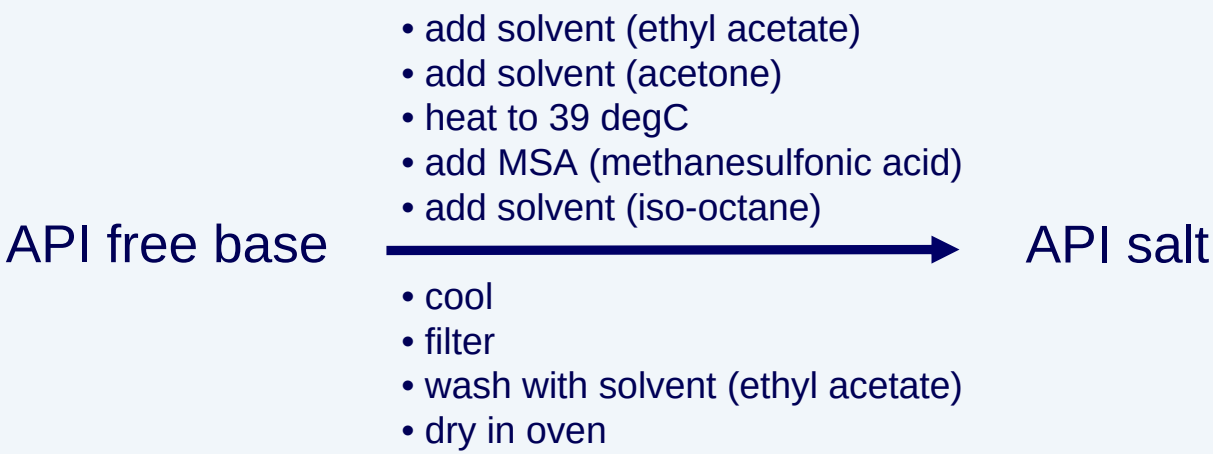
Case Study #2

"***Understanding sources of variability and their impact on downstream processes or processing, intermediate products and finished product quality can provide flexibility for shifting of controls upstream and minimize the need for end-product testing.***"

[from Annex to ICH Q8]

Case Study #2: Control of an API Critical Quality Attribute

- The final formation and isolation of an API methanesulfonate salt was performed as follows:

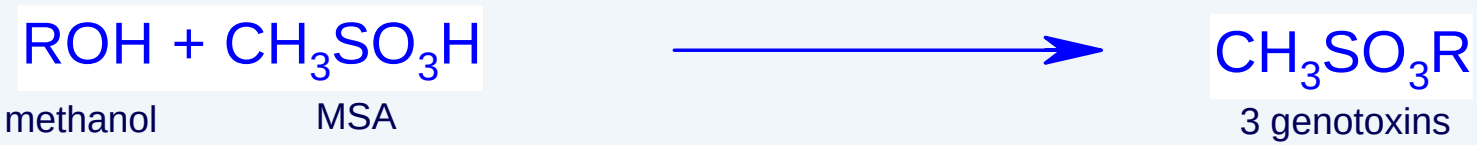


- A risk assessment identified **3 genotoxic impurities (alkylmethane sulfonates)** that could potentially contaminate the API, these genotoxins are **Critical Quality Attributes of the API.**
- Based on a Threshold of Toxicological Concern of <1.5 μg/day and a maximum drug dose of 150 mg/day, these impurities had to be controlled to **<10 ppm**.

Case Study #2: The Risk Assessment

A risk assessment using prior process knowledge, identified the unit operations that could potentially impact levels of the 3 genotoxins in the API salt:

Unit Operation	Potential to Impact Genotoxin Control	Rationale
add ethyl acetate	High	potential for ethanol
add acetone	High	potential for isopropanol
add API Free Base	Low	
heat	Medium	potential genotoxin formation
add MSA	High	potential genotoxin impurities
stir	Medium	potential genotoxin formation
add iso-octane	Low	
cool	Low	
filter	High	genotoxin purging
ethyl acetate wash	High	potential for ethanol genotoxin purging
dry	Medium	potential genotoxin formation



methanol
ethanol
isopropanol

MSA

3 genotoxins

Case Study #2: Studies to Mitigate the Risks

The risk assessment informed the design of a series of experiments to develop process knowledge to reduce the risk of producing API containing the 3 genotoxins:

Experimental Study	Purpose
Test the salt formation step outside of typical operating ranges.	To test the likelihood of formation of the 3 genotoxins.
Test the filtration and washing steps outside of typical operating ranges.	
Test the drying step outside of typical operating ranges.	
Perform the filtration and wash steps in the presencce of high levels of the 3 genotoxins.	To test the likelihood of removing the 3 genotoxins.

Case Study #2: The Process Knowledge

The ability to form the genotoxic impurities under the process conditions was studied:

Unit Operation	Conditions	Alcohol (ROH) Levels	Genotoxins Formed	Genotoxins in API
Salt Formation	Standard	2-150 ppm	not tested	<1 ppm
	Standard	1000 ppm	<1 ppm	<1 ppm
	Stressed (>time, >temp, >MSA)	7500 ppm	2-3 ppm	<1 ppm
Filtration & Wash	Stressed (>time, >temp)	2000 ppm	<1 ppm	<1 ppm
Drying	Stressed (>temp)	2000 ppm	<1 ppm	<1 ppm

Conclusion:

The genotoxic impurities are not easily formed under the process conditions, even when large excesses of the alcohols are present.

Case Study #2: The Process Knowledge

Extreme spiking experiments were carried out by adding the genotoxin impurities directly into the process stage to study the ability to purge the impurities.

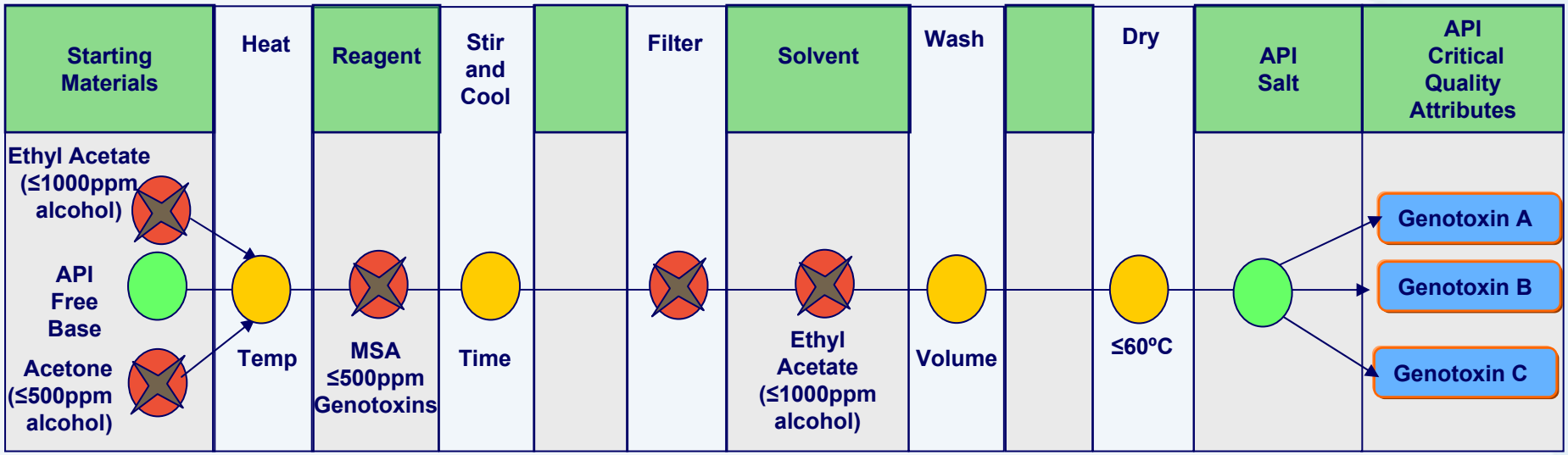
The following results were obtained when 4500-7000 ppm of genotoxins were added to the final solution prior to API crystallization and isolation:

Cake Wash	Genotoxins in Wet API Cake
No Wash	1-2 ppm
1 wash	<1 ppm
2 washes	<1 ppm

Conclusion:

The genotoxin impurities are easily purged under the process conditions.

Case Study #2: The Control Strategy



The API CQA is not impacted by attributes or parameters in this stage

The API CQA is impacted by attributes or parameters in this stage but tight control is not required

Control point of the API CQA, control implemented through parameters or attributes in this stage

Case Study #2: The Control Strategy

Unit Operations	Process Knowledge	Controls	Tests & Specifications	Quality Systems
	DoE and univariate experiments to set standard operating ranges.	Proven Accenptable Ranges for process parameters.	Quality Process Parameters: solvent volumes, temperature, time	Compliant batch record.
	Batch data.	Specifications for input materials.		Compliant batch record.
Salt Formation	Process stretching experiments.	Specifications for solvents.	≤0.1% alcohol in ethyl acetate. ≤0.05% alcohol in acetone.	Compliance with specification.
		Specification for MSA.	≤0.05% genotoxins in MSA.	Compliance with specification.
		In-Process-Control check.	≤0.1% alcohols in crystallization solution.	Compliance with specification.
Filtrations and Washings	Spiking and purging experiments.	Minimum wash volume.	Quality Process Parameters: wash volume	Compliant batch record.
Drying	Process stretching experiments.	Maximum temperature.	Quality Process Parameter: temperature	Compliant batch record.

Genotoxin control is assured, without end-product testing.

Conclusions

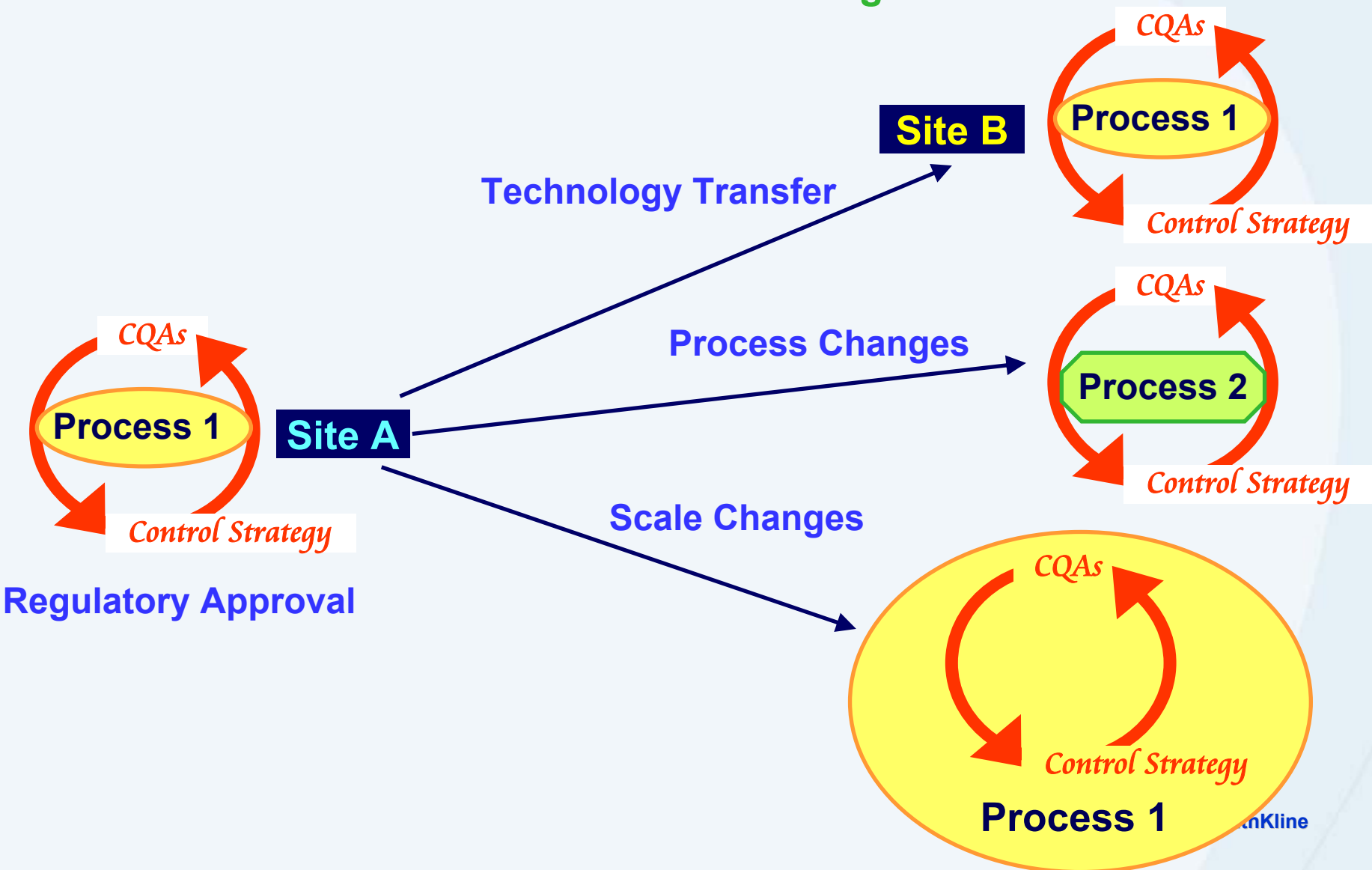
- The Quality-by-Design principles outlined in ICH and other guidance provide a structured approach to gaining process knowledge and developing robust manufacturing control strategies.

- Significant amounts of process knowledge are now included in regulatory submissions in order to justify the control strategy.

- There are significant benefits to the approach ..
  - **for patients** … a quality product is placed on the market, and is kept on the market,
  - **for regulators** ... the scientific rationale for the control strategy is transparent,
  - **for pharmaceutical companies** …a clear control strategy is identified which ultimately facilitates product launch and subsequent manufacturing changes.

Benefits Derived by a QbD Approach

Demonstrated Product & Process Understanding Facilitates:



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