Pharmaceutical Quality System (ICH Q10) Conference
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Saxagliptin (Onglyza): A Case Study in Quality Risk Management

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Objectives of this Presentation

To illustrate how Q10 was applied in the development of a new drug product and used in Production

To provide insight of knowledge management [1.6.1.] and quality risk management [1.6.2]

ICH Q10 (Scope 1.2) … the product lifecycle included the following technical activities for new and existing products:

Pharmaceutical Development

- Formulation development
- Manufacturing process dev't & scale-up

Technology Transfer

Commercial Manufacturing

ICH Q10 Knowledge Management (1.6.1)

- Product and process knowledge should be managed from development through the commercial life of a product…
- Knowledge management is a systemic approach to acquiring, analyzing, storing, and disseminating information related to products, mfg. processes, and components.

Knowledge Acquisition

- Defining the Product Profile
- Public domain literature, patent review
- API attributes and limitations
- Definition of the DP manufacturing process
- Ranging the manufacturing process

Knowledge Analysis

- Determining elements of intrinsic criticality, e.g. API attributes, process parameters, environmental conditions
- Risk analysis of the critical elements, e.g. FMEA, HACCP
- Defining a Control Strategy, e.g. integration of the process controls into facility QMS

Knowledge Storage

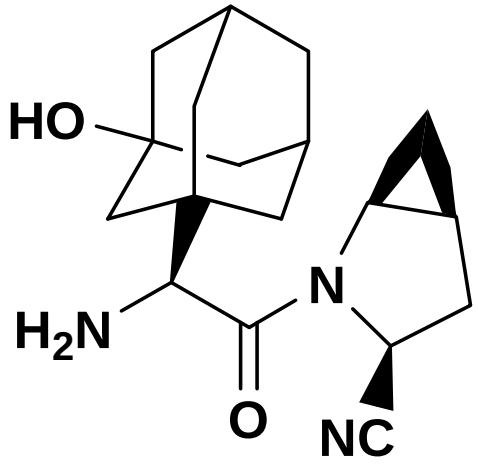
- Development reports
- E-notebooks
- E-network databases
- Manufacturing Orders
- SOPs, work instructions, best practices

Knowledge Dissemination

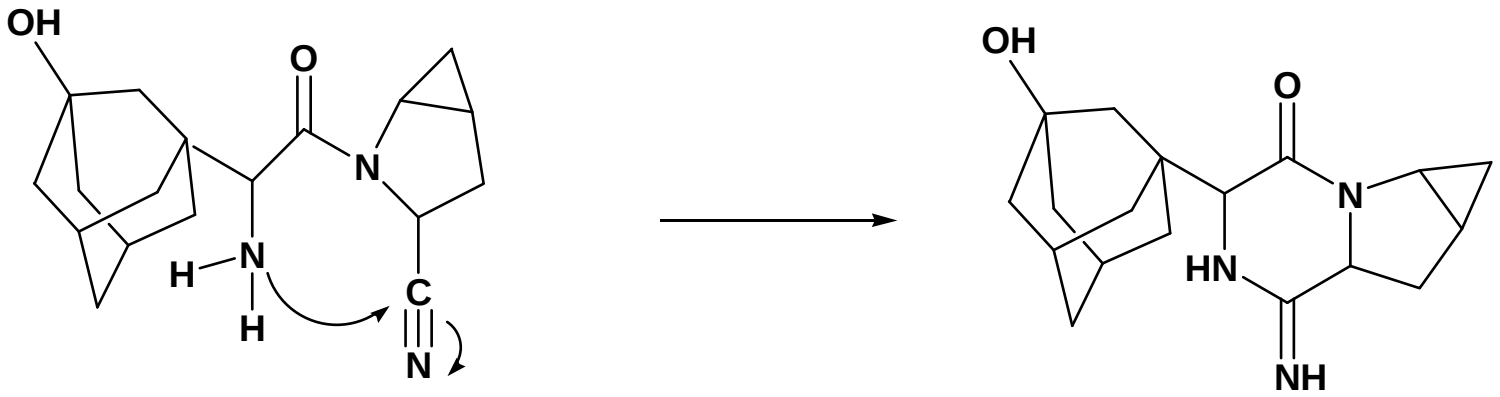
- Joint functional area meetings, deep dives
- Technology transfer- “go to the customer”
- On-site technology seminars
- Demonstration runs

KM and QRM- A Case Study Saxagliptin

- Dipeptidyl peptidase IV inhibitor (DPP4) for Type II diabetes
- pKa = 7.2
- BCS Class III



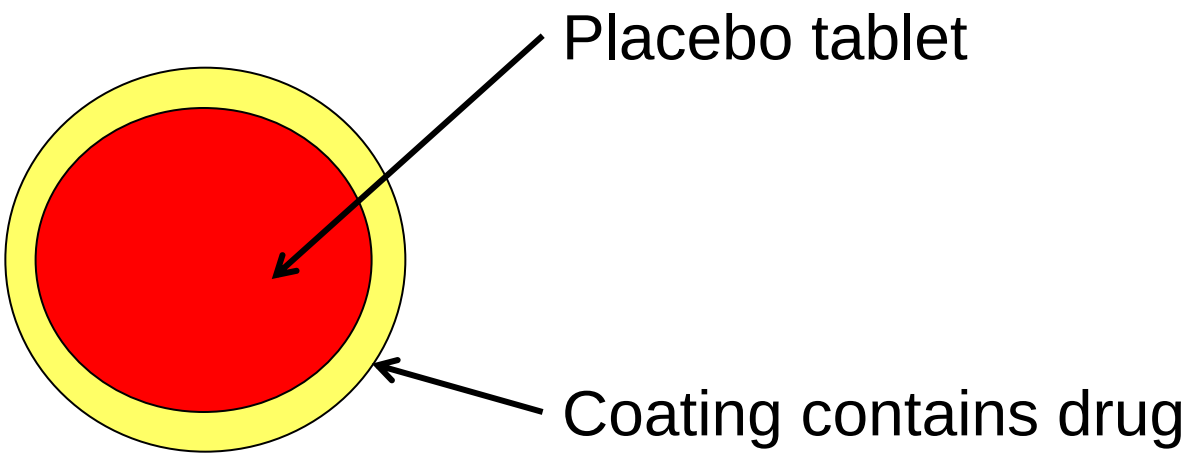
Controlling Intramolecular Cyclization



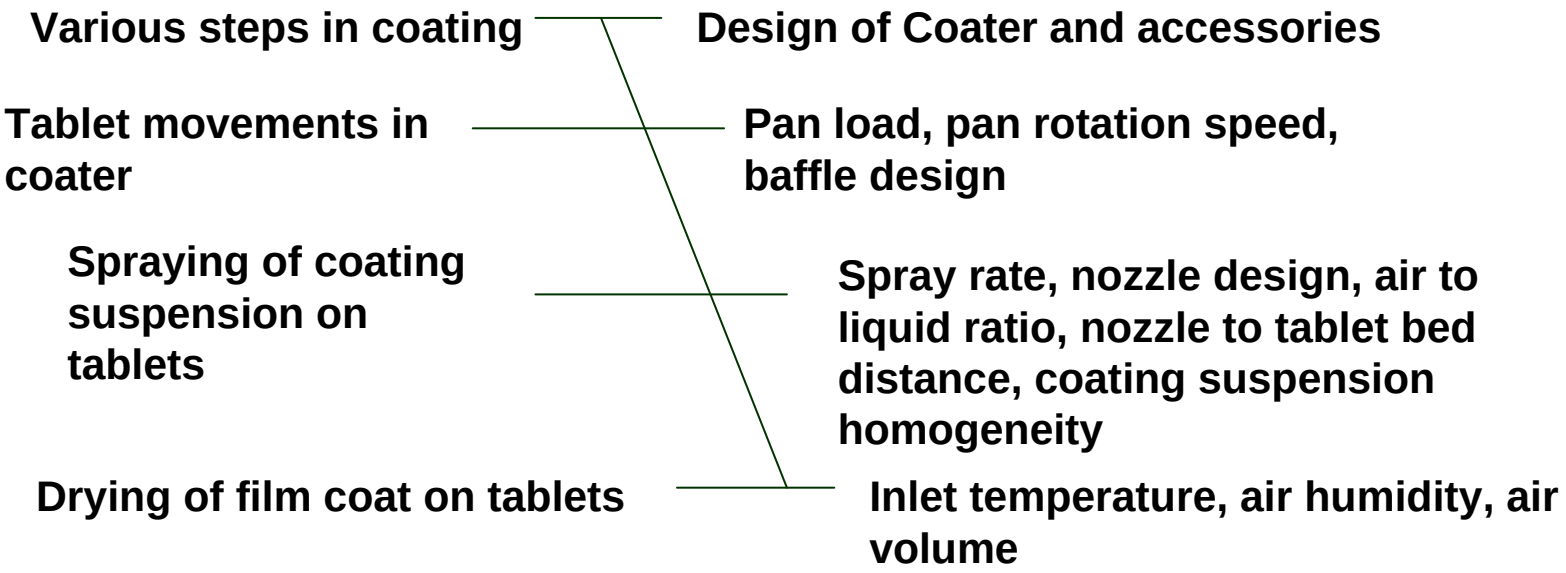
Saxagliptin **Cyclic amidine**

Cyclization
- Occurs in solid and solution state
- Accelerates with commonly used excipients
- Accelerates when processed under wet & dry granulation
- Acidic environment stabilizes saxagliptin

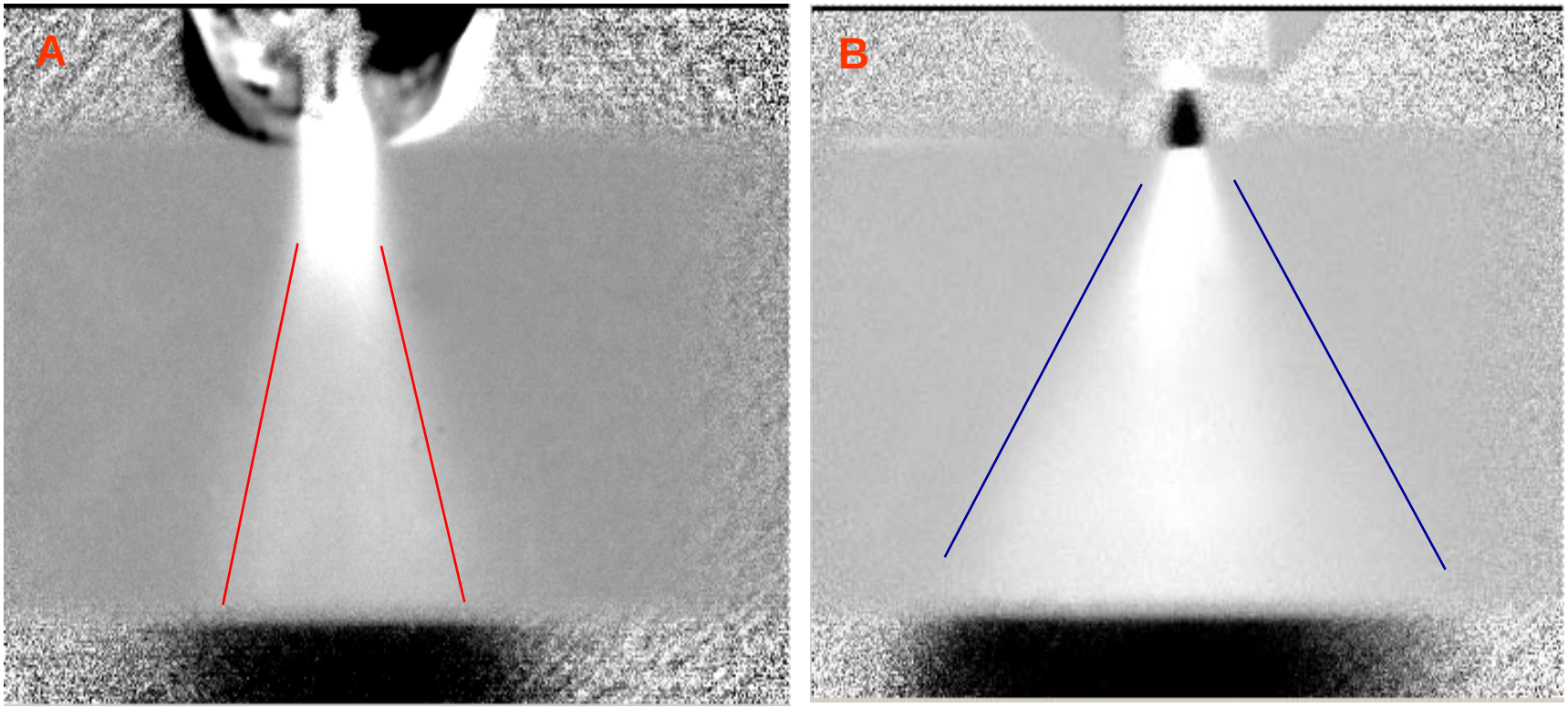
DP Strategy- Film Coat Saxagliptin
The Critical DP Manufacturing Step



Analysis of Variables That May Impact the Coating Process

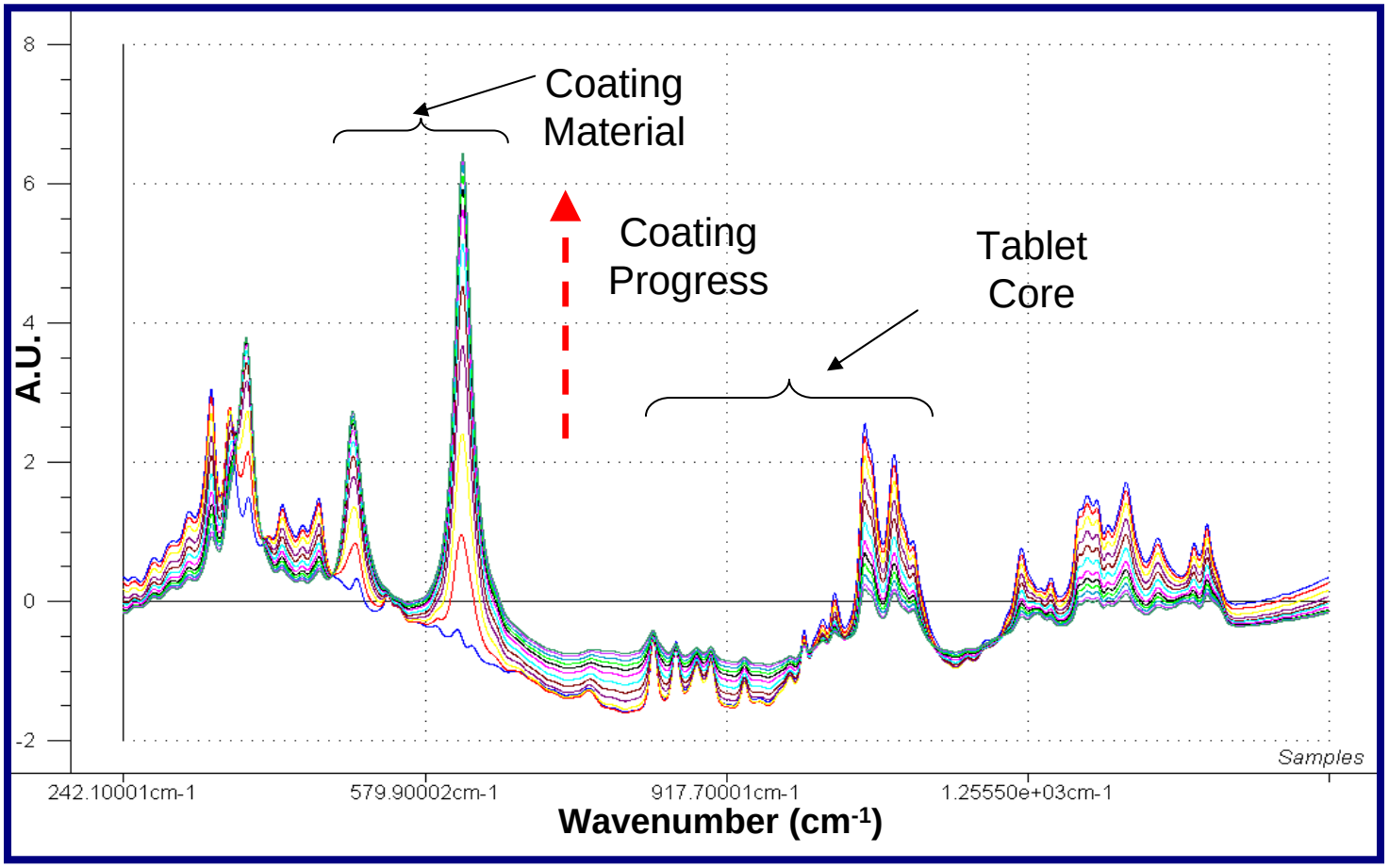


Comparison of different spray nozzles and spray patterns



Cone angle of (A) nozzle vs. (B) nozzle

Use of Raman to Monitor Coating



Process Optimization DOE was performed on Commercial Scale Equipment

Design: Saxagliptin Film Coated Tablets 2^(5-1) Fractional Factorial with 3 Center Points Design - 19 Runs

Actual Levels used for LOW(-1), CENTER(0), and HIGH(+1)

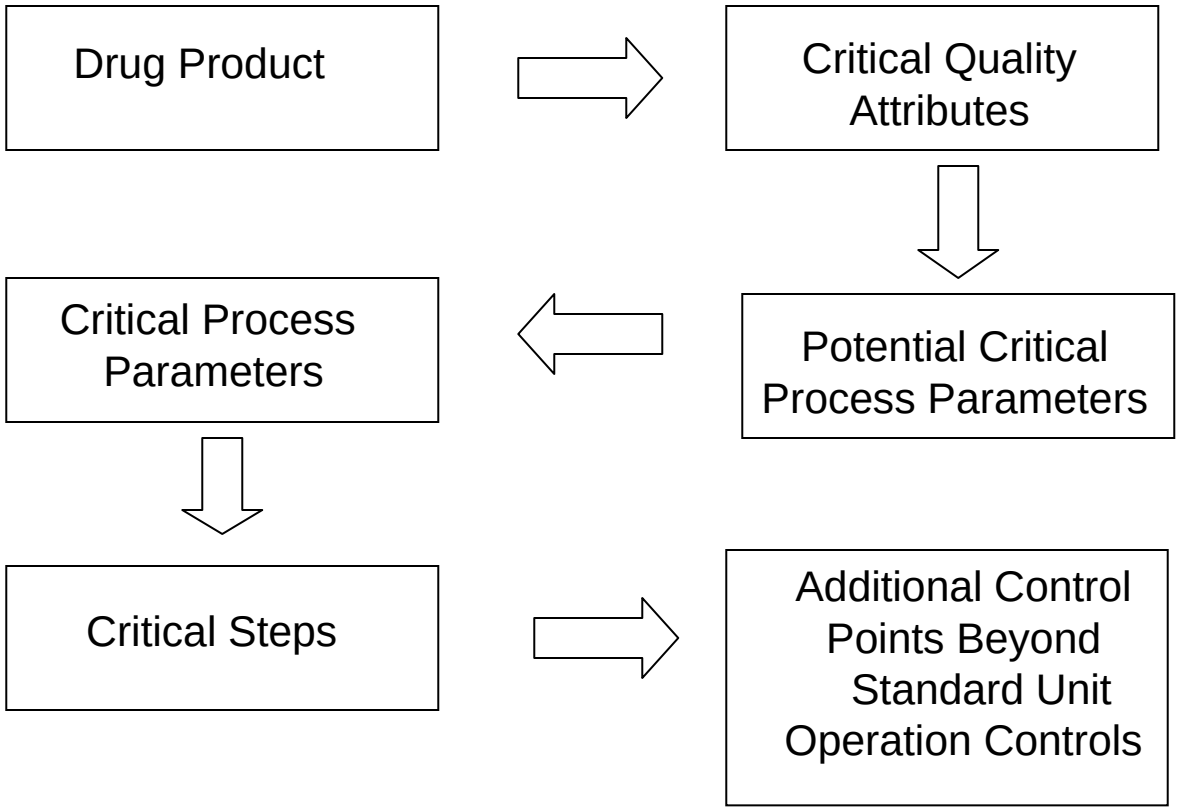
	API concentration	API/Polymer Ratio	Inlet Temperature ^{o}C	Total Spray Rate from 3 guns (g/min)	Atomizing Air+Pattern air per gun (SLPM)	Air Volume (CFM)
LOW(-1)	2%	1:8	50.00	60.00	200.00	525.00
CENTER(0)	4%	1:4	52.50	81.00	250.00	560.00
HIGH(+1)	8%	1:1	55.00	105.00	300.00	600.00

A constant ratio of 1.5:1 was maintained between atomizing and pattern air for all runs.

Process Knowledge Acquired in Development and Transferred Forward to Production

- Key Quality Attributes identified after risk assessment
  - content uniformity
  - potency
- Design space established using fundamental process understanding, modeling and Design of Experiments (DOE)
- A predictive model for CU and potency created for the Coating Step

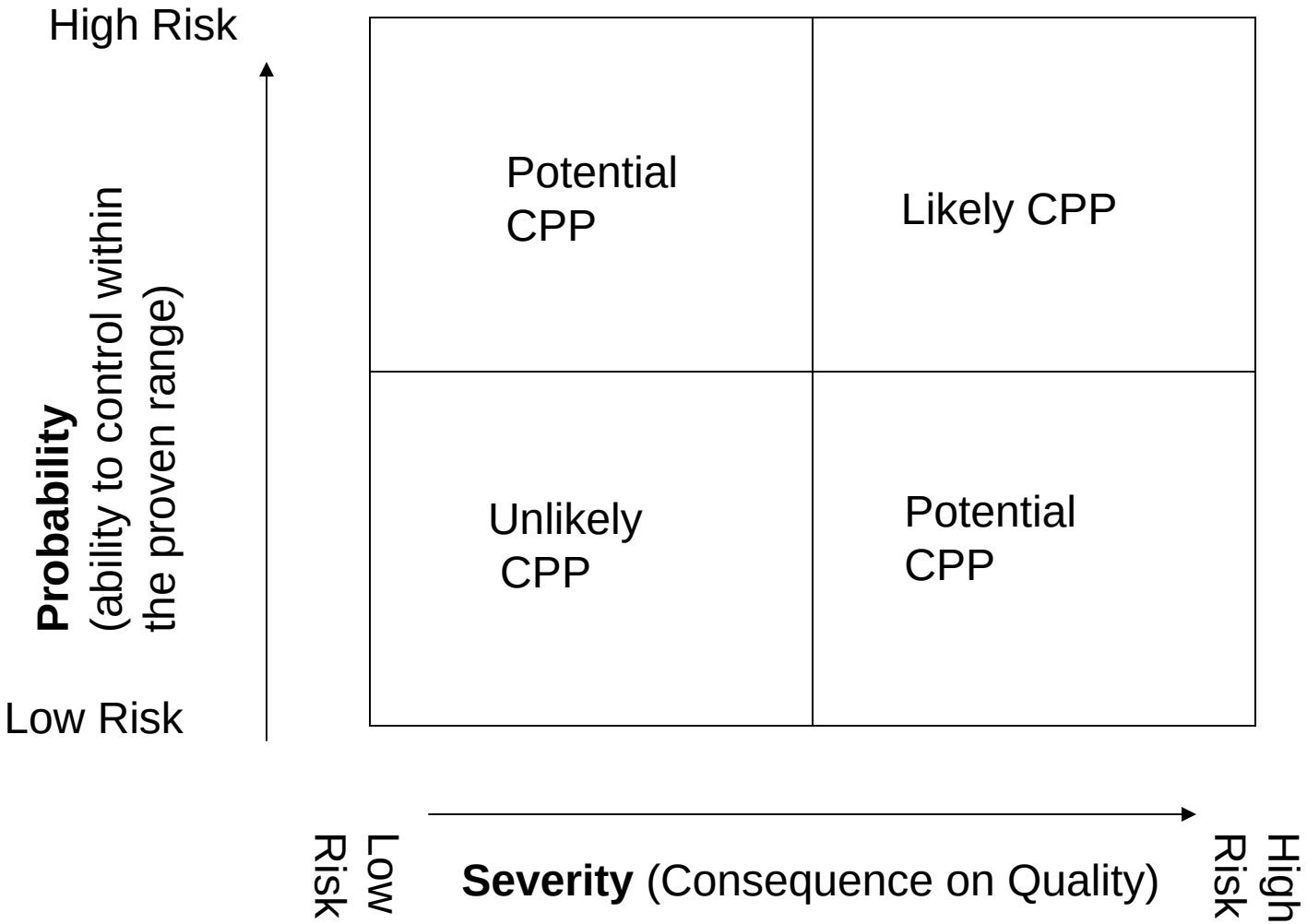
Data Analysis to Define a Control Strategy



Quality Risk Analysis (ICH Q10 1.6.2)

Event	A potential CPP because of impact and frequency
Severity	Consequence on Quality = HIGH Risk for potential CPP = LOW Risk for non CPP
Probability	= LOW Risk: operating range is well within the boundaries of proven range = MEDIUM Risk: operating close to the boundaries of proven range = HIGH Risk: operating close to the boundaries of proven range and the edge of failure
Overall Risk	Combination of severity and probability

Communicating Risk Assessment



Production Process was Assessed for Criticality, Risk and Control

- A 5 Step Approach was taken
- Applicable for either drug substance or drug product
- When considering CPPs, determine what is critical and then how to control it
- Control of CPPs are additional to the standard level of controls

Drug Substance Process Controls

An Example of Process Parameter Risk Assessment using the 5 step approach

1. Lay out all the process parameters in each step

	Operation	Measure-ment	Parameter	Units
	Deprotection Reaction			
1	**Charge intermediate**		Basis	moles
2	**Charge solvent**	**Concentration of intermediate**	2.5	mL/g
3	**Set agitation**		50	rpm
4	**Cool to**		10	deg C
5	**Charge reagent**	**Equivalents of sodium methoxide**	1	equiv
6	**Heat to**		19	deg C
7	**Age**	**Temperature**	19	deg C
		time	1	hr
		agitation	100	rpm

2. Compile Experimental conditions (target, proven, operating ranges) and establish Design Space

					Propose Proven Range									
						Design Space								
							Expected Control Range for Factory							
								Operating Range						
	Operation	Measurement	Parameter	Units	Min		Min	Min	Target	Max	Max		Max	
	Deprotection Reaction													
1	**Charge BMS-645402**		Basis	moles										
2	**Charge solvent**	**Concentration of BMS-645402**	2.5	mL/g	**2.2**			**2.38**	**2.5**	**2.63**			**2.7**	
3	**Set agitation**		50	rpm					**50**					
4	**Cool to**		10	deg C				**5**	**10**	**15**				
5	**Charge reagent**	**Equivalents of sodium methoxide**	1	equiv	**0.95**			**0.99**	**1**	**1.01**			**1.1**	
6	**Heat to**		19	deg C					**19**					
7	**Age**	**Temperature**	19	deg C	**0**			**10**	**19**	**23**			**27**	
		time	1	hr					**1**					
		agitation	100	rpm					**100**					

3. Understand the consequences of high and low points of a range Overlay the likely Production Control Capabilities

	Operation	Measurement	Parameter	Units	Exp Routine Factory Capabilities	Consequence of operating outside proven range low	Data ref for min proposed proven range	Propose Proven Range: Min	Design Space:	Expected Control Range for Factory: Min	Operating Range: Min	Target	Max	Expected Control Range for Factory: Max	Design Space:	Propose Proven Range: Max	Data ref for max proposed proven range	Consequence of operating outside proven range high
	Deprotection Reaction																	
1	**Charge Intermediate**		Basis	moles														
2	**Charge solvent**	**Concentration of intermediate**	2.5	mL/g	± 5%	Thick slurry	63556-103	**2.2**		**2.38**	**2.38**	**2.5**	**2.63**	**2.63**		**2.7**	63556-101	Sluggish reaction
3	**Set agitation**		50	rpm								**50**						
4	**Cool to**		10	deg C	± 5C					**5**	**5**	**10**	**15**	**15**				
5	**Charge reagent**	**Equivalents of sodium methoxide**	1	equiv	± 5%	Possible residual BMS-645402 remaining as impurity	63556-066 to 077 1st DoE	**0.95**		**0.95**	**0.99**	**1**	**1.01**	**1.05**		**1.1**	63556-066 to 077 1st DoE	Hydrolysis or methanolysis in alkylation reaction
6	**Heat to**		19	deg C								**19**						
7	**Age**	**Temperature**	19	deg C	± 5C	slow or imcomplete reaction	63556-102	**0**		**14**	**10**	**19**	**23**	**24**		**27**	63556-092	High impurities, but still purgable
		time	1	hr								**1**						
		agitation	100	rpm								**100**						

4. Assess the risk of the process parameter on quality (CQA) to determine if it's a likely CPP and consider needed controls

									Propose Proven Range														
										Design Space													
											Expected Control Range for Factory												
												Operating Range											
	Operation	Measurement	Parameter	Units	Exp Routine Factory Capabilities	Consequence of operating outside proven range low	Data ref for min proposed proven range	Min		Min	Min	Target	Max	Max		Max	Data ref for max proposed proven range	Consequence of operating outside proven range high	Impact on API CQA	Is proven range outside expected control range	Risk of failing outside proven range?
	Deprotection Reaction																						
1	**Charge intermediate**		Basis	moles																			
2	**Charge solvent**	**Concentration of intermdiate**	2.5	mL/g	± 5%	Thick slurry	63556-103	**2.2**		**2.38**	**2.38**	**2.5**	**2.63**	**2.63**		**2.7**	63556-101	Sluggish reaction	**Yes** for low values	Yes	Low
3	**Set agitation**		50	rpm								**50**											
4	**Cool to**		10	deg C	± 5					**5**	**5**	**10**	**15**	**15**									
5	**Charge reagent**	**Equivalents of sodium methoxide**	1	equiv	± 5%	Possible residual BMS-645402 remaining as impurity	63556-066 to 077 1st Dose	**0.95**		**0.95**	**0.99**	**1**	**1.01**	**1.05**		**1.1**	63556-066 to 077 1st Dose	Hydrolysis or methanolysis in alkylation reaction	**Yes**	marginal	Low to medium, undercharge is corrected by IPC
6	**Heat to**		19	deg C								**19**											
7	**Age**	**Temperature**	19	deg C	± 5	Slow or imcomplete reaction	63556-102	**0**		**14**	**10**	**19**	**23**	**24**		**27**	63556-092	High impurities but still purgable	**Yes**	Yes	Low to medium
		time	1	hr								**1**											
		agitation	100	rpm								**100**											

5. Assess what additional work is needed to determine if parameter is characterized as a CPP

Impact on API CQA	Is proven range outside expected control range	Risk of failing outside proven range?
Yes for low values	Yes	Low
Yes	marginal	Low to medium, undercharge is corrected by IPC
Yes	Yes	Low to medium

QRM in Manufacturing- Going Beyond Product Development

- QRM begins in Product Development and continues in Manufacturing as part its life-cycle management
- Knowledge gained during development is foundational to a process, and the manufacturing history builds on that knowledge base

QRM as Part of the Life-Cycle Management of a Product

- Process Changes- internal and external to the Design Space
- Input Material Changes
- Scale Changes
- Process Equipment Changes
- Site Changes
- Process Improvements

KM and QRM Summary

- KM and QRM begin in Product Development and continues through a product's life cycle
- Understanding the product and its manufacturing process are needed to create an effective control strategy
- QRM is integral to executing an effective control strategy and maintaining the product

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