2nd FDA/PQRI Conference on Advancing Product Quality

Generic Pharma Perspective on the Identification of Critical Quality Attributes and Critical Process Parameters

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October 6, 2015

Outline

- *Introduce Perrigo*
- *Mandate of QbD for the Generic Pharmaceutical Industry*
  - Pharmaceutical Development Differentiators - Generic vs. Innovator
  - Impact to ANDAs
- *Implementation Perspectives*
  - CPPs & CQAs
  - Risk Assessment
- *Case Study*

Global Presence

Positioned to Capture Expanding Global Healthcare Needs

>$5B	>80	31	~ 13K	>22.8K	>6K
In Sales*	Markets	Operating Locations	Employees	SKUs	Formulations

*CY15 Pro Forma, Includes only 9 months for Omega acquisition translated at €1:$1.09

Our Capabilities make Perrigo One of the World's Leading Pharmaceutical Development & Manufacturing Organizations

Perrigo

- ***47 Billion*** *oral solid doses/year*
- ***3 Billion*** *liquid/cream doses/year*
- ***3,000+*** *formulations*
- ***18,000*** *SKUs*
- ***Launching*** *1+ new product/week*
- ***Investing $120-$180M/year*** *in new capabilities*

Capabilities

- ✓ Tablets
- ✓ Capsules
- ✓ Solutions
- ✓ Suspensions
- ✓ Sprays (Nasal)
- ✓ Suppositories
- ✓ Creams/ointments
- ✓ Powders
- ✓ Lozenge
- ✓ Foam
- ✓ Aerosols
- ✓ Gums
- ✓ Injectables
- ✓ Spot-on pesticides
- ✓ Extruded pellets

Every second of every day, somewhere in the world, nearly 1,600 people will use a Perrigo product

Perrigo™
Quality Affordable Healthcare Products™

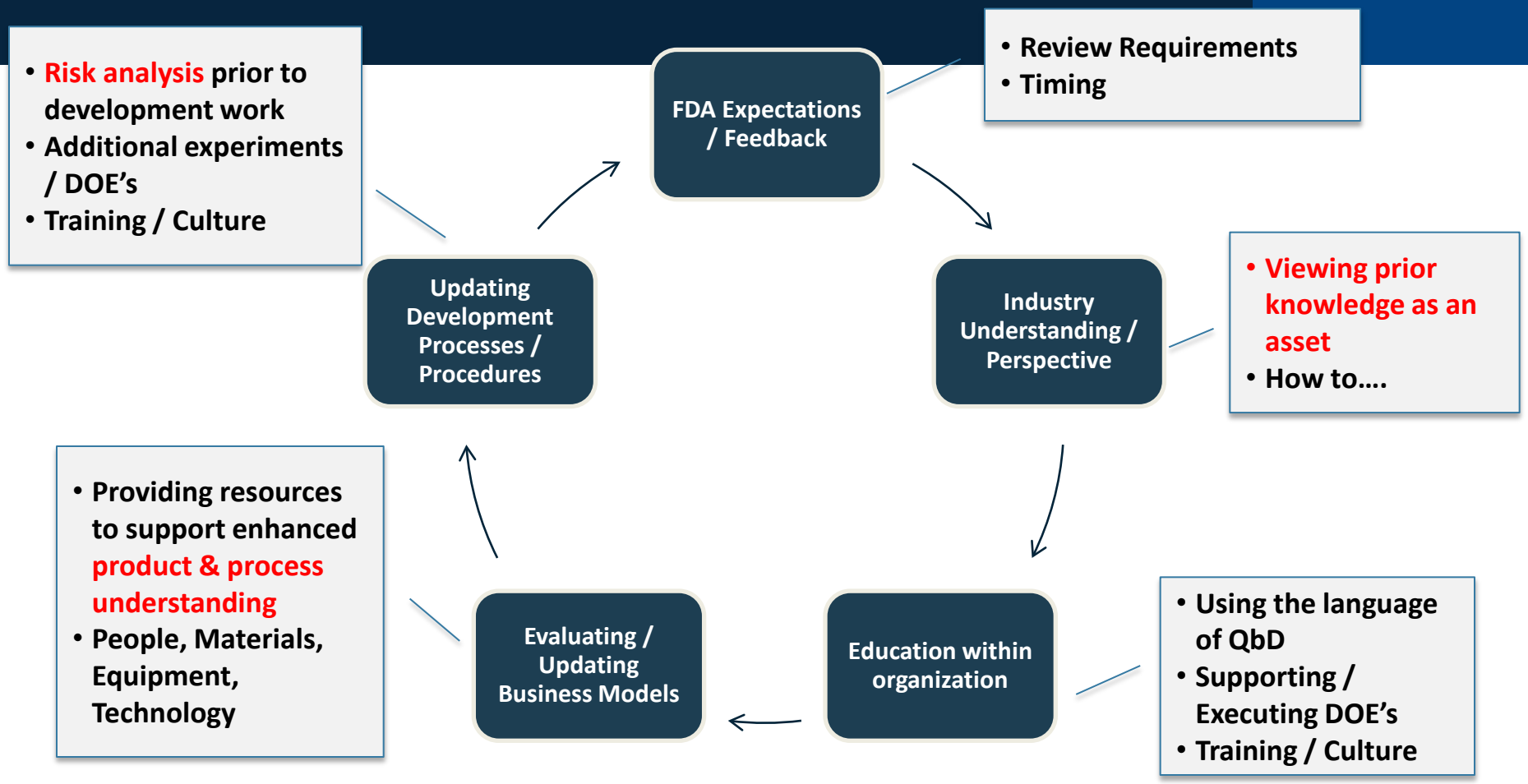
FDA Message – QbD is Essential to Quality

U.S. Food and Drug Administration
Protecting and Promoting Public Health

- *"**80%** of prescriptions are being filled with **generic products** and branded drugs coming off patent every day."*
- *"There is a **more crucial need** to develop more efficient, reliable, and versatile manufacturing methods.*
- *"**Complexity** of pharmaceuticals is rapidly increasing…"*
- *"Quality by design is an **essential part of the modern approach** to pharmaceutical quality."*
- *"In order for quality to increase, it must be **built into the product**. "*
- *Generic Manufacturers Need to be Full Participants in **FDA's Pharmaceutical Quality for the 21st Century Initiative***
- *"An **initial investment** is necessary to achieve the cost effective manufacturing of the Future."*

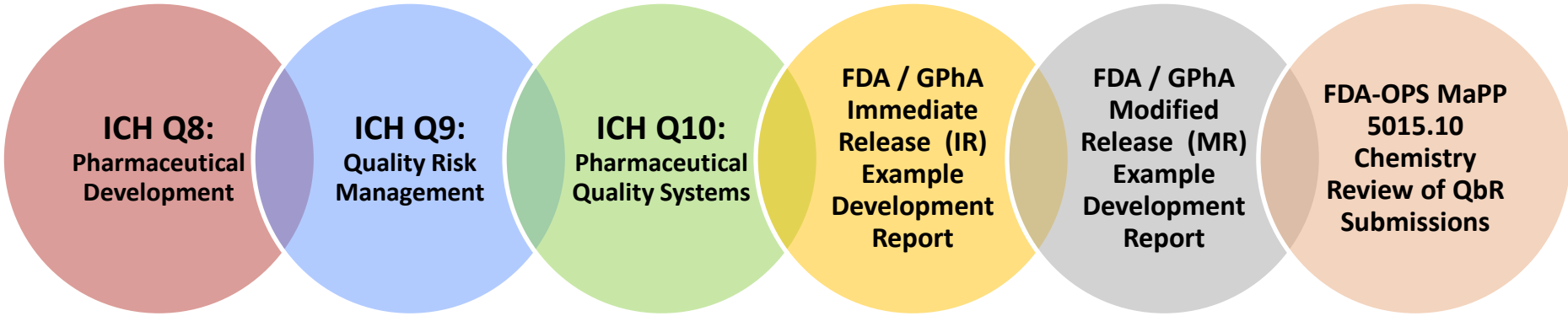
"Implementation of QbD is essential to ensuring the availability of affordable, high quality generic drugs."

General Approach for Implementing QbD



Implementation of QbD has been both ***Technical*** and ***Strategic***

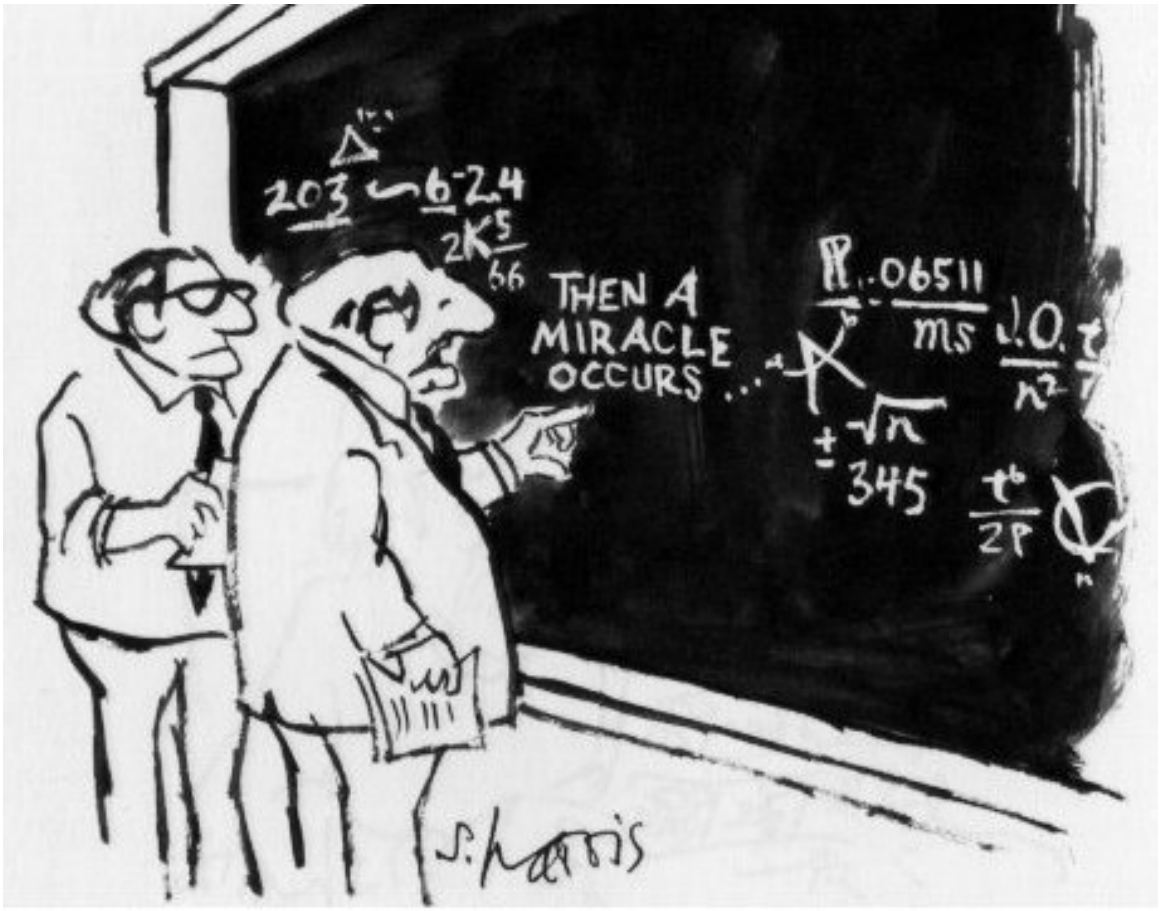
Available Tools / Resources



- MaPP 5015.10 (QbR) – published November 2014
  - Revised to better capture QbD expectations
  - Reviewer Companion Documents contains additional details for what the applicant should provide for each question

- Others:
  - ICH Q1 (A-E): Stability Guidances
  - ICH Q11: Development and Manufacture of Drug Substances
  - USP <1059> Excipient Performance

Development without QbD?



"I think you should be more explicit here in step two."

from *What's so Funny about Science?* by Sidney Harris (1977)

Pharmaceutical Product Development Timelines to Market

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Originator (NDA)

~ 8 years CMC development window

Generic (ANDA)

~ 2 years CMC development window

FTF or FTM

What Differentiates Generic Product Development in QbD?*

CMC product development is ***always*** on the critical path, thereby forcing a generic firm to be very efficient with QbD development processes (including identification of CPPs and CMAs)

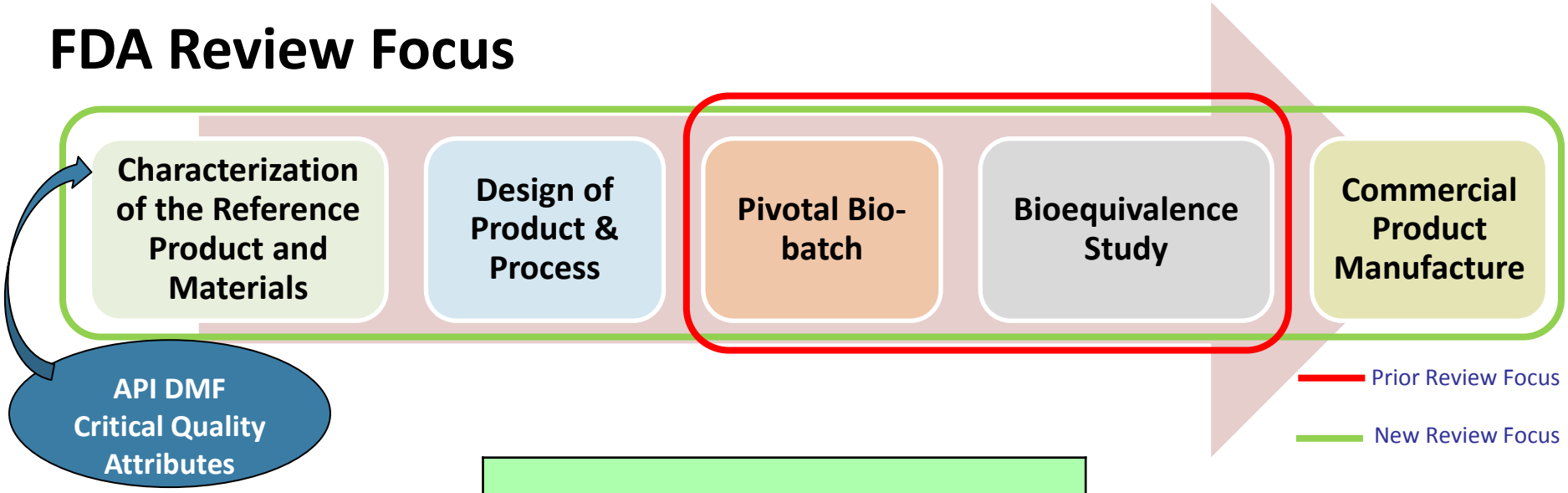
- Documented prior knowledge
  - Internal data mining
  - Research articles, review papers, patents or reference books
  - Reference Listed Drug (RLD) labeling**
- Risk assessment
  - Evaluation
  - Mitigation
  - Control Strategy with Justification

*Predominant early adopters were generic pharma's 85% vs. 14%: *Generic Industry Has Made Progress Implementing QbD* / "The Gold Sheet" February 28 2013

**QTPPs are typically already established by the RLD (unless new Rx to OTC product)

Impact to ANDAs

FDA Review Focus



QbD is a development process

QbD elements must be integrated into the development process

Perrigo Implementation – *What's Been Done*

Created a common QbD vision with processes & structured thinking…

Defined / Updated Development Cycles

- Clear targets defined throughout development
- Target defined at project initiation
- Risk Assessments drive development work
- Improved processes for data & documentation compilation
- Enhanced Statistical application

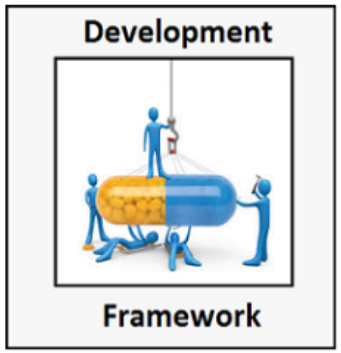
Enhanced Governance

- Drives discipline & consistency
- Increases awareness & transparency of technical risks
- Input by stakeholders & key participants (cross-functional)

Invested in training & processes that are sustainable, not individual based

Perrigo Customized Drug Development Process

Custom interactive platform for integrating development process flows with templates, tools, guidance documents, and procedures



Supports:

- Enhanced data & documentation compilation
- Alignment across multiple developing sites
- Clear expectations for what is required within each development phase
- Improved access and transparency to development data & information
- Technical Governance with awareness of risks / risk management

Drug Product Development through a QbD Process (Identification of CQAs, CPPs & CMAs)

QTPP identified based on the:

- Clinical and pharmacokinetic characteristics of RLD
- RLD Product label
- In-vitro drug release and physicochemical characteristics

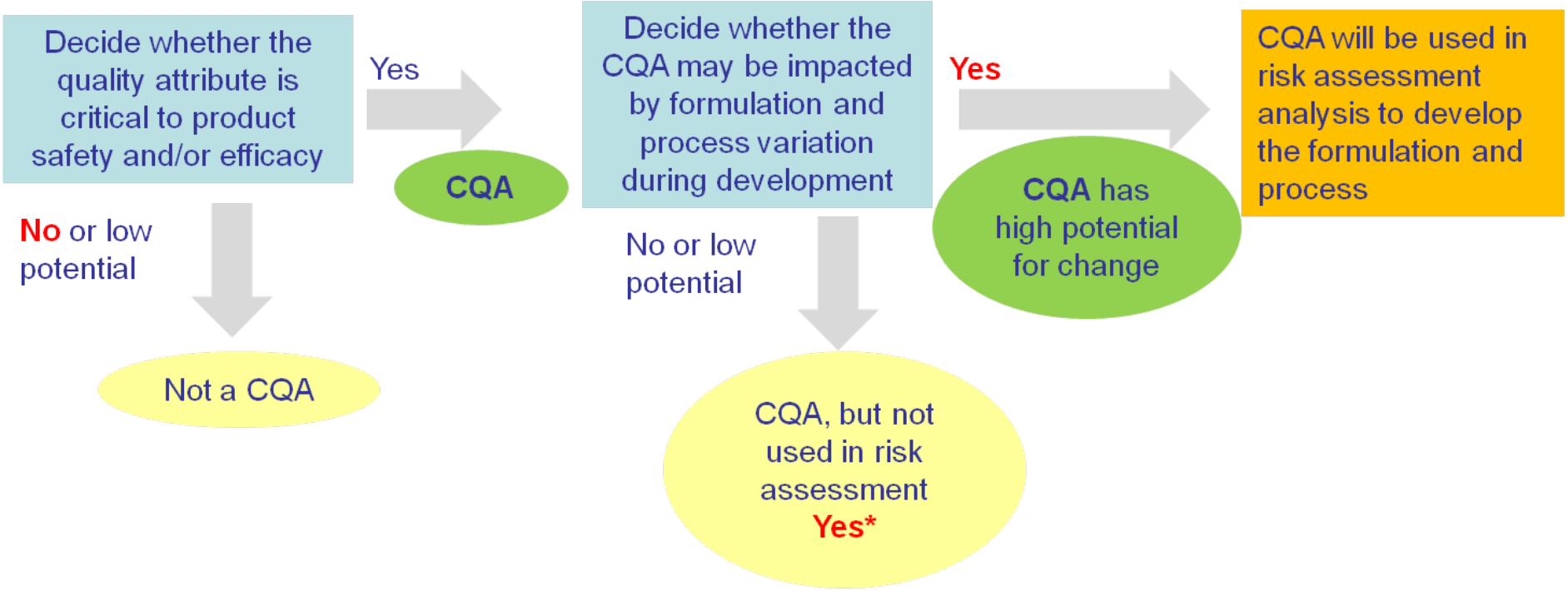
Quality Target Product Profile (QTPP)		
QTPP Element	Target	Justification

Critical Quality Attributes (CQA):

- From the QTPP, Quality Attributes (QAs) of the drug product will be identified

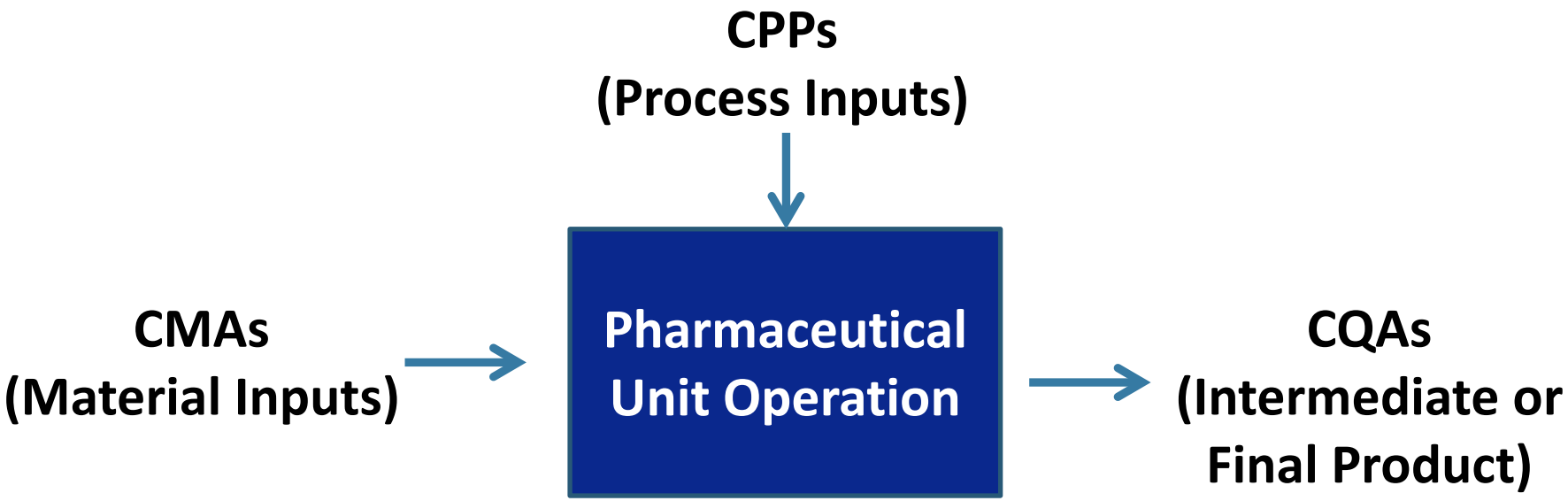
Drug Product Critical Quality Attributes (CQA's) Evaluation			
Quality Attributes of the Drug Product	Target	Is this Critical?	Justification of Criticality

Identification of CQAs



CQA's are the most important measurable product attributes that are used to make design & optimization decisions and to identify CMA's & CPP's later in development

Relationship of CMAs, CPPs & CQAs



Note: A CQA of an output may become a CMA if it becomes an input material of another unit operation.

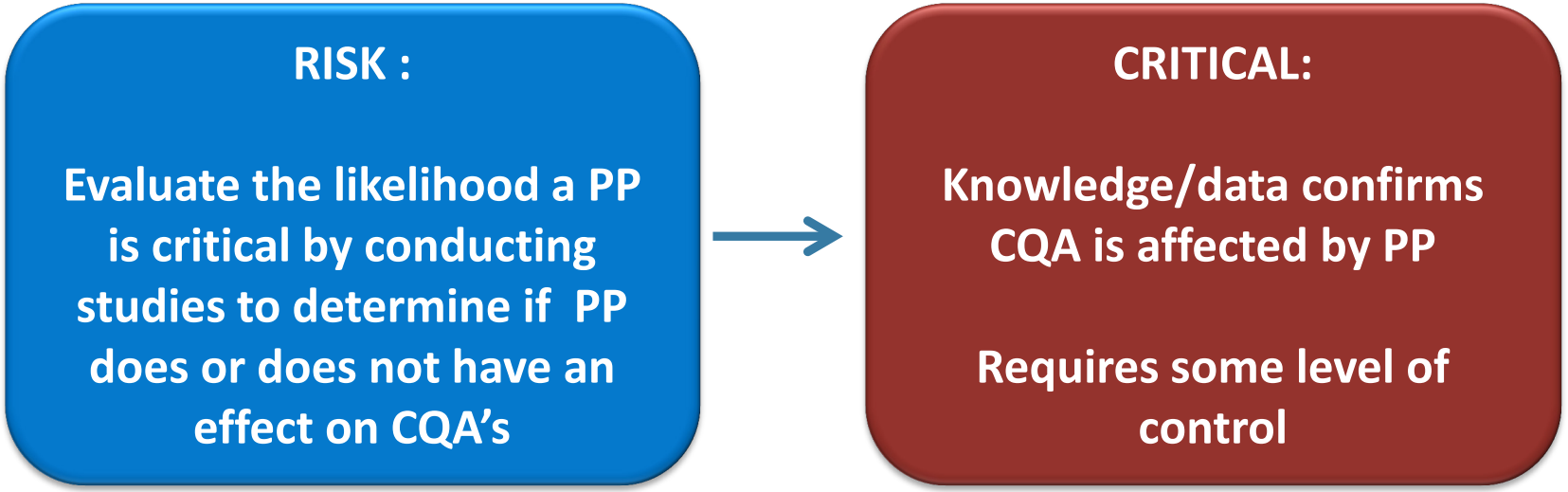
Risk Assessments connect CQAs to the CMAs and CPPs and are the basis for identifying Control Strategies

Identification of CPP

Definition:

A process parameter (PP) whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

"Risk" vs. "Critical"



Risk Assessment

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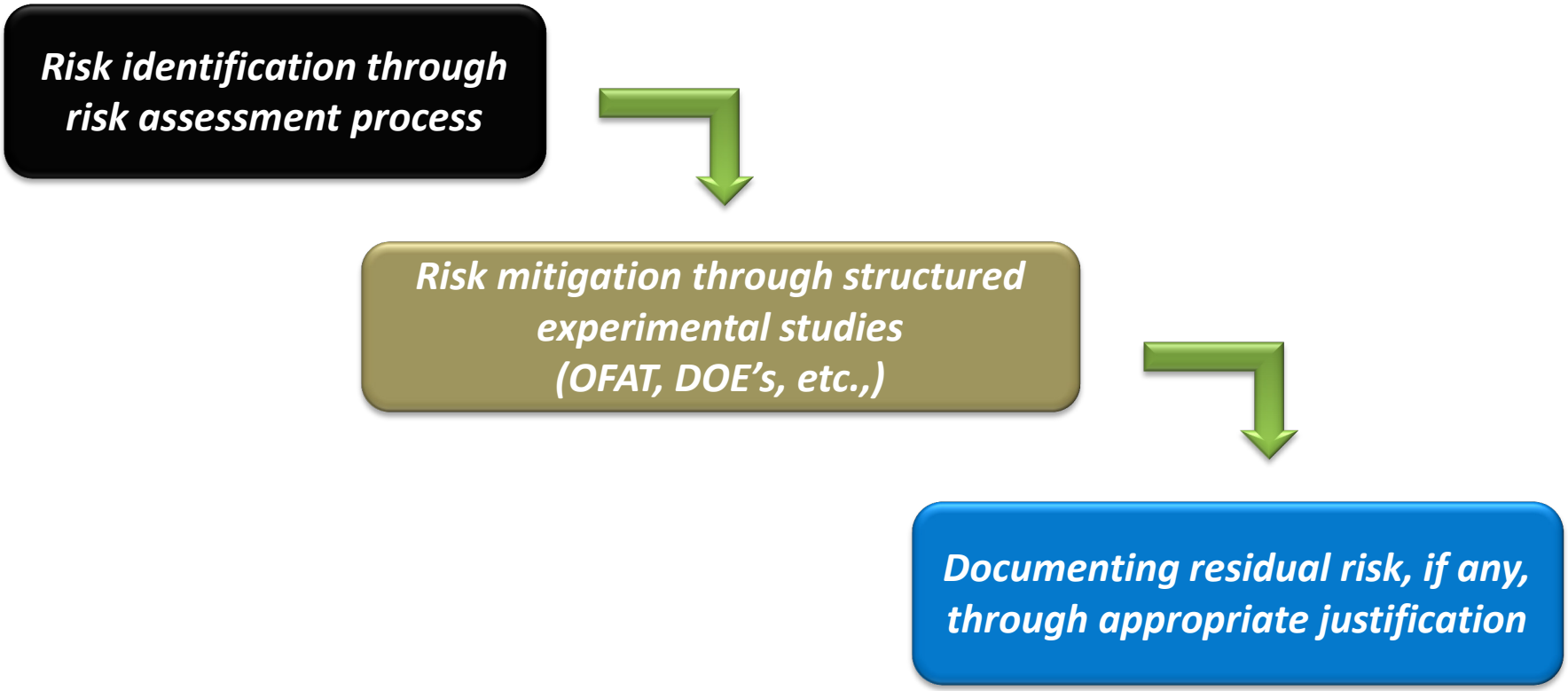
It is neither always appropriate nor always necessary to use a formal risk management process….. The use of informal risk management processes can also be considered acceptable. -ICH Q9

- Documented prior knowledge & apply sound scientific principles
- Tools - FMEA, Fishbone, Databases
  - Standardization / knowledge base for attributes & parameters
- Justification

Drug Product CQA's	Variables & Unit Operations			
	ER beads – drug layering	ER coating	Final blending	Compression
Appearance	Low	Low	High	Medium
Assay	High	Low	Medium	Medium
Degradation Products	Medium	High	Medium	Low
CU	Medium	Low	High	High
Drug Release	Medium	High	Medium	High

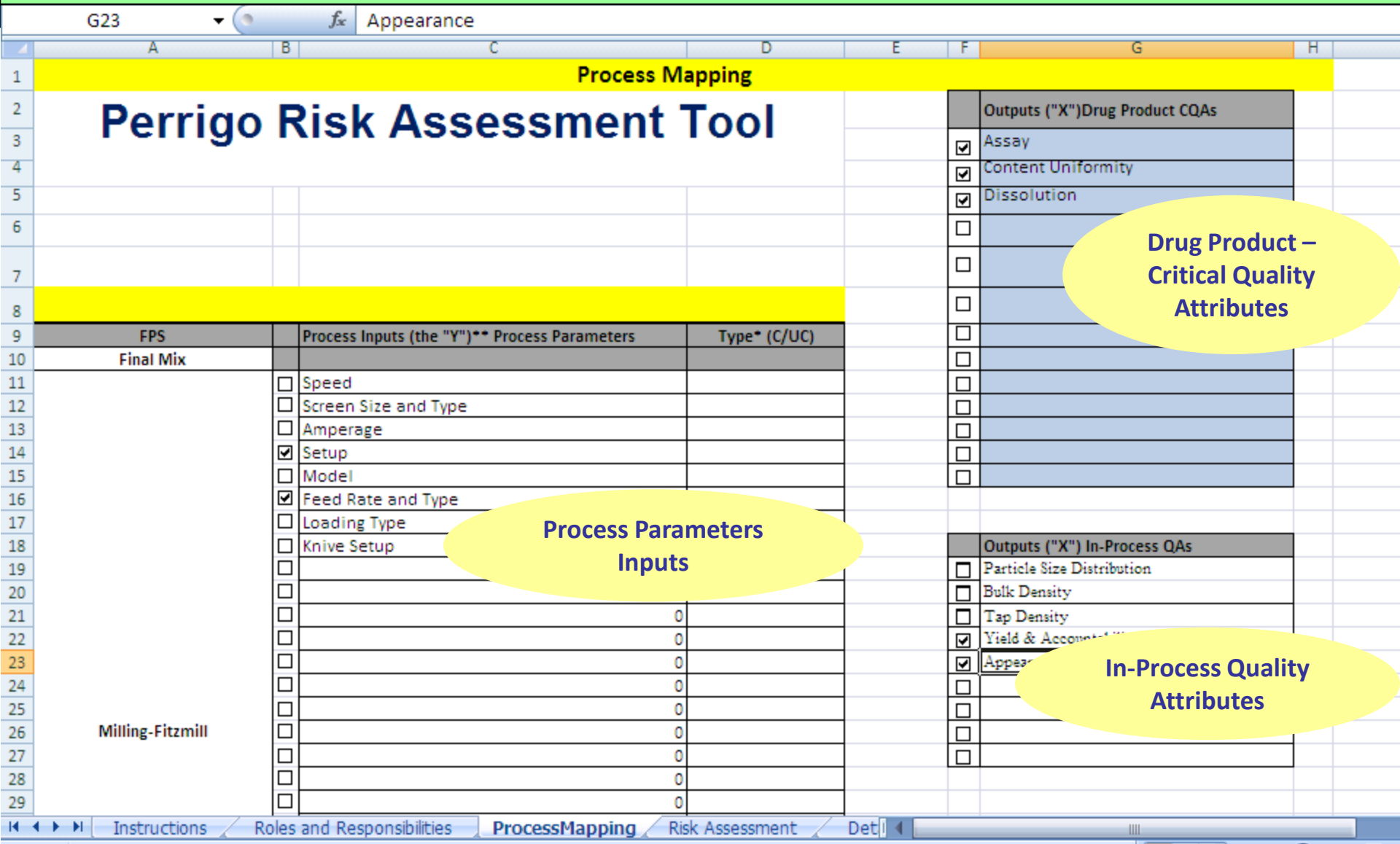
Risk Management Process

Risk Assessment of the Drug Substance, Material Attributes, Formulation Variables, and Processing Parameters:



How Perrigo Brings QbD into Development

Example of Process Mapping for Risk Assessment of Process Parameters



CPPs & CMAs

Risk assessment, risk mitigation studies, development/scale-up studies

Critical Process Parameters (CPPs)			
Formulation Processing Stage:		**Drug Layering: Solution mixer**	
Process Parameter	**Is this Critical?**	**Range**	**Type of Control**

Critical Material Attributes (CMAs)			
Material:	**API**		
Material Attribute	**Is this Critical?**	**Range**	**Type of Control**

Identification of Critical Processing Parameters

Identification of Critical Material Attributes

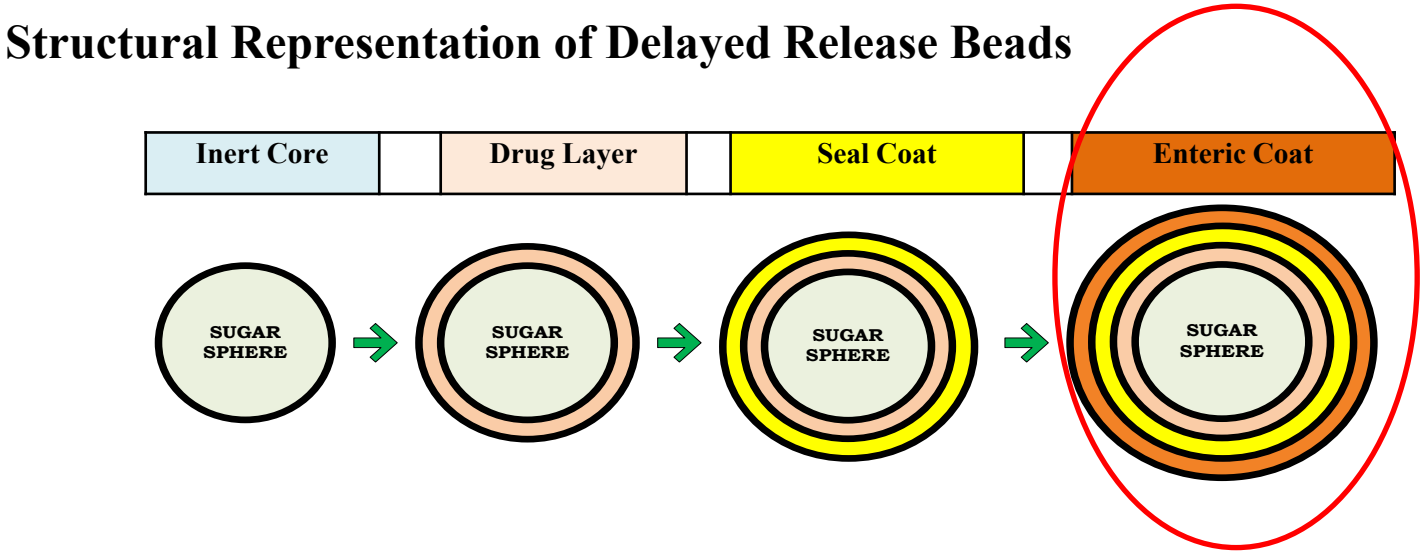
Control Strategy

Selection of Final Formula & Process and finalization of the control strategy

Drug Product CQA	Incoming materials	Process parameter controls	In-process controls (measurements)	Release Testing
Identity	ID testing on drug substance	None	None	Tested at release
Assay	Drug substance purity	Blend Time Press Speed	In-process core tablet assay measured by NIR	None

Case Study

Introduction



- Identified CQA's for the DR beads based upon prior knowledge and RLD
  - Assay
  - CU
  - Drug Release (Acid & Buffer Stage)
  - Impurities

Risk Assessment & Risk Mitigation for Enteric Coating Stage

Initial Risk Assessment

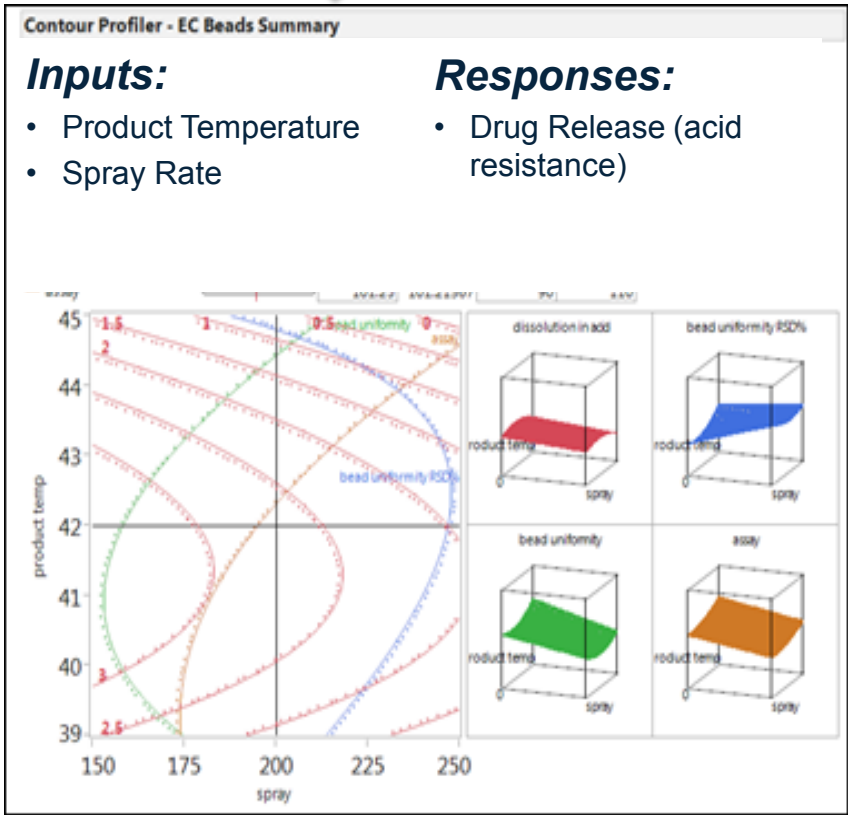
CQA:	Acid Stage Dissolution	
Input Process Parameters	**Risk**	**Justification and Initial Strategy**
Coating Load Size	Low	Based upon scientific literature and/or documented prior knowledge
Atomization Air Pressure	Low	
Spray (Flow) Rate	Medium	
Product Temperature	Medium	

Risk Mitigation Study:

- Fluid Bed Coating Process via GPCG 30 (Glatt fluid bed system)
- Design DOE (full factorial design) to evaluate impact of process parameters (factors and ranges) upon CQAs

DOE for Enteric Coating Stage

DOE Study
(EC Beads)



Outcome

The contour plot provides the relationship of drug release to the product temperature and spray rate inputs resulting in the ability to have a control strategy.

Risk Mitigation for Enteric Coating Stage

CQA:	Acid Stage Dissolution	
Input Process Parameters	**Risk**	**Justification and Initial Strategy**
Coating Load Size	Low	Based upon scientific literature and/or documented prior knowledge
Atomization Air Pressure	Low	
Spray (Flow) Rate	Medium	
Product Temperature	Medium	

Before Studies

After Studies

CQA:	Acid Stage Dissolution	
Input Process Parameters	**Risk**	**Justification and Strategy**
Spray (Flow) Rate	Low	Based upon DOE outcome resulting in effective control strategy
Product Temperature	Low	

Risks mitigated through process understanding and control strategy

CPPs for Enteric Coating Stage

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Identification of Critical Process Parameters

Formulation Processing Stage		Enteric Coating-Wurster Coating	
Process Parameter	**Is this Critical?**	**Range**	**Type of Control**
Atomization Air Pressure	No	See Batch Record	Operating Range
Spray (Flow) Rate	Yes	See Batch Record	In-Process Control
Coating Load Size	No	See Batch Record	Fixed
Product Temperature	Yes	See Batch Record	In-Process Control

Technology Transfer to Commercial Scale Enteric Coating Process

Pilot Scale

Glatt GPCG 30

"Scale-Out"

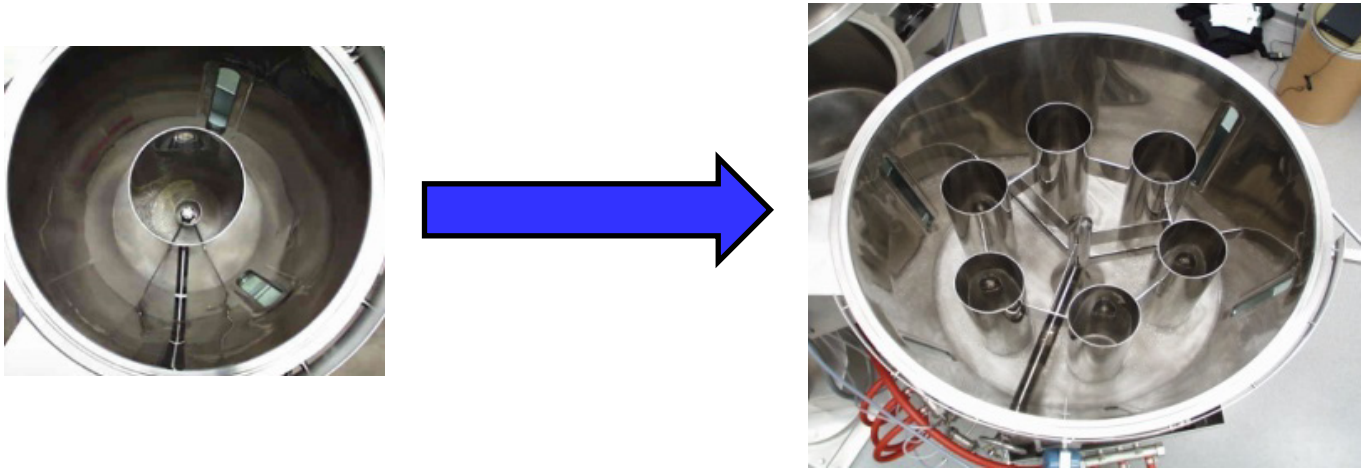
Batch size increase 10 X

Commercial Scale

Glatt GPCG 500

Scale-up of Enteric Coating Process

1. *Apply scale-up factors based upon*
   - *Literature*
   - *Equipment Manufacturers Recommendations*
   - *Prior Knowledge*



2. *Verify CPP control strategy via augmented DOE at commercial scale*
   - *Design space verified at target and min/max of ranges identified at pilot scale*

Case Study Conclusion

- Systematic process parameter risk assessment followed
- Structured experimental study completed to ensure process understanding
- Risk mitigation of CPPs achieved via control strategy
- Successful process scale-up by utilizing scale-up factors
- Verified CPPs from pilot scale studies

✓ ***Robust Process is Established at Commercial Scale***

QbD-Recap

Perrigo

Structure → **Technology** → **Knowledge**

- ✓ Disciplined Development Approach
- ✓ Risk Assessment Driven Development
  - Fo…

- ✓ Experimental Design
- ✓ Data Management

- ✓ Knowledge…
- …nding
- …s
- …Parameters
- …ate Studies
- …aterials &
- …s

Efficient, Robust and Controlled Product to Commercial Market

Acknowledgements

Raj Thota, Director, CHC Formulation Research & Development

Stefanie Rentfrow, Associate Director, CHC Analytical R&D