Quality by Design
Process Development

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Agenda

- What is QbD and Why do we use it?
- Process Development via Quality by Design
  - Create a living Quality based Review
- Identification and testing of Critical Process Parameters (CPP's)
- Process Scale up requirements

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What is Quality by Design? (QbD)

- Growing industry trend
- Regulatory agencies expectation
- Effectively incorporates ICH Q8, Q9, Q10

The three phases of QbD

- Formulation & Process Development
- Formulation & Process Control
- Continual Improvement

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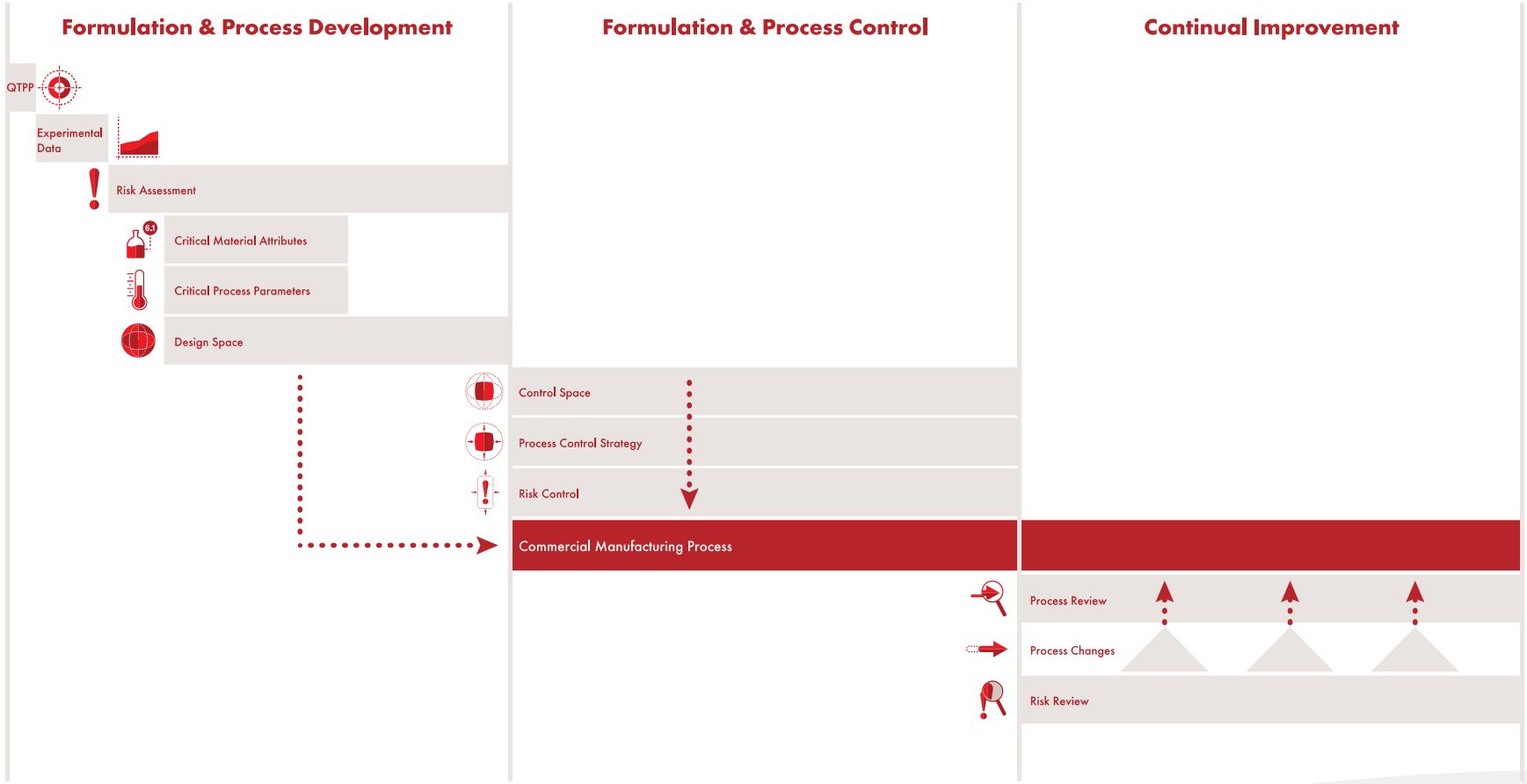
The three phases of QbD



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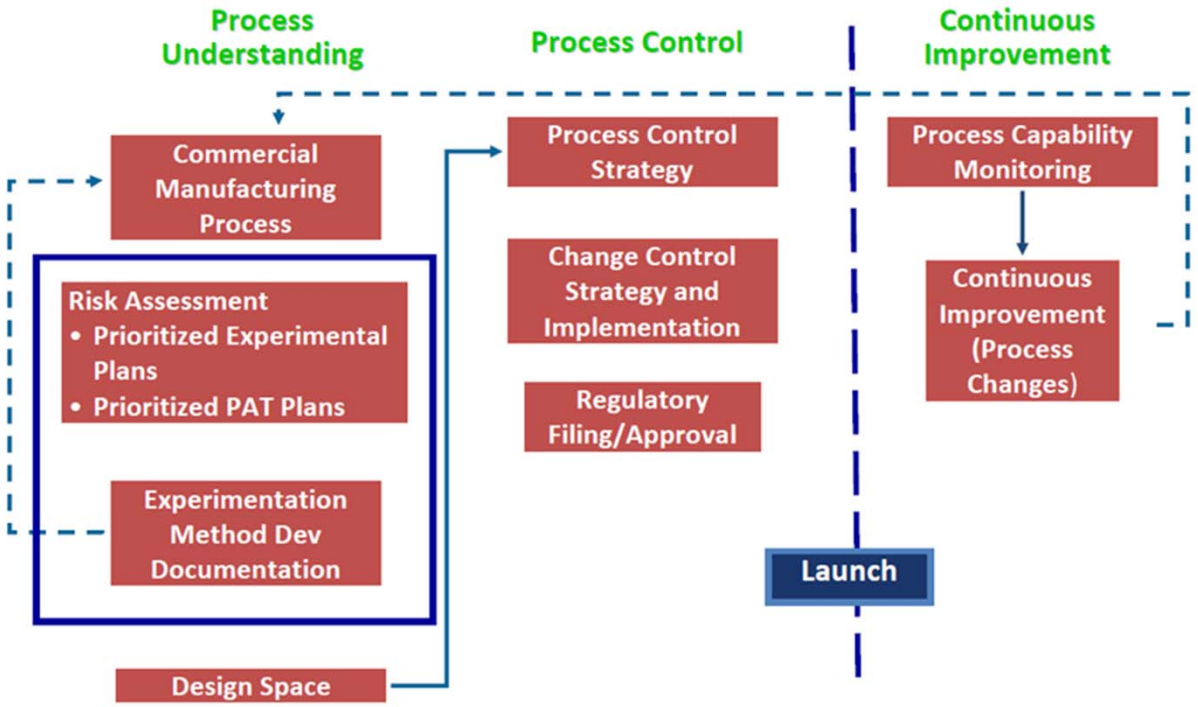
Quality by Design

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov



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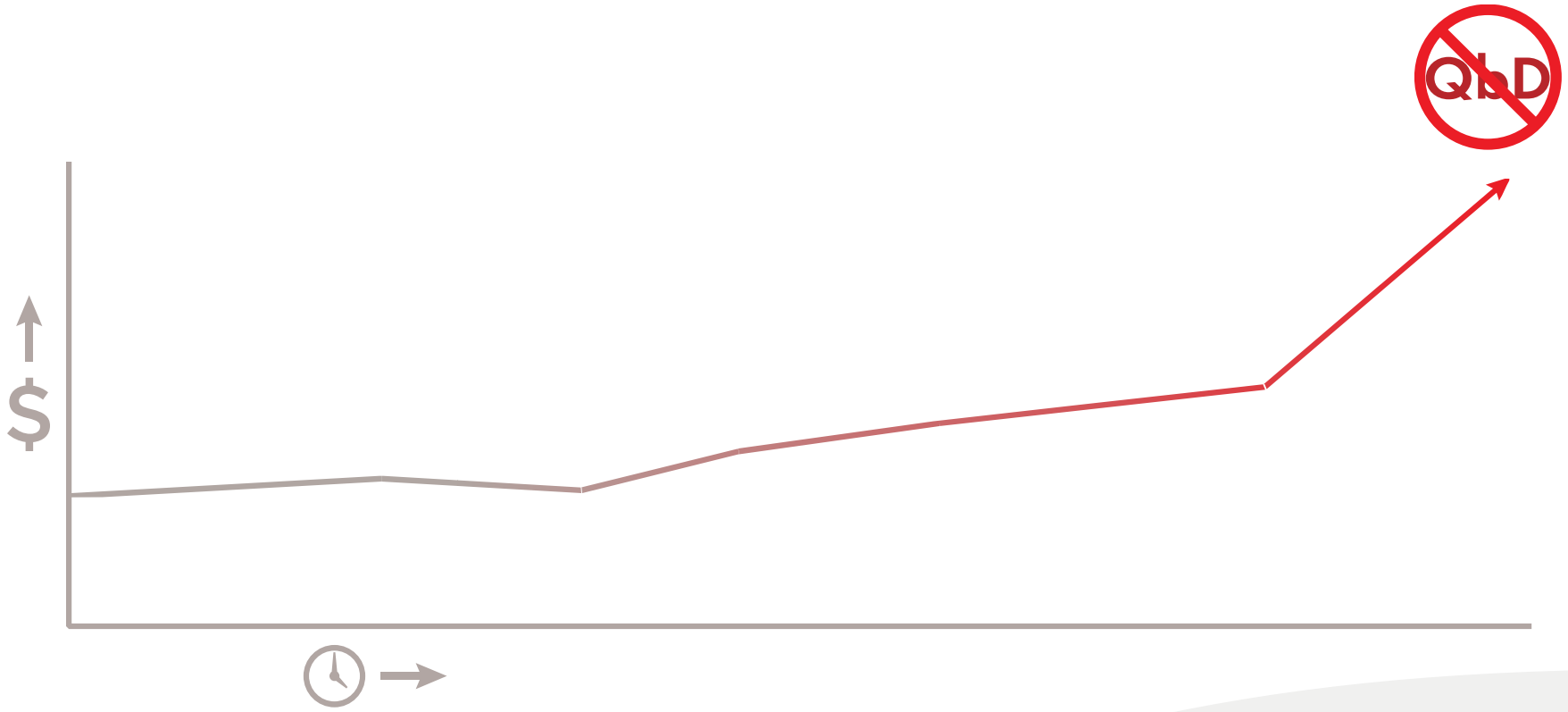
The financial implications of QbD



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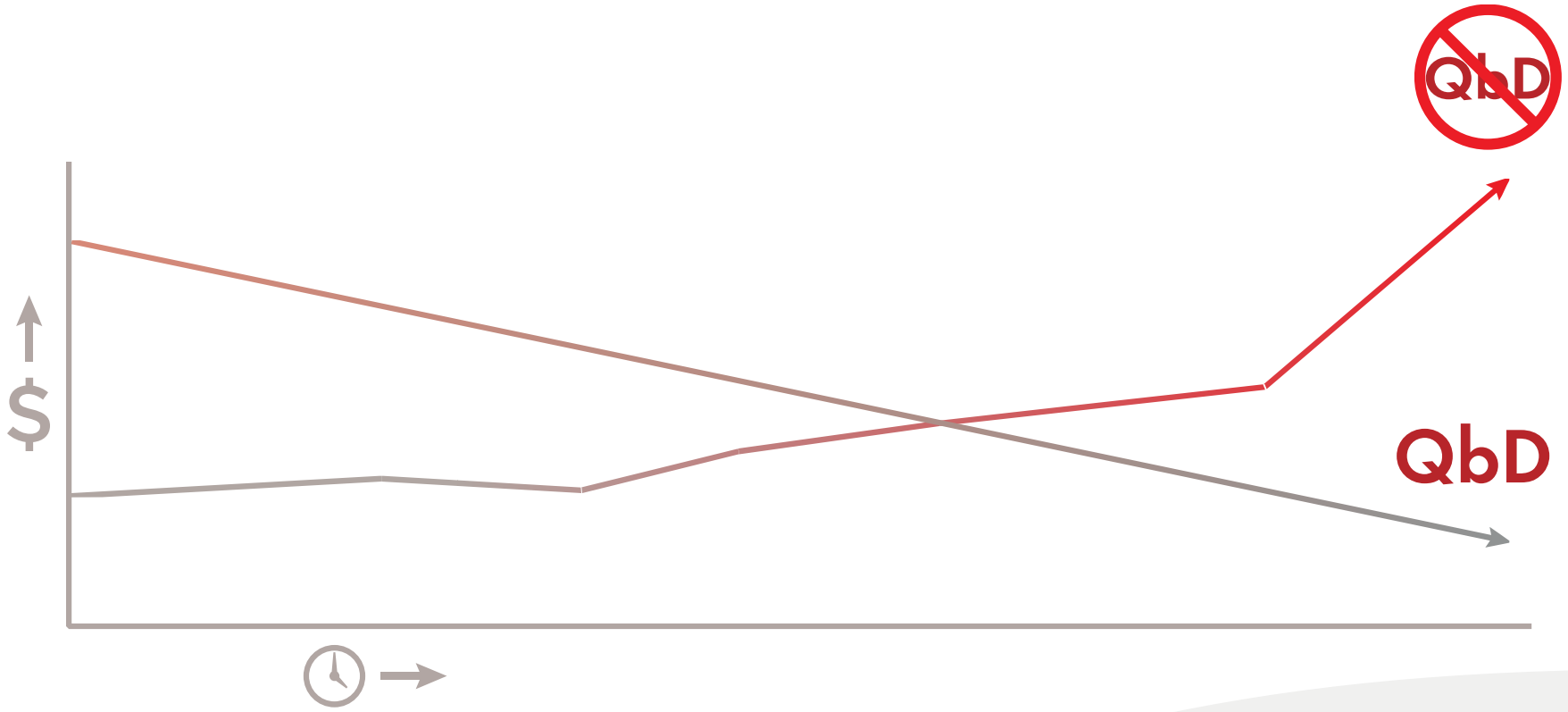
The financial implications of QbD



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Goals of Process Development

- Provide robust process
- Provide process appropriate for scale up
- Incorporate risk assessment
- Minimize risks

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Process Development is Important

- For Industry:
  - Enables specific scale-up and decreases variations in product quality
  - Ability to justify choice made
    - It can be used for justification of the proposed process, in-process controls, and scale-up to commercial size

- For FDA:
  - Facilitates review and risk-based supplement review
    - It may be used to justify regulatory relief in the future and build knowledge base of firms' capabilities
  - May equal less questions and comments…perhaps quicker approval

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To Begin Process Development

Manufacturing Process Development

- Why was the manufacturing process selected for this drug product?

  Why was the process chosen? Connect to drug substance properties.
- How are the manufacturing steps (unit operations) related to the drug product quality?

  Connect the process to the product and identify critical steps.
- How were the critical process parameters identified, monitored, and/or controlled?

  Summarize the process development studies used to do this.
- What is the scale-up experience with the unit operations in this process?

  Summarize the process development studies that support scale up.

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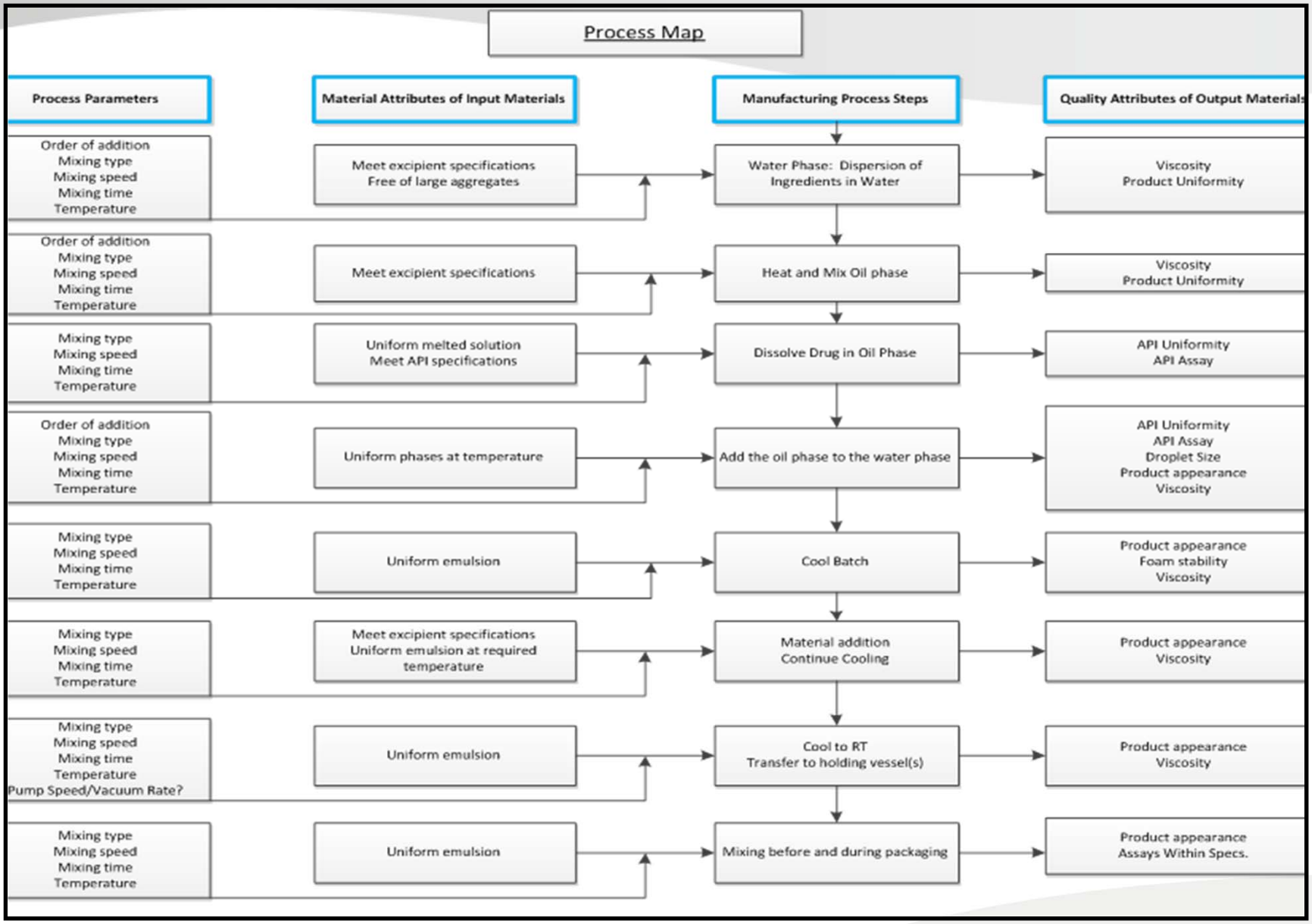

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Process Risk Assessment to identify Critical Process Parameters with the most potential to affect CQA's.

	Process Steps						
Drug Product CQA's	Water Phase: Dispersion of Ingredients in Water	Heat and Mix Oil Phase	Dissolve Drug in Oil Phase	Add the oil phase to the water phase	Material Addition Continue Cooling	Cool to RT and transfer to holding vessel(s)	Mix Before Packaging and During Packaging
API Assay	LOW	LOW	HIGH	MEDIUM	LOW	LOW	MEDIUM
Identity of API	LOW	LOW	LOW	LOW	LOW	LOW	LOW
API-related Impurities	LOW	LOW	MEDIUM	LOW	LOW	LOW	LOW
Content Uniformity for API	LOW	MEDIUM	MEDIUM	MEDIUM	LOW	LOW	LOW
Preservative Assay	LOW	HIGH	LOW	LOW	LOW	LOW	MEDIUM
Identity of Preservative	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Product Appearance	LOW	LOW	LOW	HIGH	MEDIUM	LOW	MEDIUM
pH	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Viscosity	MEDIUM	MEDIUM	LOW	HIGH	HIGH	HIGH	HIGH
Specific Gravity	MEDIUM	LOW	LOW	LOW	LOW	MEDIUM	LOW
Microbial Limits	LOW	HIGH	LOW	MEDIUM	LOW	LOW	LOW

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Process Development and CPP's

Question: How were the critical process parameters identified, monitored, and/or controlled?

- Identification
  - Prior knowledge base of process/similar drug product
  - A Key Process Parameter is one that may be critical
  - Experimental work, (DOE studies, small scale batches, etc.)

    -Determines which key parameters are critical
- Monitoring
  - In-process tests and criteria
  - PAT continuous monitoring (if used)
- Control
  - Feedback control system that adapt to variability in input material or environment
  - How is data from the monitoring used to ensure quality?

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Design of Experiments

- Perform Design of Experiments for:
  - Determining potential parameters impacting product quality
  - Interactions with material attributes
  - Development of control strategy and in process controls
  - Determining and understanding Critical Process Parameters (CPP)
  - Understanding scale-dependent parameters
  - Number of batches depends on factors
  - Identify equipment design and operating principles based on process parameters and product attributes

Complex DOE performed to maximize one of CQA's of a non-traditional emulsion.

Batch	Primary Solubilizer	Secondary Solubilizer	Secondary Emulsifier	Primary Thickener	Primary Emulsifier	Secondary Thickener
1	-1	+1	+1	-1	+1	+1
2	-1	0	+1	0	0	0
3	-1	+1	+1	+1	+1	-1
4	-1	0	+1	0	0	0
5	-1	+1	-1	-1	-1	-1
6	+1	+1	+1	-1	-1	-1
7	+1	-1	+1	-1	-1	+1
8	+1	+1	+1	+1	+1	+1
9	-1	+1	-1	+1	+1	+1
10	+1	-1	+1	-1	+1	-1
11	-1	+1	+1	+1	-1	+1
12	-1	-1	-1	-1	-1	+1
13	+1	-1	-1	-1	-1	-1
14	+1	-1	-1	-1	+1	+1
15	+1	-1	-1	+1	-1	+1
16	-1	-1	+1	+1	+1	+1
17	+1	-1	+1	+1	-1	-1
18	+1	+1	-1	+1	-1	-1
19	+1	-1	-1	+1	+1	-1
20	+1	+1	-1	-1	-1	+1
21	+1	+1	-1	-1	+1	-1
22	-1	-1	-1	+1	-1	-1
23	-1	0	+1	0	0	0
24	-1	-1	-1	-1	+1	-1
25	-1	-1	+1	-1	-1	-1
26	-1	-1	-1	-1	-1	-1

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Critical Process Parameters

- Temperature and rates of heating and cooling
- Mixing methods and speeds
- Time
- Flow rates
- Order of addition
- Protection from degradation (UV light and O_2)
- Equipment constraints

Critical Process Parameters

Temperature:

- Too much heat may result in chemical degradation
- Not enough heat during processing can lead to batch failures
- Too much cooling can cause precipitation

Heating and Cooling rates:

- Heating too slowly may result in poor yields from evaporative loss
- Rapid cooling may result in precipitation/crystallization or increased viscosities

Optimal flow rate:

- Emulsification – Rate of Oil to Water or Water to Oil
- Recirculation through a high shear mixer compared to use of internal high shear mixer
- Transfer pump at completion of process and during packaging

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Critical Process Parameters

High shear or low shear:

- What are the requirements for each?
  - Emulsification typically requires high shear
  - Mixing of a Gel may require low shear mixing

Obtaining proper mixing speeds for each phase at every batch scale:

- Development batches

Setting Time parameters:

- Mixing times
  - What is the minimum time required to obtain optimal effectiveness
  - What is the maximum time allowed before product failure
- Dissolution times for ingredients
  - Preformulation studies

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Design of Experiments to Test for Critical Process Parameters

Batch #	Emulsification RPM	Time of Emulsification	Temperature of Emulsification	High Shear on cool down	Temperature switch to CMM	CMM Speed	Initial	1 week
1	High	"x" minutes	75 - 80°C	Low	Low	"x" rpm	110,000	70,000
2	High	"x" minutes	75 - 80°C	Low	Medium	"x" rpm	100,000	80,000
3	High	"x" minutes	75 - 80°C	Low	High	"x" rpm	100,000	70,000
4	High	"x" minutes	75 - 80°C	Medium	Low	"x" rpm	120,000	110,000
5	High	"x" minutes	75 - 80°C	Medium	Medium	"x" rpm	70,000	60,000
6	High	"x" minutes	75 - 80°C	Medium	High	"x" rpm	60,000	50,000
7	High	"x" minutes	75 - 80°C	High	Low	"x" rpm	120,000	120,000
8	High	"x" minutes	75 - 80°C	High	Medium	"x" rpm	100,000	70,000
9	High	"x" minutes	75 - 80°C	High	High	"x" rpm	90,000	70,000

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Combination Raw Material and Process Study

Propylene Glycol	Acrylates Copolymer	Zinc Oxide Type	Mix Time	Viscosity	Zinc Oxide Particle Size (um)
-1	-1	1	-1	12000	60
-1	-1	-1	1	10000	18
-1	-1	-1	-1	8000	24
1	1	1	-1	26000	50
-1	1	-1	-1	27000	26
-1	1	1	1	20000	62
-1	1	1	1	17250	46
1	-1	-1	1	18000	17
1	1	-1	1	32000	15
1	-1	1	-1	19500	51
1	-1	1	1	15000	45
1	1	-1	-1	25000	15

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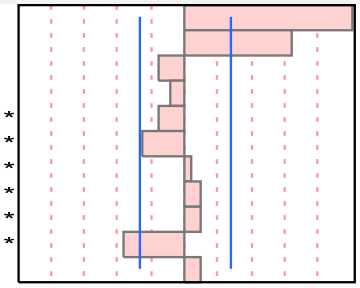
Data Analysis via: JMP

Screening

Screening for Viscosity

Contrasts

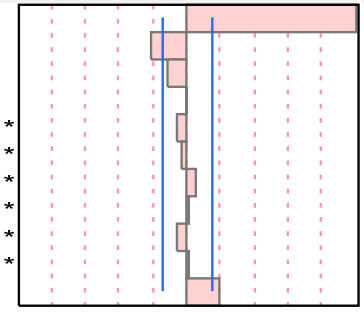
Term	Contrast		Lenth t-Ratio	Individual p-Value	Simultaneous p-Value
Acrylates Copolymer	5395.83		6.41	0.0029*	0.0163*
Propylene Glycol	3437.50		4.08	0.0113*	0.0696
Zinc Oxide Type	-854.17		-1.01	0.2809	0.9747
Mix Time	-437.50		-0.52	0.6510	1.0000
Acrylates Copolymer*Propylene Glycol	-842.55	*	-1.00	0.2870	0.9777
Acrylates Copolymer*Zinc Oxide Type	-1382.05	*	-1.64	0.1106	0.6143
Propylene Glycol*Zinc Oxide Type	215.17	*	0.26	0.8182	1.0000
Acrylates Copolymer*Mix Time	493.01	*	0.59	0.6086	1.0000
Propylene Glycol*Mix Time	529.57	*	0.63	0.5816	1.0000
Zinc Oxide Type*Mix Time	-1952.99	*	-2.32	0.0445*	0.2773
Null12	561.34		0.67	0.5002	1.0000



Screening for Zinc Oxide Particle Size (um)

Contrasts

Term	Contrast		Lenth t-Ratio	Individual p-Value	Simultaneous p-Value
Zinc Oxide Type	16.5833		12.16	0.0005*	0.0018*
Propylene Glycol	-3.5833		-2.63	0.0312*	0.2134
Mix Time	-1.9167		-1.41	0.1578	0.7750
Acrylates Copolymer	-0.0833		-0.06	0.9562	1.0000
Zinc Oxide Type*Propylene Glycol	-0.8504	*	-0.62	0.5750	1.0000
Zinc Oxide Type*Mix Time	-0.5455	*	-0.40	0.7188	1.0000
Propylene Glycol*Mix Time	1.0328	*	0.76	0.4072	1.0000
Zinc Oxide Type*Acrylates Copolymer	0.3099	*	0.23	0.8368	1.0000
Propylene Glycol*Acrylates Copolymer	-0.9684	*	-0.71	0.4417	1.0000
Mix Time*Acrylates Copolymer	0.1961	*	0.14	0.8965	1.0000
Null12	3.2660		2.39	0.0398*	0.2526



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Deliverables of Process Development

- Raw material testing and supplier information
- Clinical/registration supplies of formulated product
- Validated analytical methods
- Process Development Report
- Pathway forward to validation and commercialization

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Process Development Report

- Process development report will include:
  - Every step of the process
  - Why it was done and scientific rationale
  - What went wrong that should be monitored (residual risk)
  - What went well and was critical
  - Overall results

Goals of Scale Up

- Manufacture product at commercial scale in reliable, consistent manner
- Transition documents from clinical scale production to commercial scale production
- Confirm CMAs and CPPs
- Understand variability at larger scale
- Isolate and identify risks
- Provide robust process and parameters for validation

Scale up Activities

- Manufacture drug product at commercial scale
- Should not exceed 10X clinical batch size
- Perform risk assessment before and after
- Manufacture feasibility batches (1-2)
- Test product uniformity
- Determine equipment size and operating principles
- Evaluate CPPs and CMAs
- Perform validation of process at target CPPs and process controls

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Process Scale up Development QbR

Question: What is the difference in size between commercial scale and the exhibit batch?

- Simply state the size difference between the commercial batch and the exhibit batch (e.g. n times)
- Indicate if any processes have a different scale-up factor
  - e.g. two phases for registration batch, but will be one in production scale batch

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Process Scale up Development QbR

Question: Does the equipment use the same design and operating principles?

- Comparison between registration batch and proposed commercial batch
- Include equipment used for development studies if used to justify limits or identify critical parameters
- Use SUPAC-SS equipment addendum if applicable

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Process Scale up Development QbR

- Identify changes in equipment, critical or quality related steps and controls
- Include rationale for changes
  - Rationale may be as simple as due to larger batch size (larger vessel) or
  - May need supportive development data in development report (change in processing parameters)

Process Scale up Development QbR

Question: In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

- Optimized parameters can be addressed in process development report and summarized here
- No scale-up from registration batch size may be an option

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Process Scale up Development QbR

Question: What evidence supports the plan to scale up the process to commercial scale?

- Assurance must be provided that proposed process will yield product that is of high quality and purity.
  - Can use:
    - Scale-up experience from development to pilot batch
    - Prior experience with similar products/processes
    - Literature references/vendor scale-up factors
- Scale-up is tied to Process Validation and/or Evaluation - required as applicable
  - Description of relevant documentation/ data for validation of critical process steps

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Process Scale up Development QbR

Question: What is the scale-up experience with the unit operations in the process?

- Prior experience manufacturing products in similar equipment with similar process
- Pilot scale-up experience
- Literature references/vendor scale-up factors
- Summary of actual experiment runs
- Assessment of scale-up risks

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In Summation: Why is QbD important?

There are many factors that impact the manufacturing process, such as:

- Drug Substance solubility
- Homogeneity
- Content uniformity
- Rheology/Viscosity
- Microbial limits
- Mixing time
- Mixing temperature
- Mixing speed
- Rate of addition
- Mixing blade

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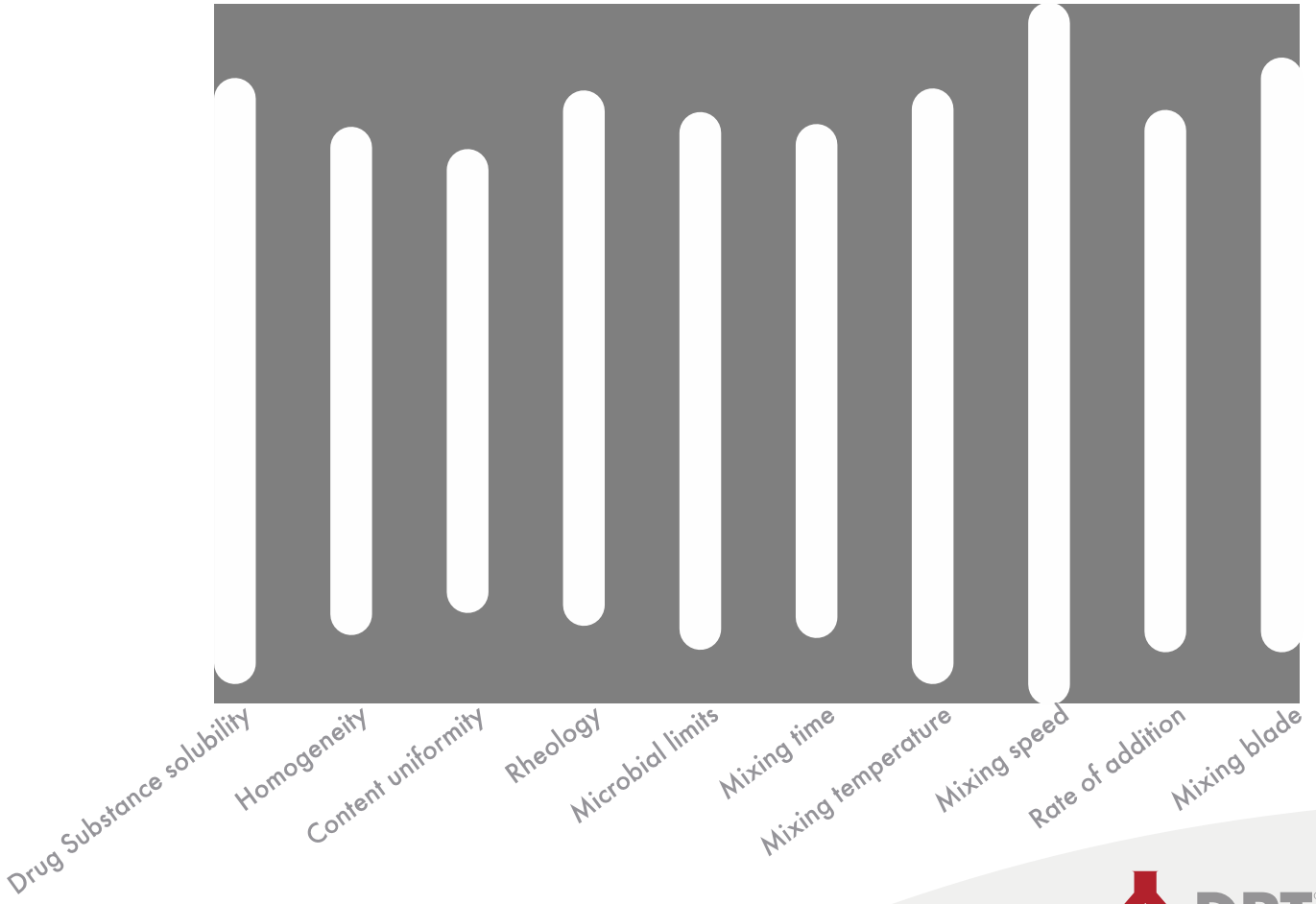
Why is QbD important?

Variability is always present



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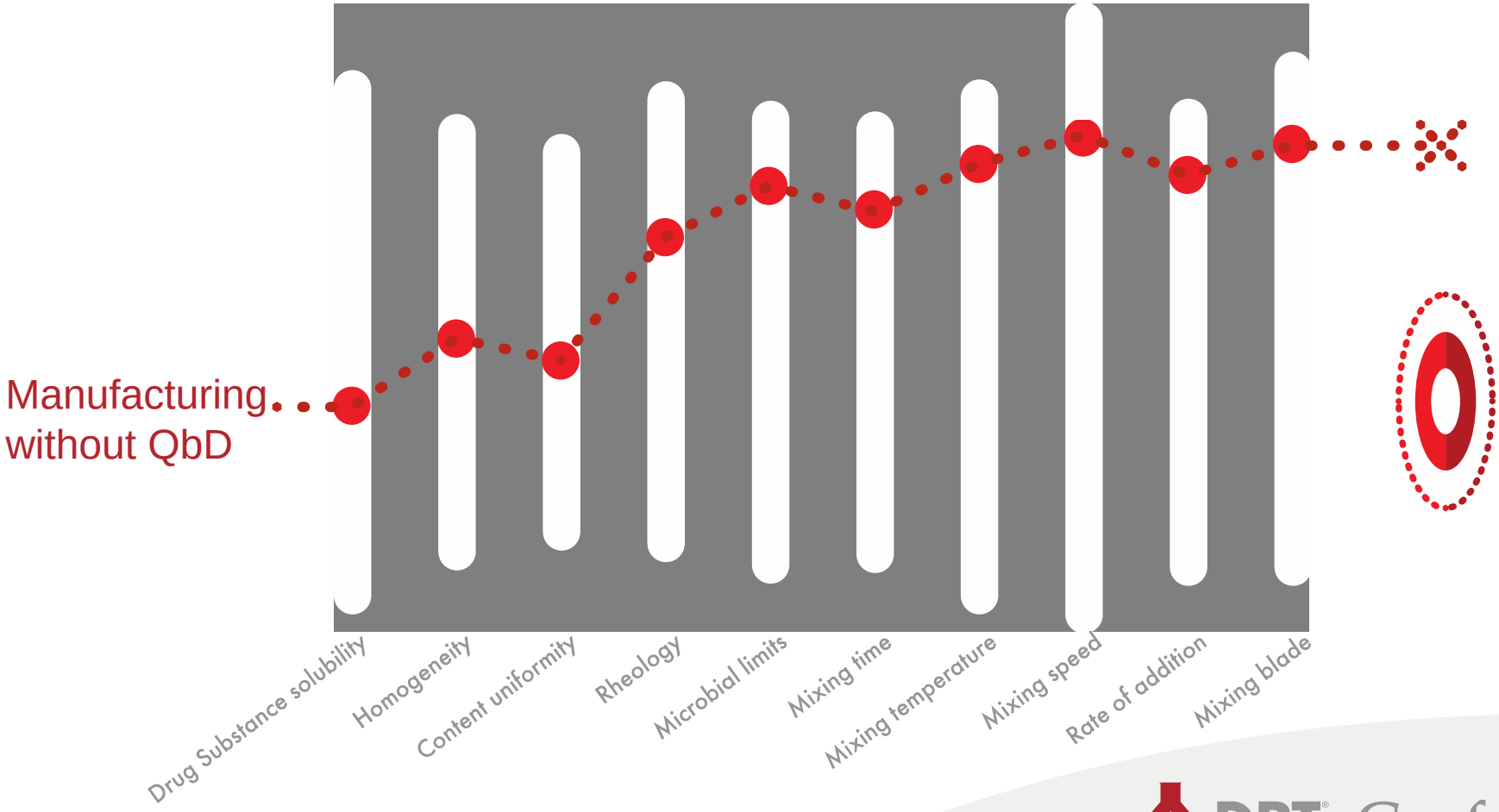
Why is QbD important?

Variability can cause target to be missed



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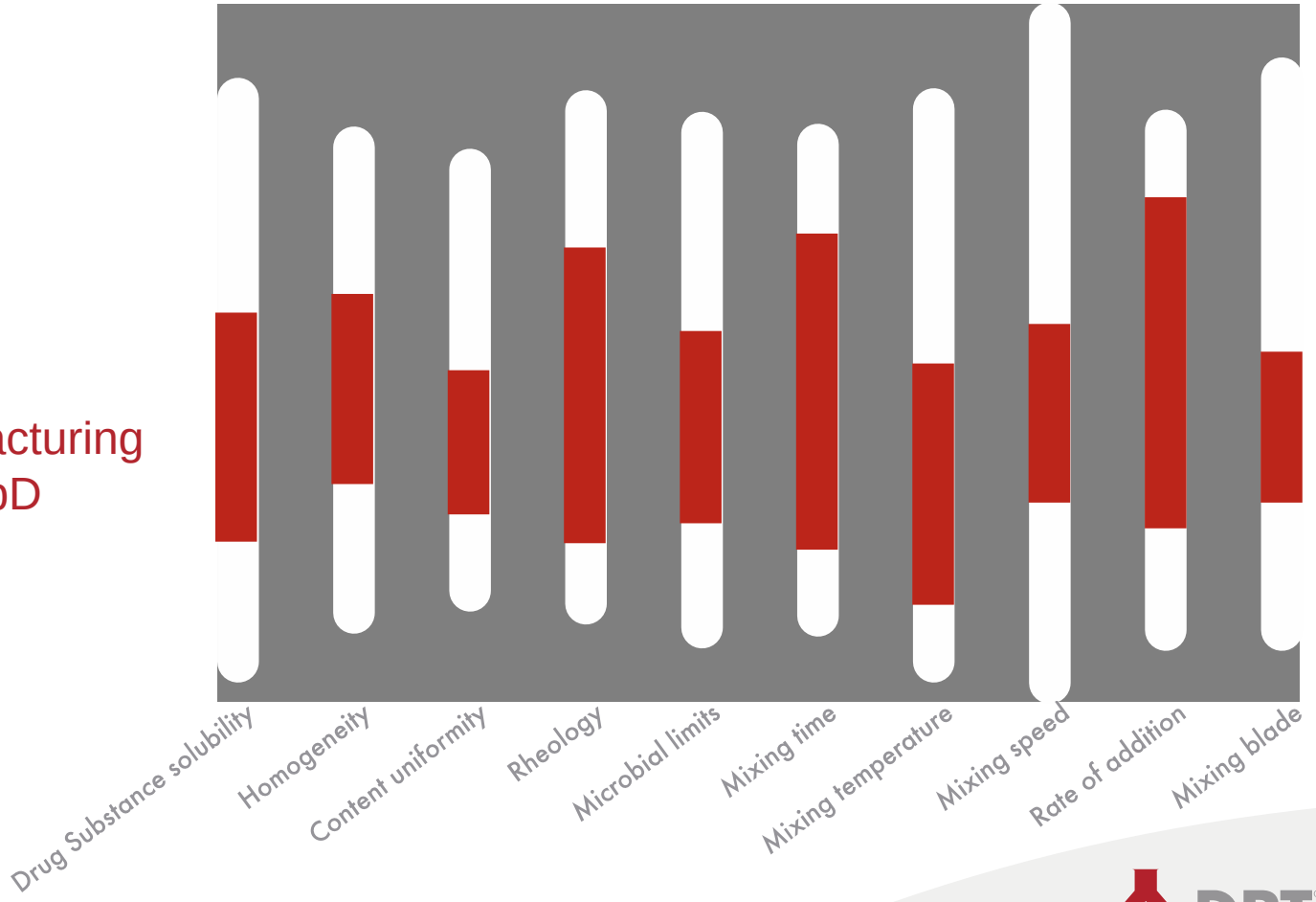
Why is QbD important?

With QbD: Design Space and Control Space

Manufacturing with QbD



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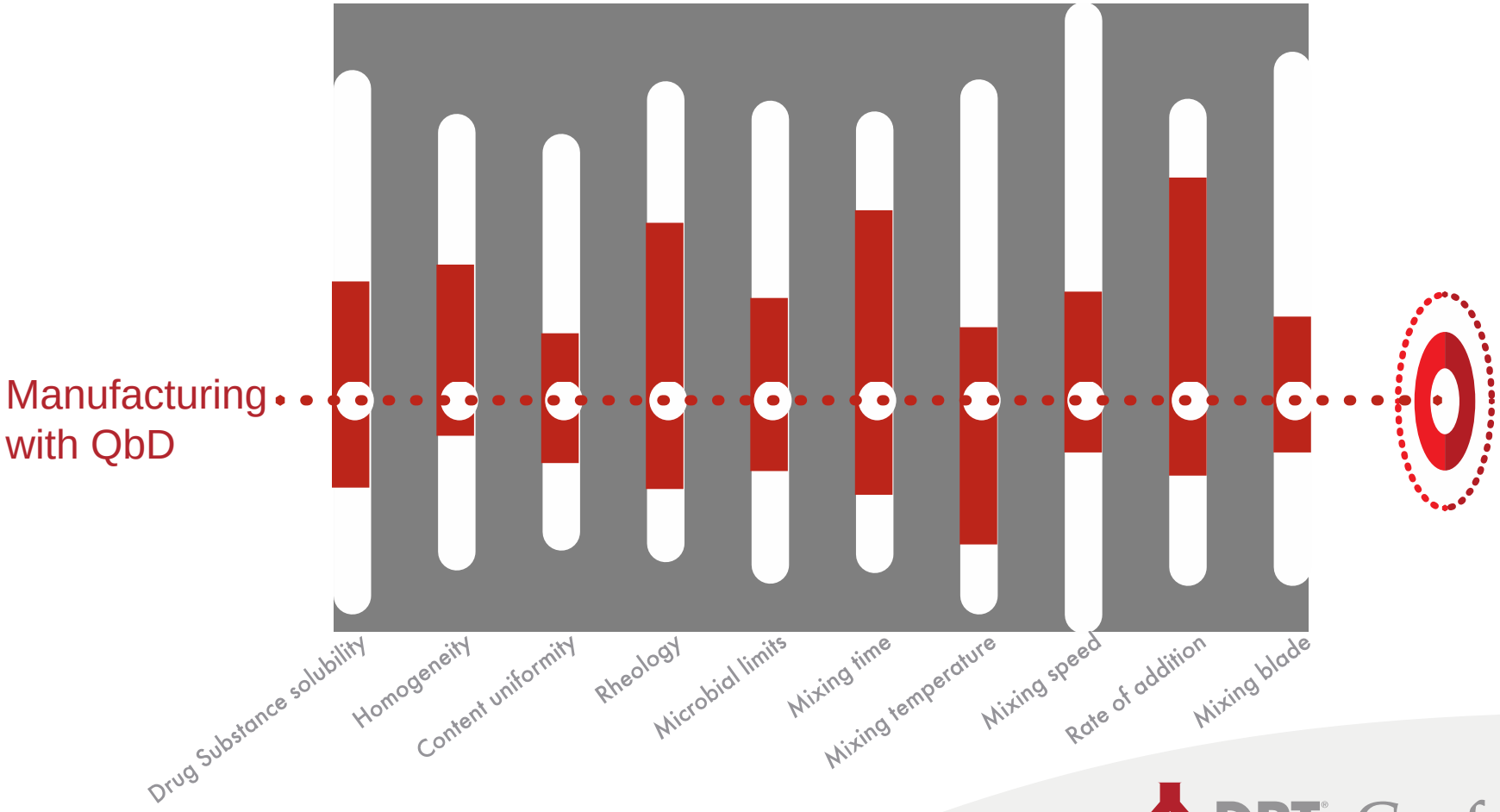
Why is QbD important?

Controls and risk assessment zero in on target



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THANK YOU VERY MUCH!

QUESTIONS?

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