INTRODUCTION OF QUALITY BY DESIGN

Sy-Dar Wang, Ph.D.

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What Is Quality by Design (QbD)?

- First introduced by **Dr. Joseph M. Juran**:

  "Juran on Quality by Design : The New Steps for Planning Quality into Goods and Services", 538 pp., Simon & Schuster, New York, 1992

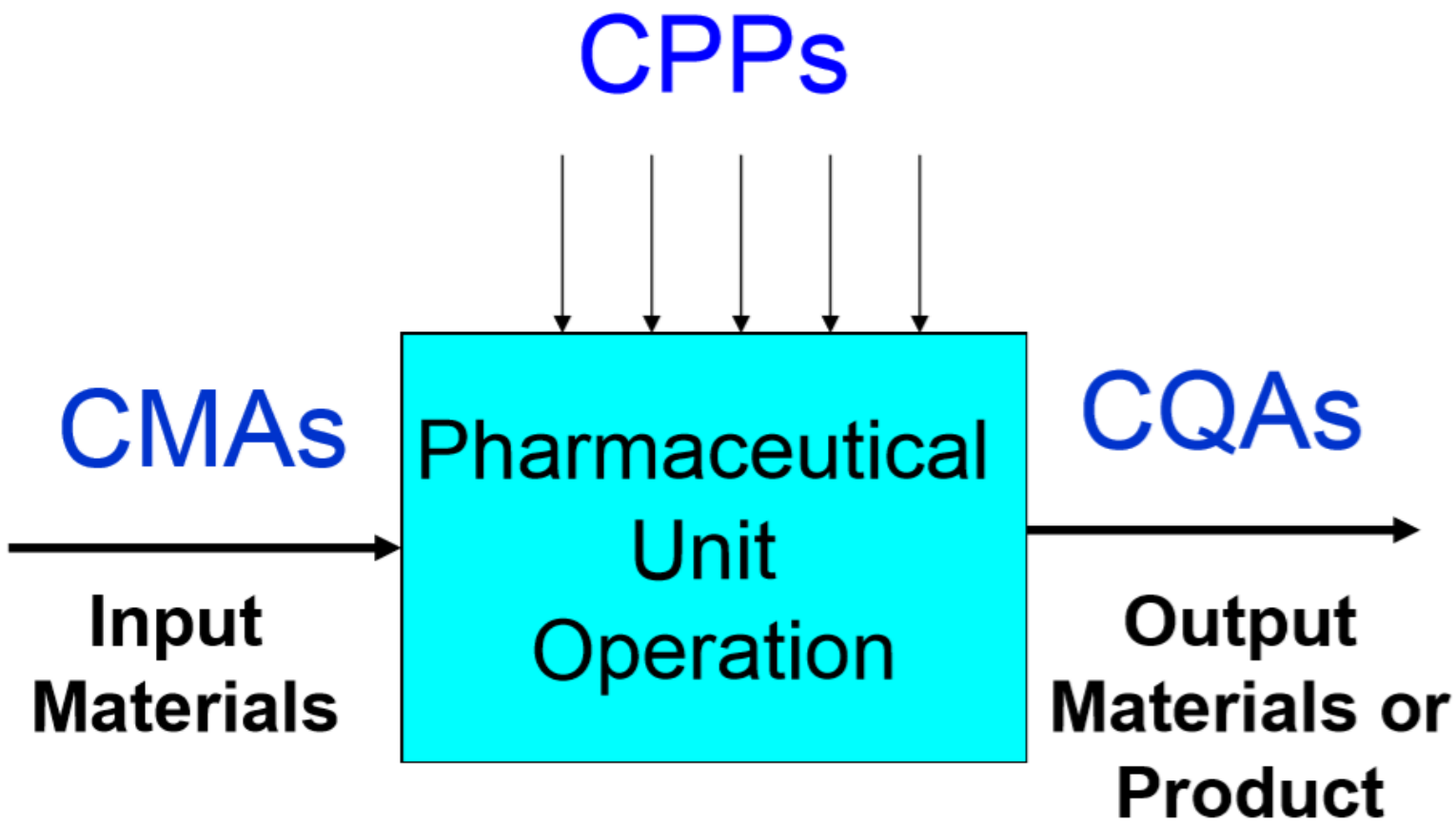
- Juran said that **most quality problems are designed into the process**. A clear plan is needed to identify and eliminate these issues
- **Pharmaceutical Quality by Design** initiative was originated from the Office of Biotechnology Products (**OBP**) within **FDA**
- No single definition….. One of the proposed definitions is:

  "**Understanding** what factors have an impact on variation in your process and also on your product's performance; then **establishing a control plan** to monitor and maintain product quality"

QbD Frequently Used Abbreviations

- **TPP**: Target Product Profile
- **QTPP**: Quality Target Product Profile
- **CQA**: Critical Quality Attributes
- **CMA**: Critical Material Attributes
- **CPP**: Critical Process Parameters
- **DOE**: Design of Experiments (required for **Design Space**)
- **PAT**: Process Analytical Technology
- **CMC**: Chemistry, Manufacturing, and Controls

Relationship between CMAs, CPPs and CQAs



$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

QbD Regulatory Guidance Documents

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

- ICH Q8(R2) – Pharmaceutical Development, (*November 2005*, and *November 2008*)
- ICH Q9 – Quality Risk Management, (*November 2005*)
- ICH Q10 – Pharmaceutical Quality System, (*June 2008*)
- ICH Q11 – Development and Manufacturing of Drug Substance, (*November 2012*)
- ICH Final Concept Paper – Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (*July 2014*)

QbD Regulatory Guidance Documents

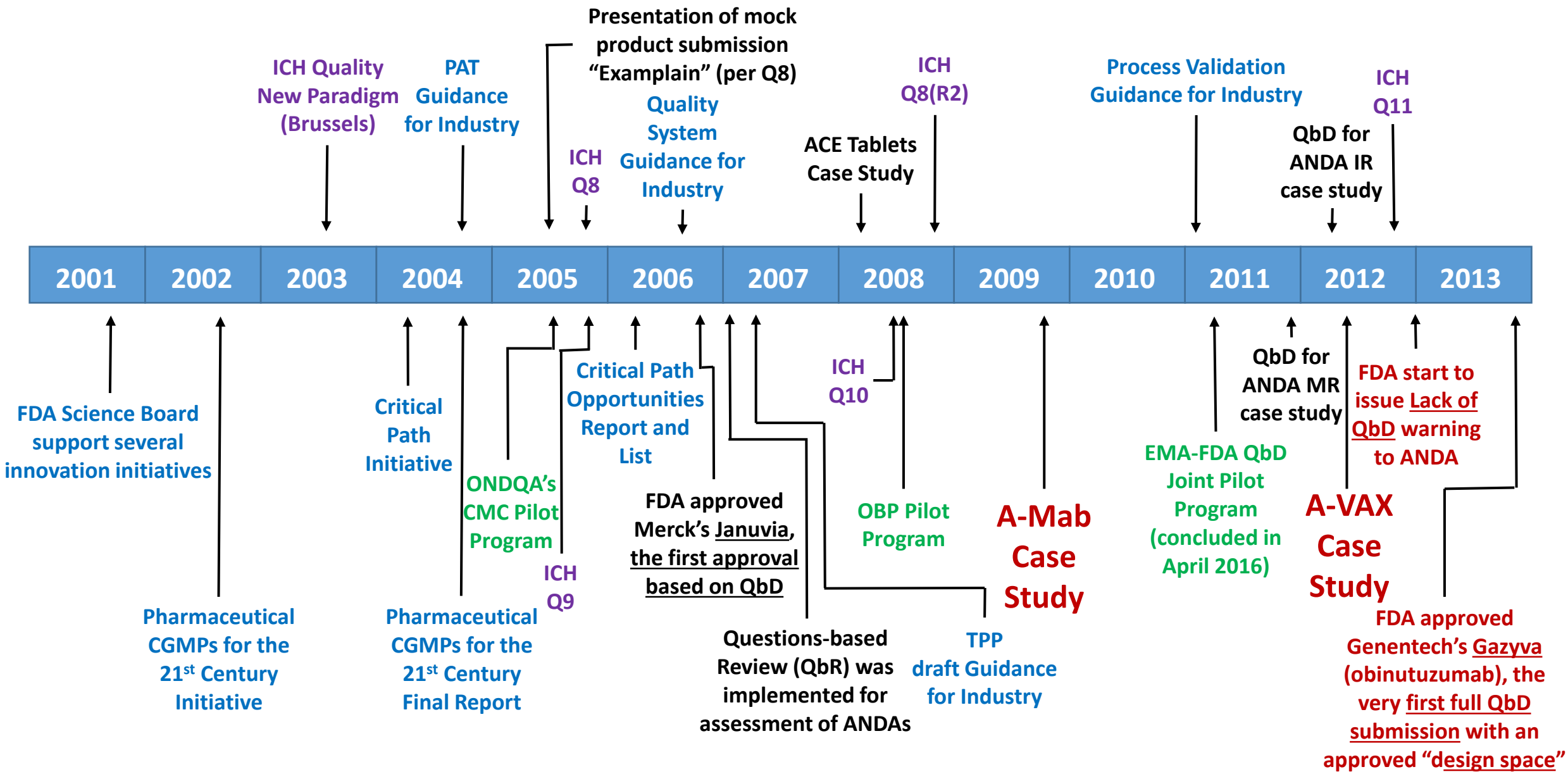
Additional References from FDA Guidance for Industry

- Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, (*September 2004*)
- Guidance for Industry: Quality System Approach to Pharmaceutical CGMP Regulations, (*September 2006*)
- Draft Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool, (*March 2007*)
- Guidance for Industry: Process Validation – General Principles and Practices, (*January 2011*)
- Guidance for Industry: Process Validation, (*December 2013*)

QbD Reference Case Studies

- Biopharmaceuticals
  - "**A-Mab**: a Case Study in Bioprocess Development" by CMC Biotech Working Group, 2009
  - "**A-VAX**: Applying Quality by Design to Vaccines" by CMC-Vaccines Working Group, 2012
- Drugs
  - "Mock P2 for "**Examplain**" Hydrochloride – Draft Discussion Paper", by EFPIA PAT Topic Group, 2006
  - "Pharmaceutical Development Case Study: **ACE Tablets**", by CMC-IM Working Group, 2008
  - "Quality by Design for ANDAs: An Example for **Modified Release** Dosage Forms" by FDA, 2011
  - "Quality by Design for ANDAs: An Example for **Immediate-Release** Dosage Forms" by FDA, 2012

Evolution in Quality by Design



Why Pursue for Quality by Design (QbD) Now?

- As of **January 2013**, after nearly three years of advance notice, workshops, and consultations, all ANDA applicants are being "**strongly encouraged**" by the FDA to use a **Quality by Design** approach. The day has arrived – **deficiency letters** will now explicitly cite the "**lack of QbD"**.

- The FDA expects these QbD components in all submissions (note that TPP and design space are **optional**):
  - Quality target product profile (QTPP)
  - List of critical quality attributes (CQAs)
  - List of critical material attributes of drug and excipients (CMAs)
  - List of critical process parameters (CPPs)
  - A **control strategy** that ensures the product reliability meets its predefined objectives.

Quality by Design (QbD) Has Several Key Components

- **Define the Product Design Goal**: Identify CQA.
  - Define the quality target product profile (QTPP)
  - Identify all the critical quality attributes (CQA)
- **Discovering the Process Design Space**: Identify CMA and CPP, and understand (if possible express mathematically) their relationship w/ CQA
  - Identify all the critical material attributes (CMA)
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  - Use design of experiment (**DOE**) to check interactions and establish the **design space**
- **Understanding the Control Space**: Design a process measurement system to allow on-line or at-line monitoring of CQA (via CMA and CPP)
  - Understand your process capability and the space it is able to control consistently (depending on the **control strategy** decided)
  - Control space must be within design space
- **Targeting the Operating Space**: Design a control system that will allow adjustment of CQA
  - Determine the best set of parameters which enable you to accommodate any natural variability in CPPs and CMAs
  - Consider to retain reference materials
  - Operating space must be within control space, and **robust**
- **Process Capability and Continual Improvement**

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TPP → QTPP → CQAs → Specifications

What is a Target Product Profile (TPP)?

- TPP is a summary of the drug development program described in terms of **labeling concepts**
- It is prepared by **all** the departments of the company involved in the development of the therapeutic or diagnostic agent
- FDA prepared a draft guidance "**Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool**" in 2007 which included a **TPP template**. Currently TPP submission to the FDA is voluntary but has specific benefits
- The TPP is a "**living document**" evolving and maturing with increasing knowledge and experience

TPP General Statement

Project Name	(Name)
Project Description	Summary description of the product
Project Category	Is the project is an additional indication for an existing drug or a new project?
Strategic Fit and Value	How well does this drug/biologic fit with the core expertise and capabilities of the company?
Value to Patients	What is the specific value of this drug/biologic to patients? Does it offer therapeutic, safety or ease of use advantages over existing or upcoming drugs/biologics
Company's competitive position	Does the company have a competitive advantage?
Company's IP position	Brief summary of the IP position regarding this drug
Rationale for success	Brief summary as to why the developing team believes that this product would
Factors for success	Brief statement as to the company's core competencies and market conditions that would drive a successful outcome
Key risk factors	Brief statement identifying possible risks
Consequences for not pursuing the project	What would happen if this project is not pursued?
Possible alternatives to this project	Are there any alternatives to this project?

TPP Summary of Efficacy

	Primary Indication				
	Primary Clinical Endpoint (s)		Target Patient Population	Route of Administration	Treatment Regimen
	Clinical Outcome 1	Clinical Outcome 2			
Optimistic	**It is possible that secondary endpoints may result in additional claims**	>Target Or =Target	>Target Or =Target	>Target Or =Target (if more than one route is tested)	> Lower doses and/or less frequent administration may provide advantages
Target	**The primary endpoint of the pivotal study or studies**	Provide entries if more than one primary endpoint	Target (Describe target population)	Target (Describe target route of administration)	Target (Describe target regimen)
Minimal	**= Target**	= Target (if essential for regulatory success)	=Target Or <Target If successful in a more limited population	= Target Or < Target If the least desirable tested route is successful	> Higher dosing and more frequent administration than target may still be acceptable

TPP Summary of Safety

	Primary Indication				
	Safety		Drug Interactions	Precautions	Contra-indications
	Clinical	Non-Clinical			
Optimistic	>Target if fewer and less severe AE profile Or =Target		>Target if fewer and less severe interactions Or =Target	>Target if no or fewer precautions Or =Target	>Target if no or fewer contraindications Or =Target
Target	Target safety is usually equivalent to the known safety of the same class or similar classes of compounds that have been approved	Laboratory or other findings similar to those observed for the same class or similar classes of compounds that have been approved	Interactions similar to those observed for the same class or similar classes of compounds that have been approved	Precautions similar to those observed for the same class or similar classes of compounds that have been approved	Contraindications similar to those observed for the same class or similar classes of compounds that have been approved
Minimal	= Target (<Target would be acceptable if risk/benefit ratio is favorable)	= Target (<Target would be acceptable if risk/benefit ratio is favorable)	=Target (<Target acceptability criteria should be explained)	= Target (<Target acceptability criteria should be explained)	= Target (<Target acceptability criteria should be explained)

Additional Elements of TPP

- **The TPP may contain additional elements regarding:**
  - Product design and formulation
    - Purity
    - Contaminants
    - Storage Conditions
    - Shelf Life
    - Any delivery system associated with the drug
  - Projected dates of submissions, regulatory approval and launch
  - Cost of goods, pricing, market size

  - Target, optimistic and minimal conditions may be set for these elements

TPP for Hospitalized Mild COVID-19 cases[1]

	Preferred	Critical or Minimal
Indication for use	For the treatment of COVID-19 in hospitalized symptomatic patients as, mono or combination therapy, without evidence of viral pneumonia or hypoxia.	
Target population	Highly preferable to include pregnant women and children < 6 years.	Adults including those >60 years of age, and with co-morbidities increasing the risk of poor outcomes. Children >6 years.
Safety/tolerability	Safety profile similar or superior to available therapeutic agents. No adverse events that require monitoring.	Safety profile shows an overall acceptable risk/benefit profile in the target population.
Efficacy	Effective at reducing mortality.	Effective at reducing progression of disease. Endpoints include duration of hospital stay.
Treatment regimen	Once per day dosing.	Twice per day dosing.
Route of administration	Oral.	Oral or parenteral.
Product Stability and Storage	Shelf life of at least 36 months. Room temperature shipping and storage in climatic Zone IV.	Shelf life of at least 6 months.

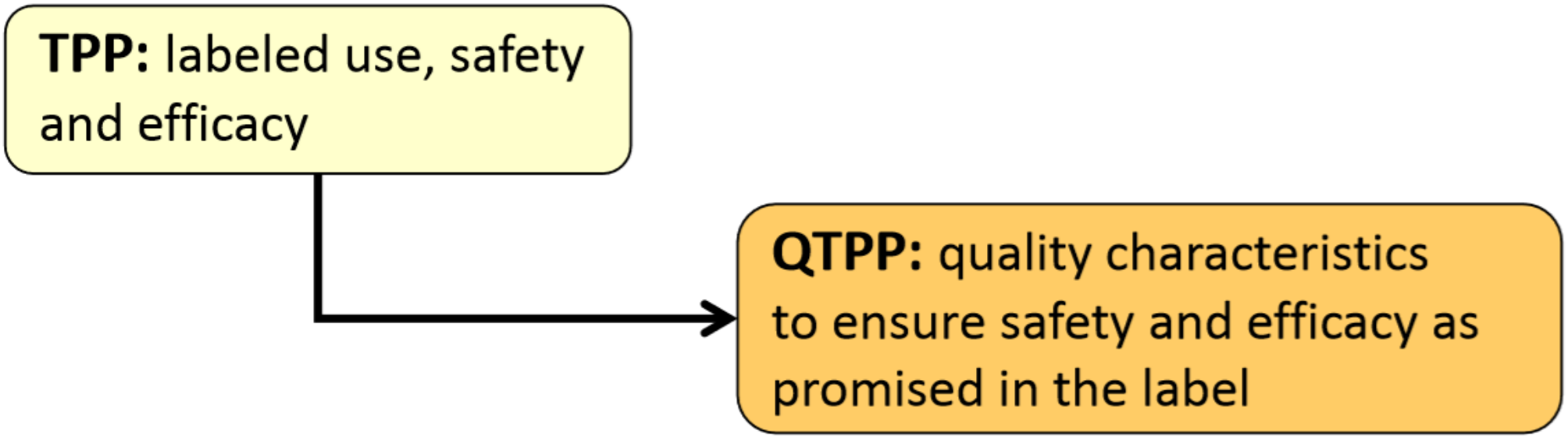
TPP for Hospitalized Mild COVID-19 cases[1]

	Preferred	Critical or Minimal
	Heat stability demonstrated to 40 °C short term	Storage and shipping at -20°C, 2-8°C or room temperature.
Interactions	No DDI.	No significant DDI with products previously licensed for COVID-19 disease or commonly used in hospitalized patients.
Formulation	Tablets/capsules, paediatric suspension with acceptable taste.	Tablets/capsules, injectables.
Accessibility	Capability to rapidly scale-up production at cost/dose that allows broad use, including in LMIC.	
Registration and Prequalification	Manufacturers are recommended to interact with the WHO Prequalification of medicines team well ahead of submission to NRAs for licensure or marketing authorization. https://extranet.who.int/prequal/information/manufacturers	

[1]Please refer to WHO Clinical Management Guidance for definitions of disease severity www.who.int/publications/i/item/clinical-management-of-covid-19

TPP → QTPP → CQAs → Specifications

Beginning with the End (Label) in Mind



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. (**ICH Q8 (R2)**)

EXAMPLE QTPP

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

TPP → QTPP → CQAs → Specifications

The QTPP Leads to Critical Quality Attribute (CQA) Definition

- Critical Quality Attribute (ICH Q8):

  "A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality."

- Potential CQAs are derived from the QTPP and guide product and process development.
- CQAs are identified by quality risk management and experimentation to determine the effect of variation on product quality.
- The CQA list can be dynamic and may be updated based on product and process knowledge.

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients [illegible] organic solvent will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables may affect content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl [illegible] w/v SLS	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process [illegible] dissolution profile. This CQA [illegible] development.

Not a CQA

CQA

QbD for ANDAs: An Example for IR Dosage Forms. April 2012.

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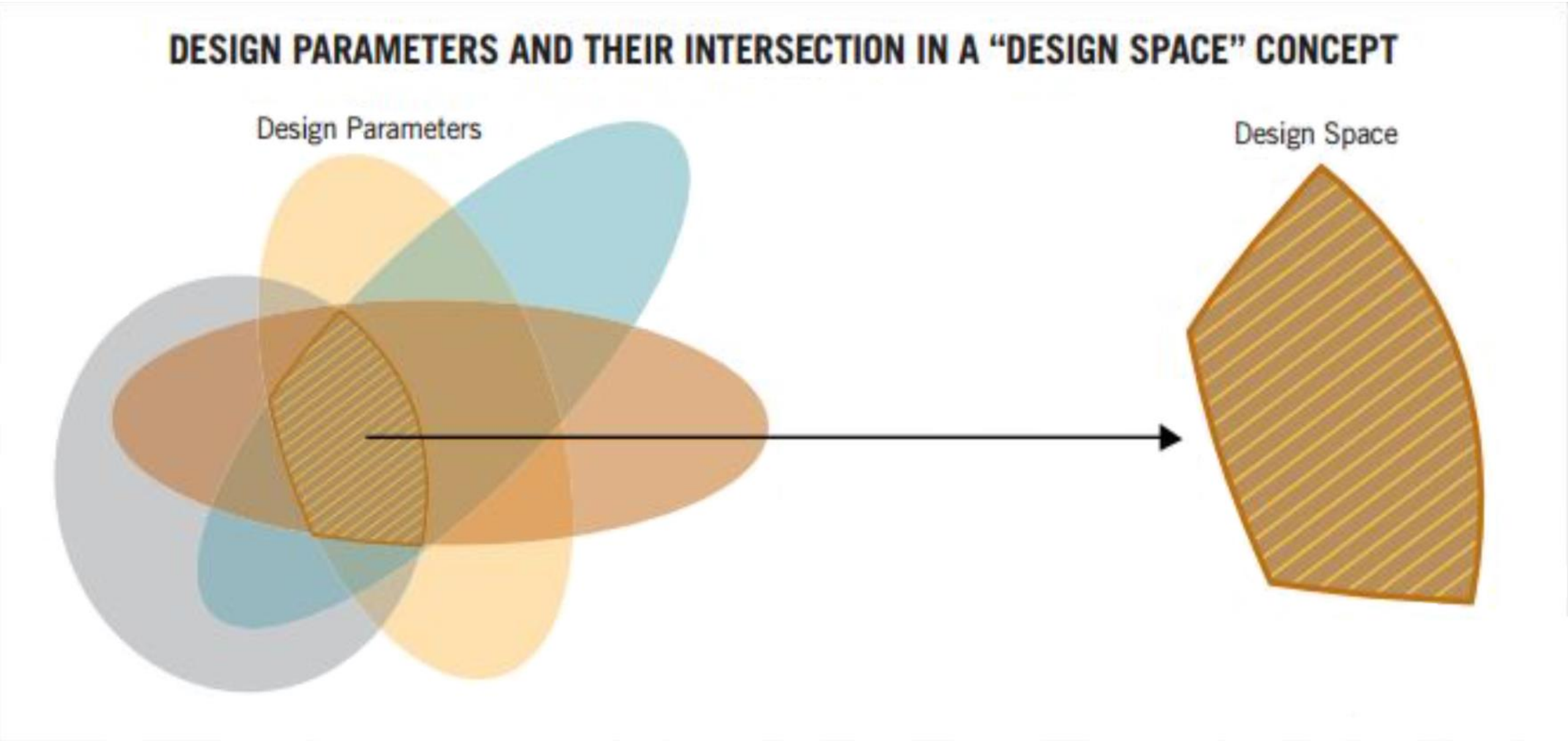
What Is Design Space?

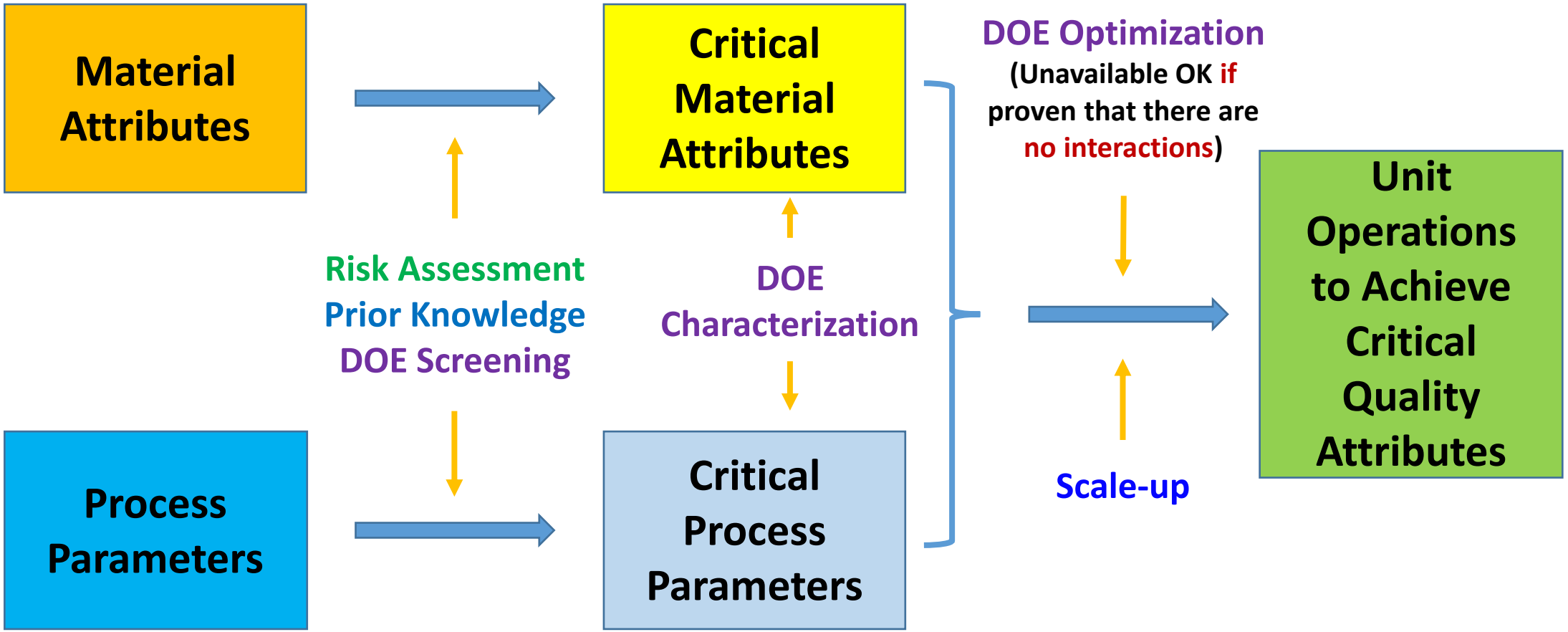
ICH Q8 Definition:

"The multidimensional combination and interaction of **input variables** (e.g. material attributes) and **process parameters** that have been demonstrated to provide **assurance of quality**" (ICH Q8 (R2))

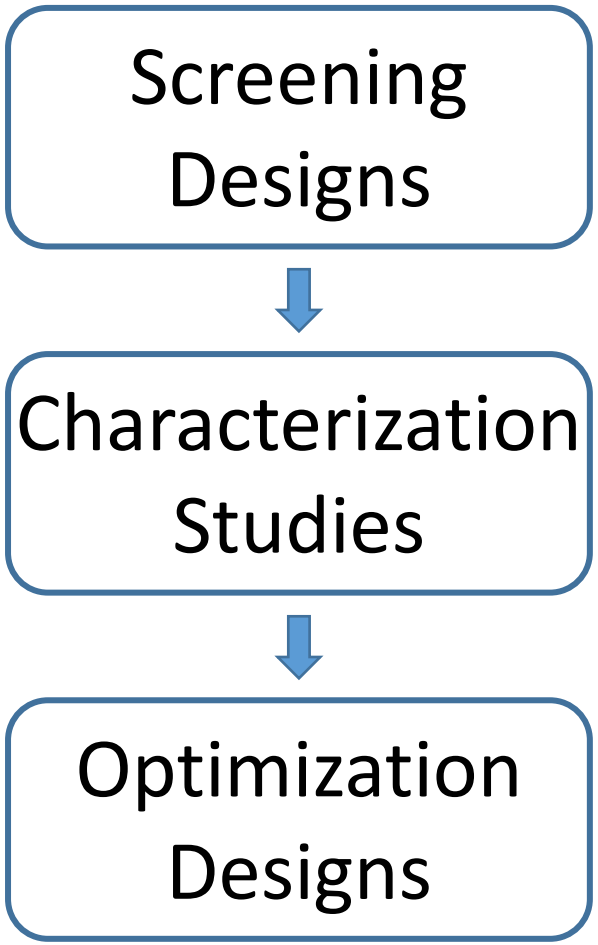
What Is Design Space?



Define Design Space from CMAs, CPPs and CQAs



High level Map of Experiments



One factor at a time
Fractional factorials
Placket Burman design

Full factorials

Response surface methods

Using DOE with Tolerance Intervals to Verify Specifications

- Define an operating window in process design space where we have 95% (or higher) confidence that 99% (or higher) of the population meet (or exceed) specifications
- Use empirical DOE to model the responses as functions of the process factors.
- Use a tolerance interval to “back off” (provide a buffer) from the specifications.
- Size the DOE for required half-width of tolerance interval.

Illustrative Example: Tableting Process

- This case study (using **MODDE** DOE software from **Sartorius**) illustrates how **DOE** and tolerance intervals can be used to set an operating window where specifications are consistently met.
  - An **optimal design** is run on **two process parameters**, granulation time and lubrification time, in a tableting process.
  - **Three responses**, dissolution, friability and hardness, are measured.
  - The specifications are:
    - Dissolution >= 75%
    - Friability <= 0.5%
    - Hardness >= 10 kP

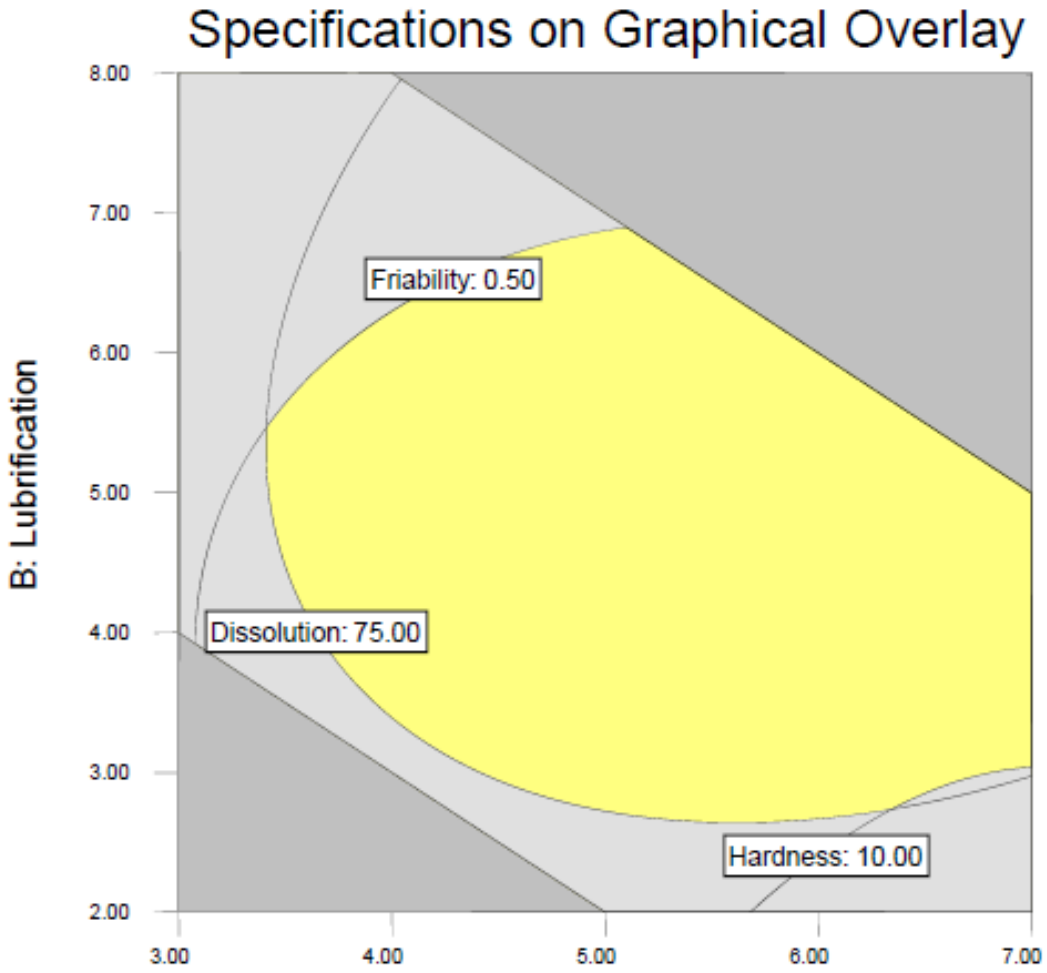
Illustrative Example: Tableting Process

Initial Operating Window (yellow colored) obtained through DOE

y_1 = Dissolution %
(specification ≥ 75%)

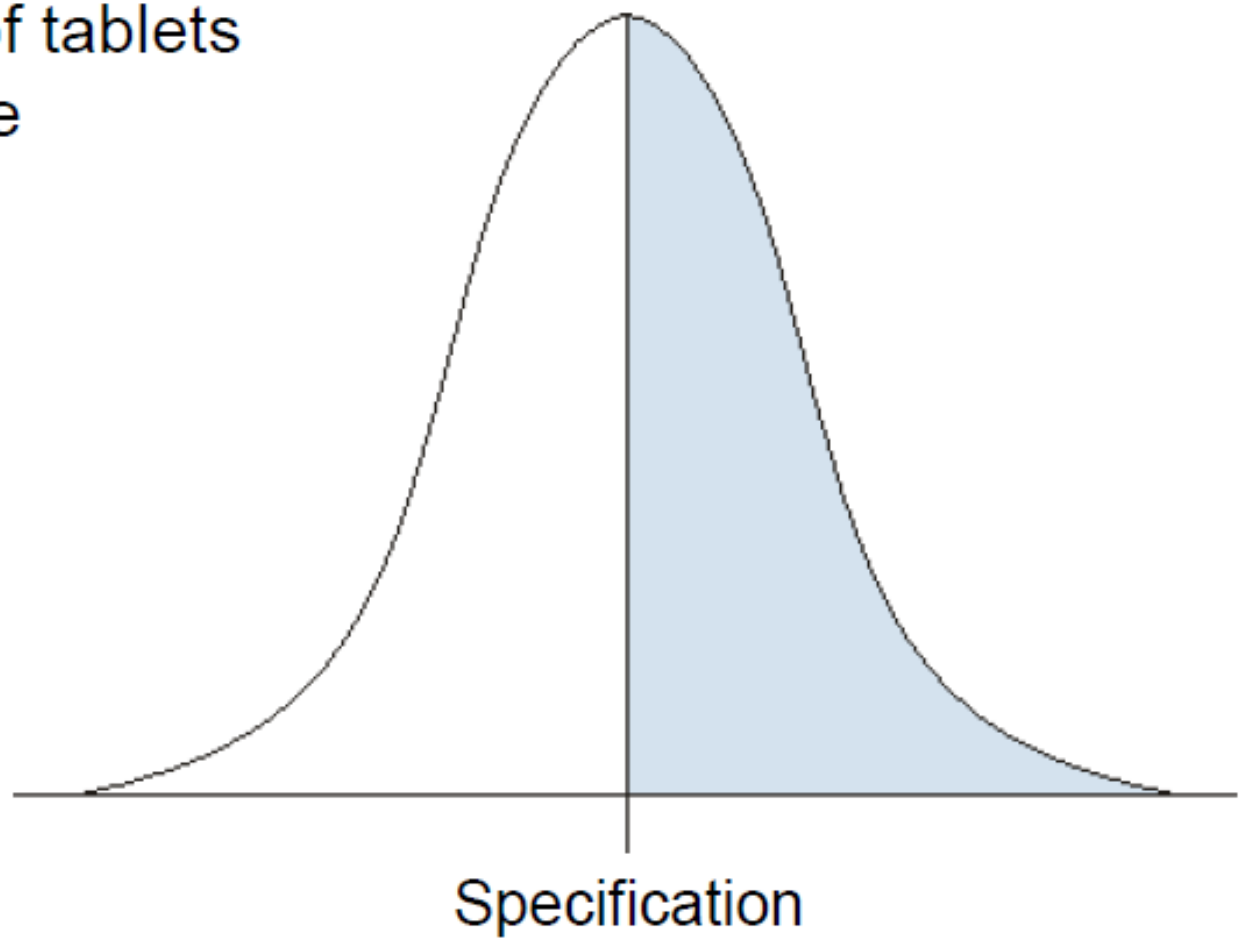
y_2 = Friability %
(specification ≤ 0.5%)

y_3 = Hardness kP
(specification ≥ 10 kP)



Illustrative Example: Tableting Process

If the tableting process is operated on a boundary, then 50% of tablets produced fall outside the specification.



Gaining Confidence That Individual Product Units Are within Specifications

- If we want more confidence that individual product units are within specifications:
  - Then we should **back off using a tolerance interval** rather than a confidence interval.
  - Specify the **confidence level**; e.g. 95%, 99%, etc.
  - Specify the **tolerance interval** (portion of the population to be within specifications); e.g. 99%, 99.9%, etc.
- Note:
  - A **confidence interval** pads our design space to give us confidence that the **process mean** is within boundaries.
  - A **tolerance interval** gives us confidence that a stated **portion of the population** is within specifications.

Illustrative Example: Tableting Process

- **Response surface methodology:**
  1. **Define objective**

     Define an operating window where we have **95% confidence** that **99% of the population** meets or exceeds specifications.
  2. **State objective in terms measurable response**
     a. **Define the precision that is required for each response:**

        Tolerance interval (α=0.05, P=99%) half width (d):

        dissolution d = 9, **friability d = 0.3**, **hardness d = 0.7**
     b. **Establish experimental error for each response:**

        dissolution s = 2, **friability s = 0.03**, **hardness s = 0.14**
  3. **Select the input factors and range to study** (consider both region of interest and region of operability)

     A = Granulation time: 3 – 7 minutes

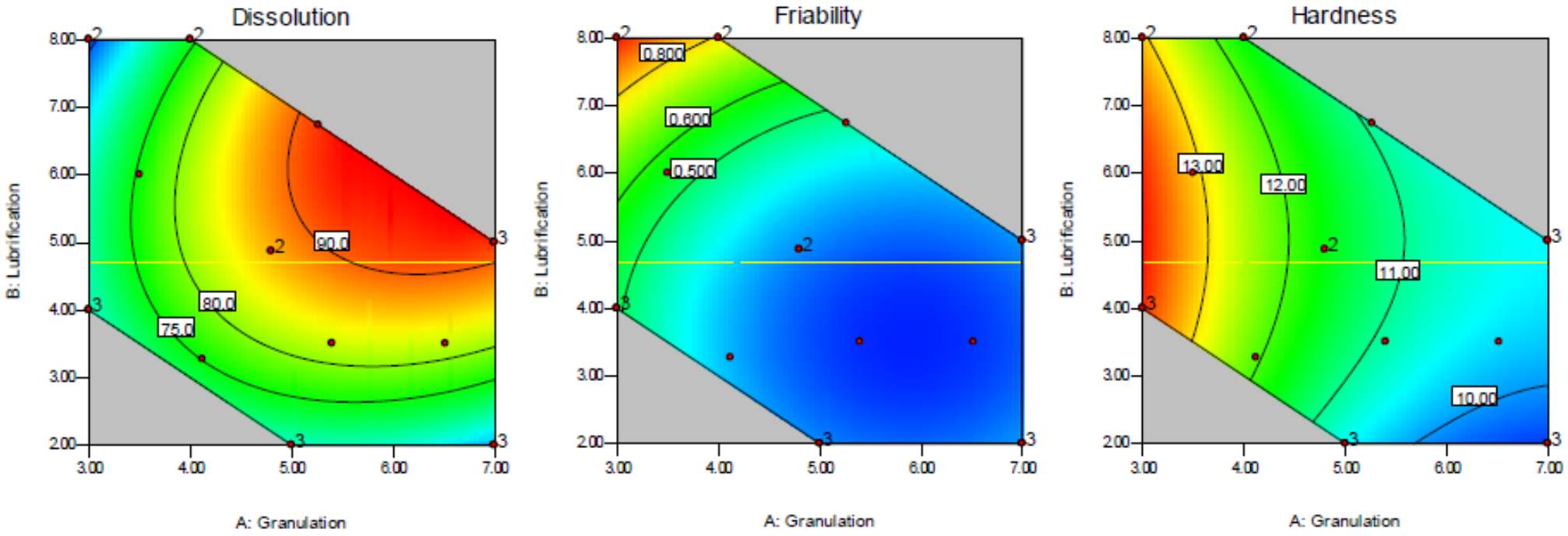
     B = Lubrification time: 2 – 8 minutes

     Total mixing time: 7 – 12 minutes

Illustrative Example: Tableting Process

Analyze responses, aim for:

- Dissolution ≥ 75%
- Friability ≤ 0.5%
- Hardness ≥ 10 kP



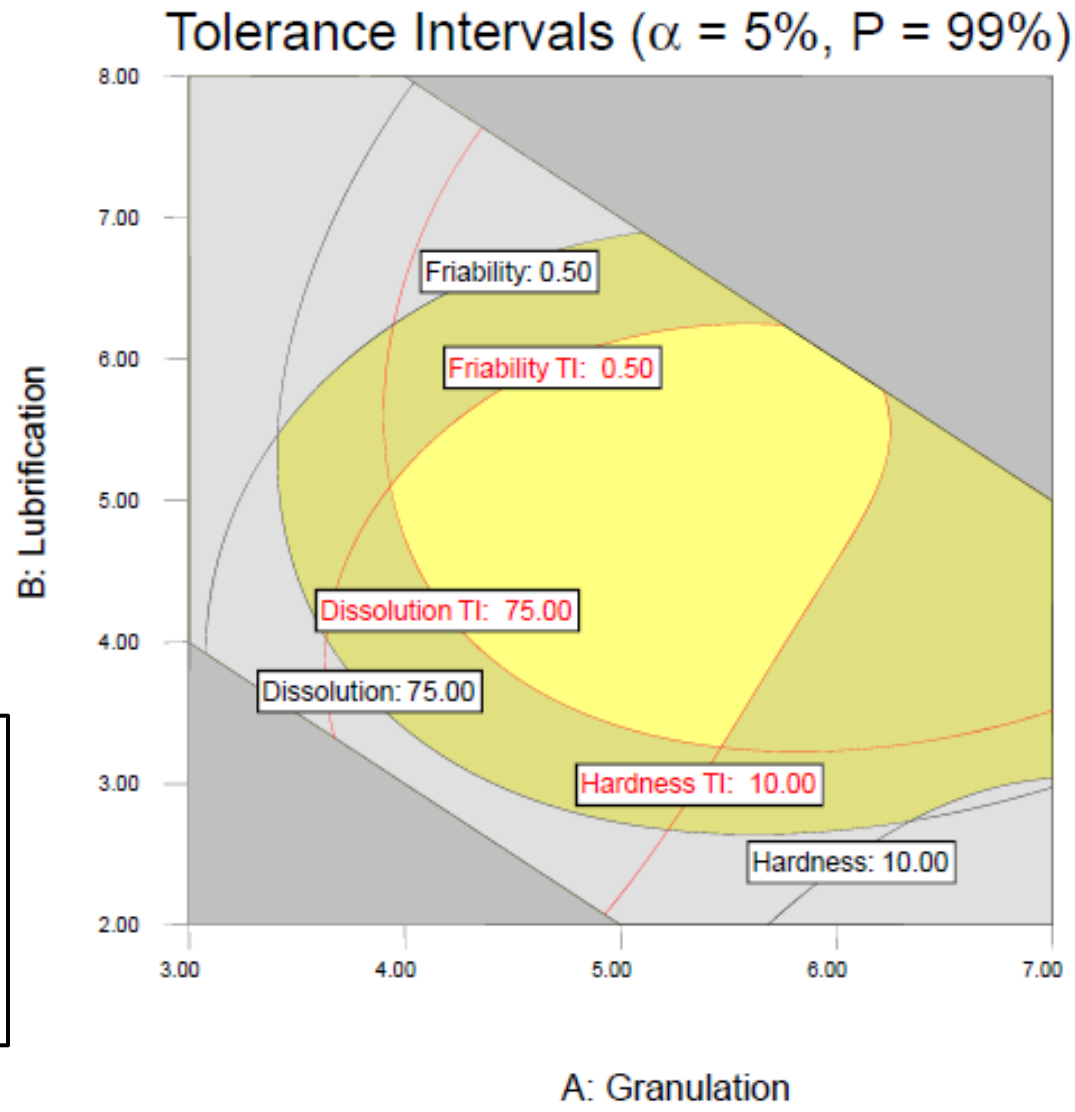
Final Operating Window: Tolerance Intervals as Bounds

y_1 = Dissolution %
(specification ≥ 75%)

y_2 = Friability %
(specification ≤ 0.5%)

y_3 = Hardness kP
(specification ≥ 10 kP)

Black: 50% of the population meet the specified specification
Red: >99% of the population meet the specified specification



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What Are the Varieties of Space?

- **Knowledge Space**

  The potential range of limits for all parameters controlled or measured during the process characterization process

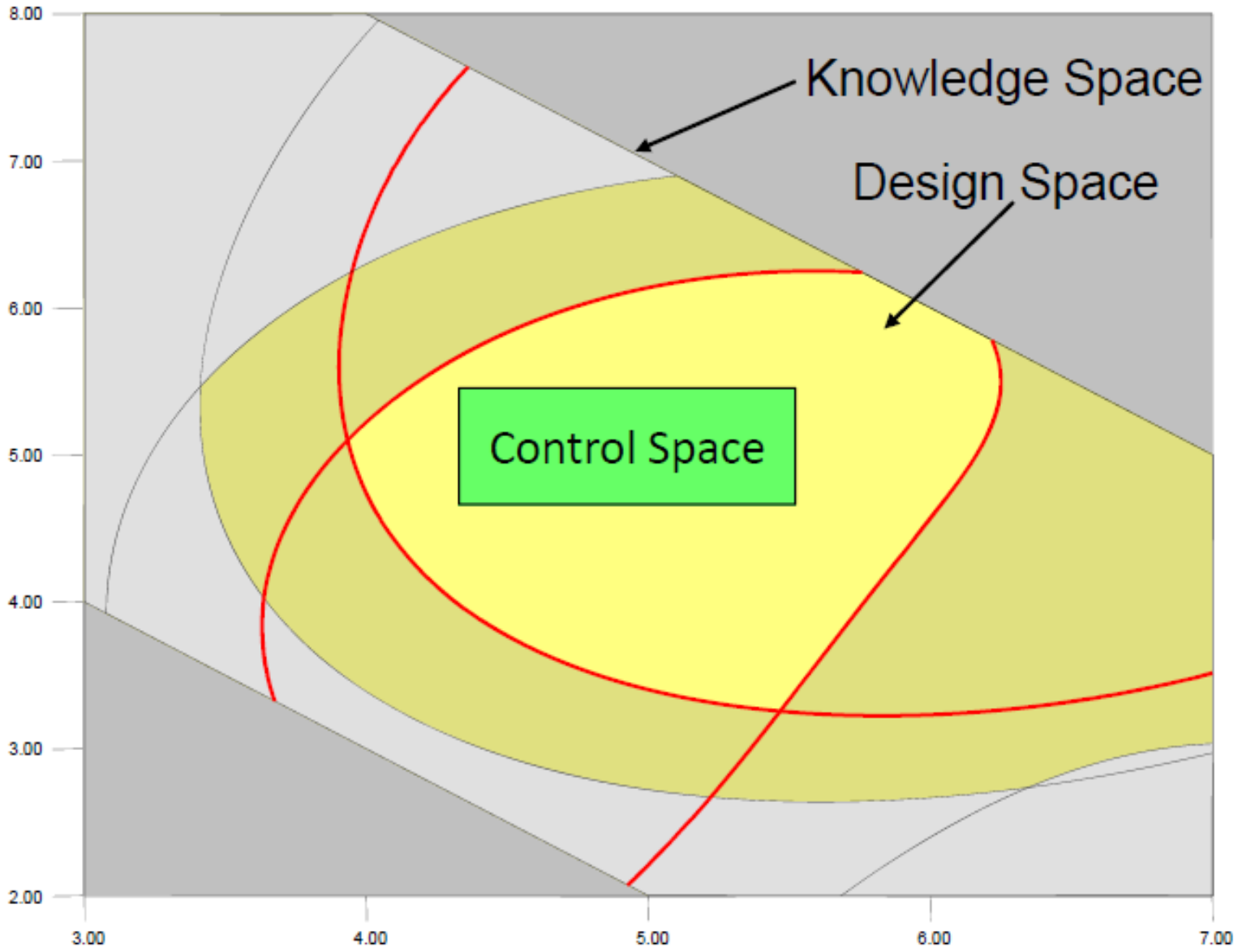
- **Design Space**

  The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been **demonstrated to provide assurance of quality**

- **Control Space**

  The FDA allows creating a **control space that floats inside the design space**. Control space **allows inevitable process drift** from changing raw materials and other sources of natural variability

Design Space & Control Space of the Tableting Process



Relationship between Design Space & Control Strategy

- **Design space** is key for claiming **process understanding**
- Process understanding is key for **quality risk management**
- Quality risk management is the base for any **control strategy**

Key Messages for Control Strategy

- Control strategy **derives from management of risk** and should lead to assurance of consistent quality of product in alignment with the Quality Target Product Profile (QTPP)

- Control strategy is:
  - Not a new concept
  - Not just specifications
  - Based on product and process understanding and risk management
  - While **design space is optional**, **control strategy is not**.

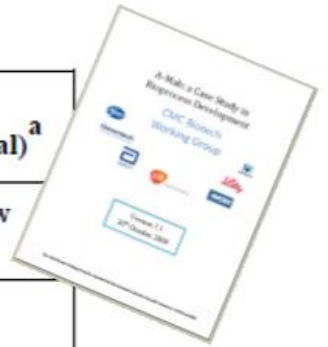
Scoring Uncertainty – example from A-Mab

Table 2.4 Uncertainty Definition and Scale for Tool #1

Uncertainty (Score)	Description (Variants and Host Related Impurities)	Description (Process Raw Material)[a]
7 (Very High)	No information (new variant)	No information (new impurity)
5 (High)	Published external literature for variant in related molecule.	---
3 (Moderate)	Nonclinical or in vitro data with this molecule. Data (nonclinical, in vitro or clinical) from a similar class of molecule.	Component used in previous processes
2 (Low)	Variant has been present in material used in clinical trials.	---
1 (Very Low)	Impact of specific variant established in Clinical Studies with this molecule.	GRAS or studied in clinical trials

GRAS = generally regarded as safe

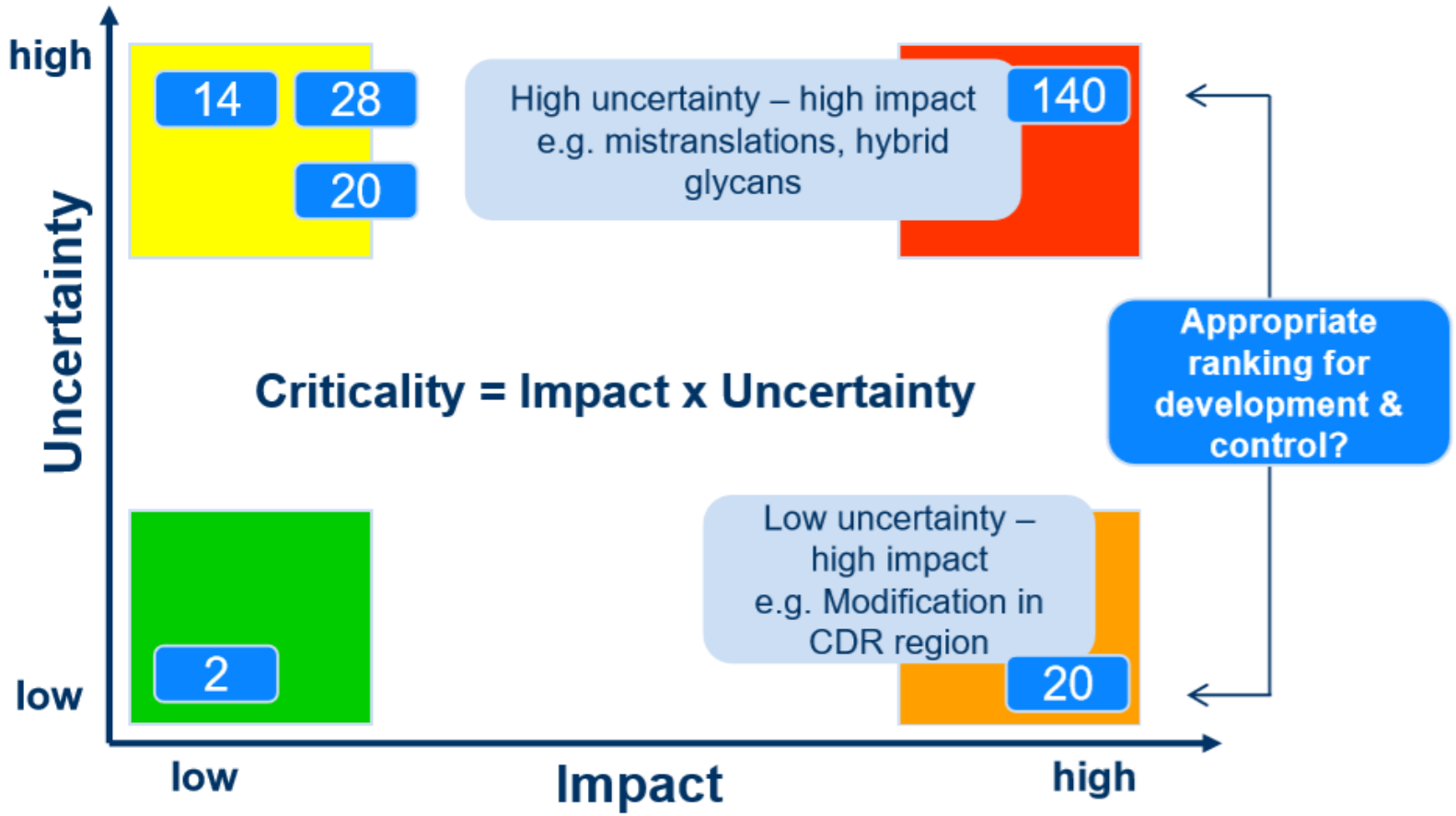
[a] Assesses the impact of a raw material as an impurity. Impact of the raw material on the product during manufacturing is assessed during process development.



- Scoring **Uncertainty** for every scored Impact
- Criticality Scores for A-Mab calculated by Impact x Uncertainty
  - Criticality Score between 2 and 140

Criticality Score: Dilemma of high uncertainties

- Highest scores for high impact – combined with high uncertainty
- Lower scores for high impact – combined with low uncertainty



What is more critical?

"I know it has an impact"

or

"It might have an impact"

What Is Process Analytical Technologies (PAT)?

- PAT is a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. (**Q8(R2)**)
- The goal of PAT is to "enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."
- PAT tools:
  - Multivariate tools for design, data acquisition and analysis
  - Process analyzers
  - Process control tools
  - Continuous improvement and knowledge management tools

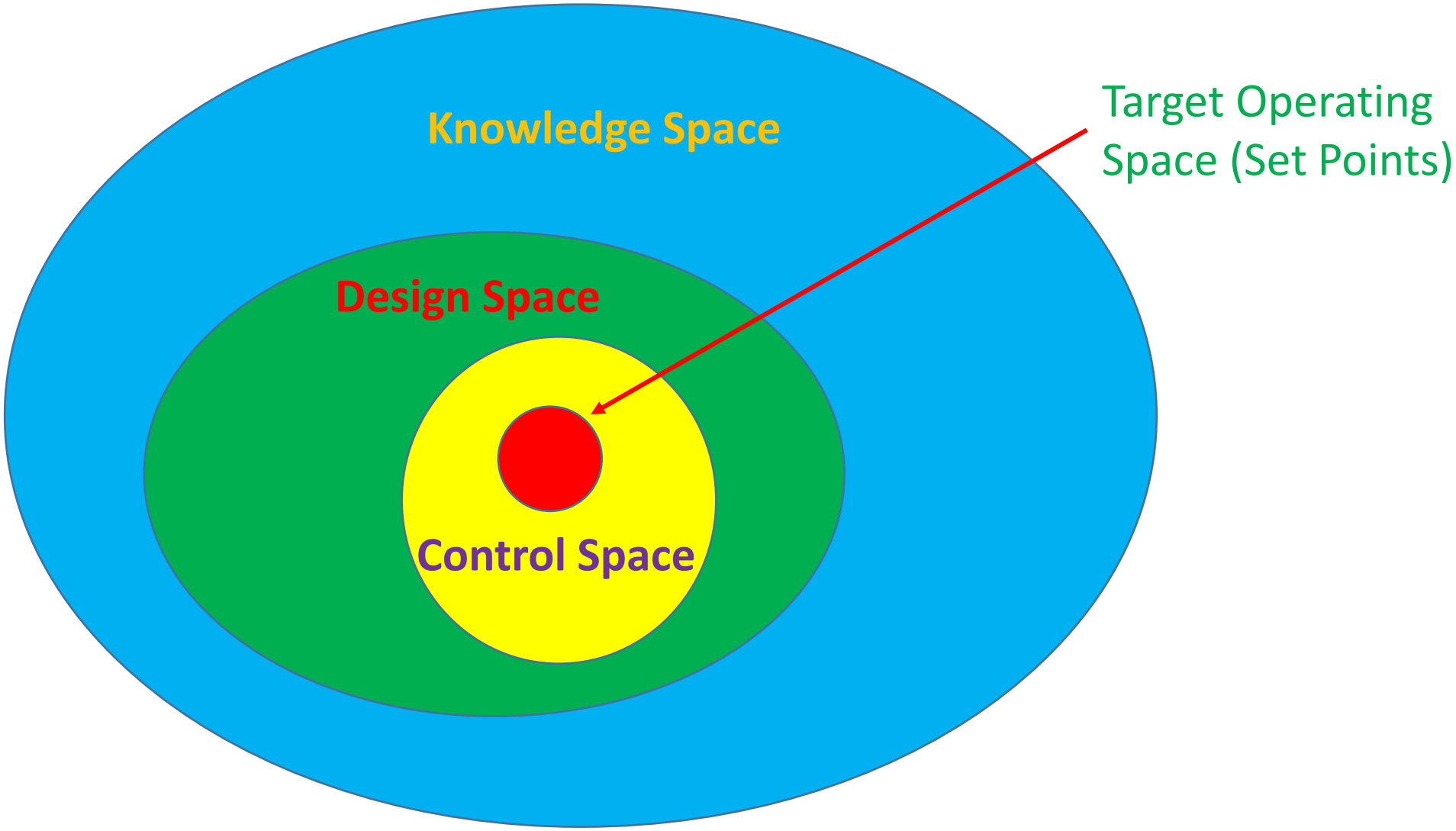
Process Analytical Technology (PAT) Is an Integral Part of Quality by Design

- Used in process development to gain process understanding
- Implemented in routine manufacturing to monitor process, control product quality and reduce release testing
- PAT testing can replace additional laboratory testing

Quality by Design (QbD) Has Several Key Components

- **Define the Product Design Goal**: Identify CQA.
  - Define the quality target product profile (QTPP)
  - Identify all the critical quality attributes (CQA)
- **Discovering the Process Design Space**: Identify CMA and CPP, and understand (if possible express mathematically) their relationship w/ CQA
  - Identify all the critical material attributes (CMA)
  - Identify all the critical process parameters (CPP)
  - Use design of experiment (**DOE**) to check interactions and establish the **design space**
- **Understanding the Control Space**: Design a process measurement system to allow on-line or at-line monitoring of CQA (via CMA and CPP)
  - Understand your process capability and the space it is able to control consistently (depending on the **control strategy** decided)
  - Control space must be within design space
- **Targeting the Operating Space**: Design a control system that will allow adjustment of CQA
  - Determine the best set of parameters which enable you to accommodate any natural variability in CPPs and CMAs
  - Consider to retain reference materials
  - Operating space must be within control space, and **robust**
- **Process Capability and Continual Improvement**

What Are the Varieties of Space?



Targeting the Best Set of Parameters

Determine the Optimization Objective:

- **Limit optimization**

  Where the objective is to reach a solution in which the response is within the specification limits (min and max limits).

- **Target optimization**

  Where the objective is to reach a solution in which the response is as close to target as possible. For the target optimization to work properly, it is necessary that the response can be optimized close to or on target.

- **Custom optimization**

  User defined customization of the target optimization.

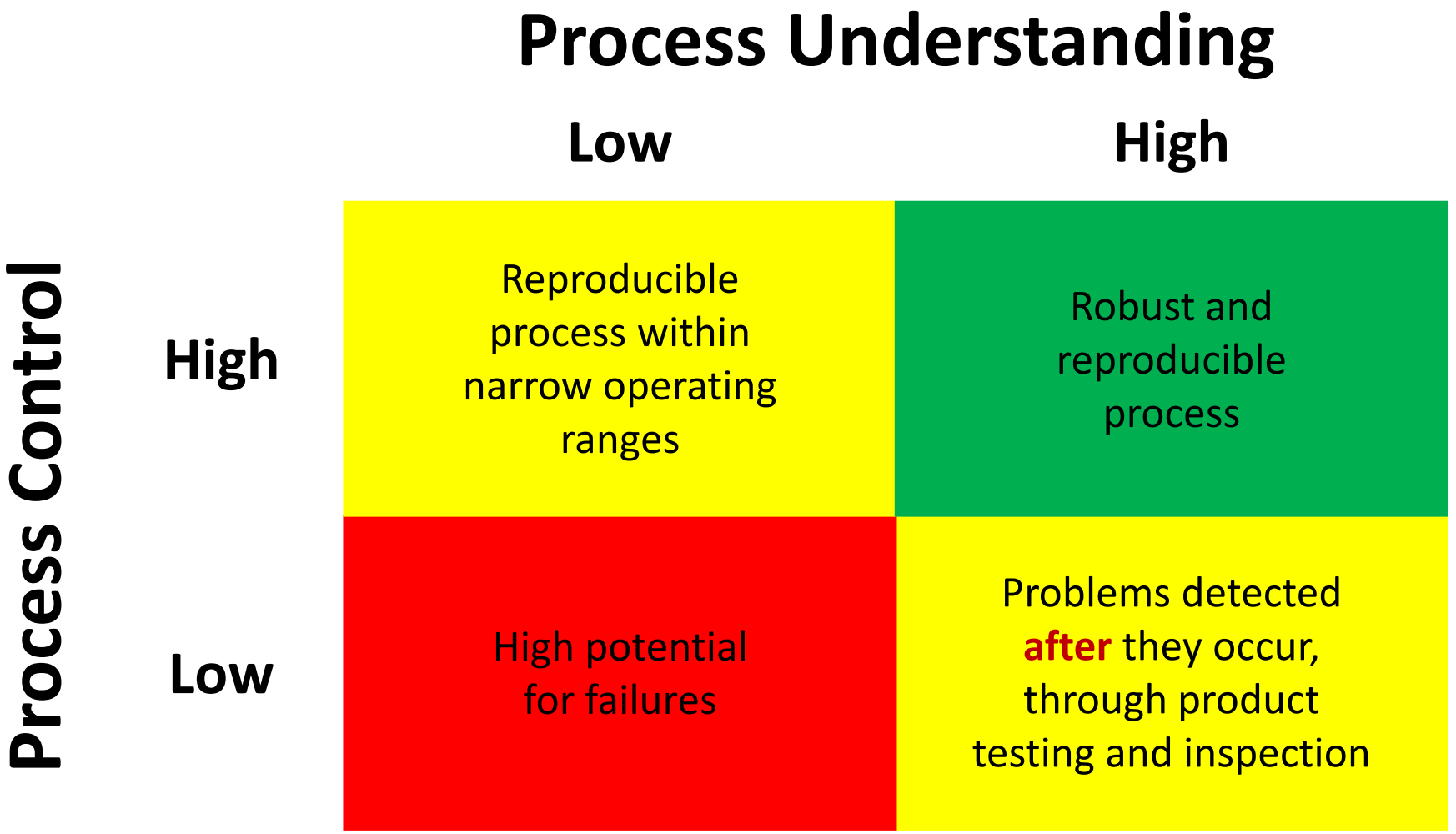
- **Focus optimization**

  Where the objective is to favor one or several responses over others; accomplished by manipulating the individual weights.

- **Robust setpoint**

  Where the most robust setpoint is found, depends on the existence of a solution based on objectives 1-4.

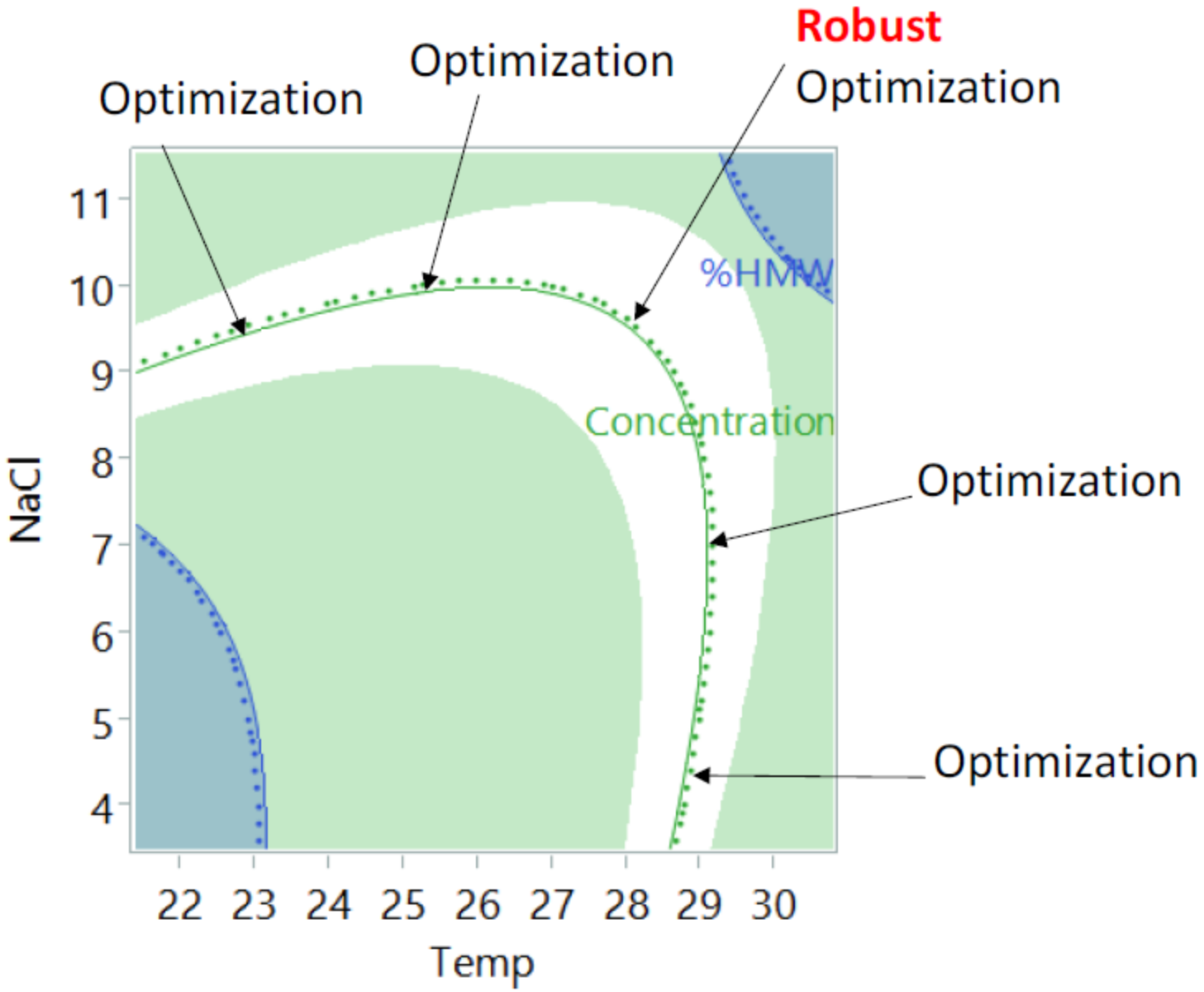
Designing a Robust Process



Find Robust Setpoint

- The **robust setpoint** will **maximize the distance from the acceptance boundaries** in the design space.
- The procedure will be to first generate the design space with selected factors and a given specification.
- To search for the robust setpoint using ‘MODDE”:
  1. In the **Optimizer** window, click **Find robust setpoint** or on the **Optimizer** contextual tab, click **Design space explore**.
  2. Select which factors to use, the resolution, iterations, acceptance limit, and if model error and factor precision should be included.
  3. Optionally change interval estimation settings on the **Interval estimation** tab.
  4. When you are happy with your settings and the number of points to be simulated, click **OK**.

Robust Optimization for a Target Concentration



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What Is Process Capability

- **Process capability** is the long-term performance level of the process after it has been brought under statistical control. In other word, process capability is the range over which the natural variation of the process occurs as determined by the system of common causes.

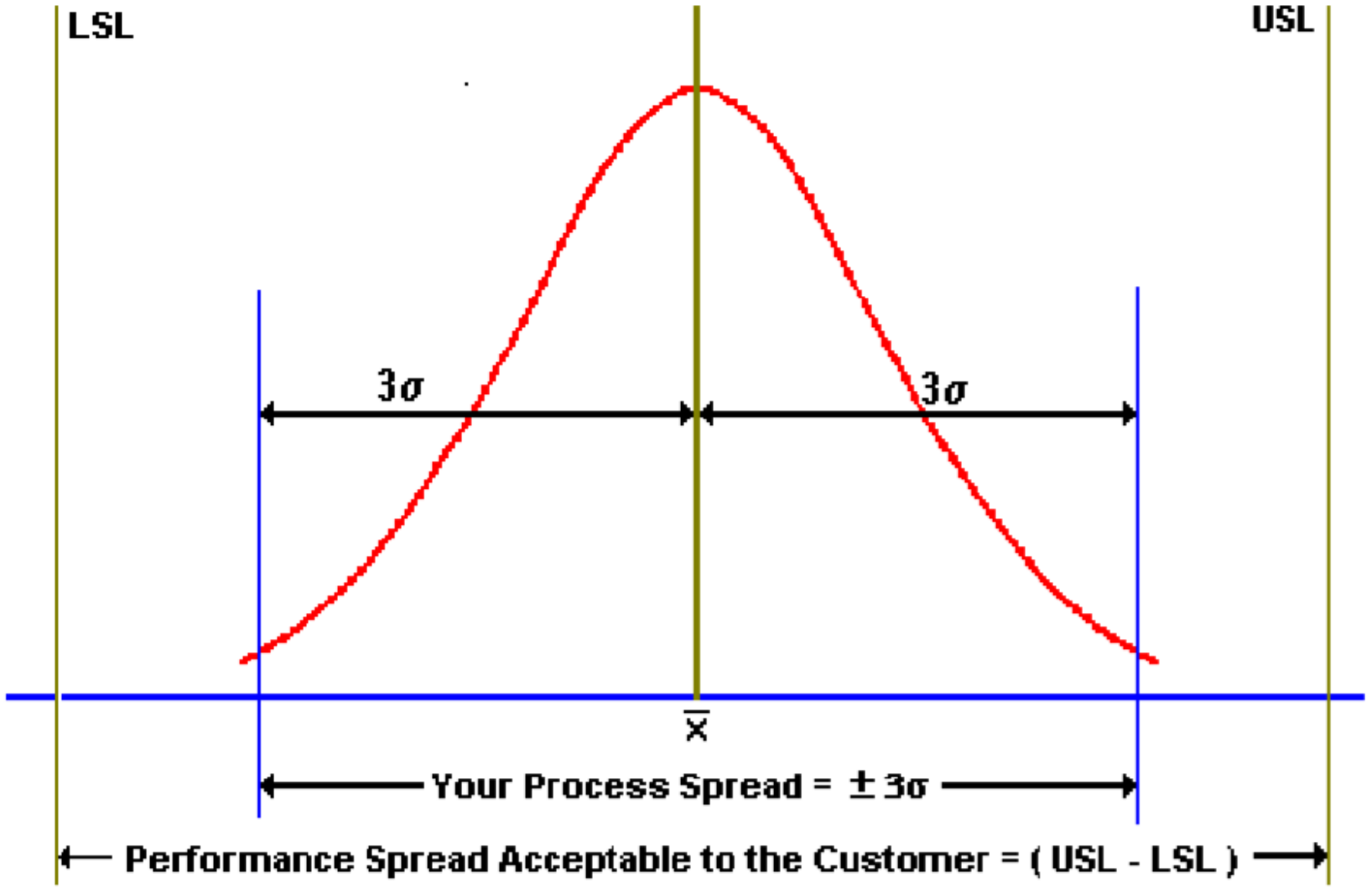
- Process capability is also the ability of the combination of people, machine, methods, material, and measurements to produce a product that will consistently meet the design requirements or customer expectation.

Measures of Process Capability – Process Capability Indices

Cp, **Cpl**, **Cpu**, and **Cpk** (definitions will be provided in the next two slides) are the four most common and timed tested measures of process capability:

- Process capability indices measures the degree to which your process produces output that meets the specifications.
- Process capability indices can be used effectively to summarize process capability information in a convenient **dimensionless** system.
- **Cp** and **Cpk** are **quantitative expressions** that personify the variability of your process (its natural limits) relative to its specification limits (quality requirements)

Graphical Details and Equations Quantifying Process Capability



Where :

USL = Upper Specification Limit

LSL = Lower Specification Limit

X-Bar = Mean of the Process

s = Standard Deviation of the Process

Process capability Indices and Their Measures

INDEX	ESTIMATED EQUATION	USAGE
Cp	(USL - LSL) / 6s	Process Capability for two - sided specification limit, irrespective of process center.
Cpu	(USL - X-Bar) / 3s	Process Capability relative to upper specification limit.
Cpl	(X-Bar - LSL) / 3s	Process Capability relative to lower specification limit.
Cpk	Min. of (Cpu , Cpl) or Distance between mean of the process and the closest spec. limit / 0.5 of the process variability.	Process Capability for two - sided specification limit accounting for process centering.

Notes :

1. If X-Bar is at target, then Cp = Cpk.
2. Cpk will always be equal to or less than Cp.

The Cpk, Ppk Quandary :

In 1991, ASQ / AIAG task force published the "Statistical Process Control" reference manual, which presented the calculations for capability indices (Cp, Cpk) as well as process performance indices (Pp, Ppk).

Why Process Capability Use Cpk Instead of Ppk?

- **Cpk** and **Ppk** calculations are using the same equation except:
  - **CpK** (process capability) calculation uses **population standard deviation**

$$s_N = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \overline{x})^2}$$

  - **Ppk** (process performance) calculation uses **sample standard deviation**

$$s = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \overline{x})^2}$$

- That means the fundamental question will be whether we are reporting **Ppk** for “Does my **current production sample** meet specification?” or reporting **Cpk** for “Does **my process in the long run** meet specification?”
- Thus, the answer for reporting process capability is **Cpk**, not **Ppk**.

Statistical Control for Cpk and Ppk Calculations

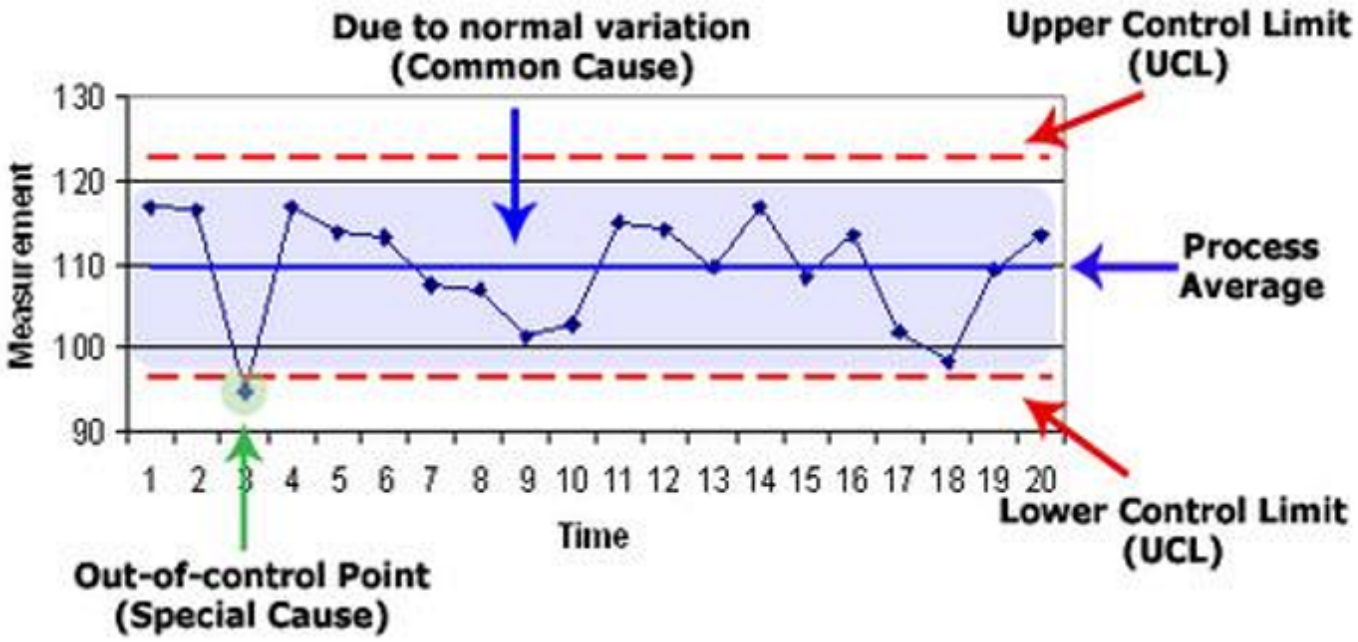
- As a rule of thumb, a minimum of **50** randomly selected samples must be chosen for process performance (**Ppk**) studies, and a minimum of **20 subgroups** (of sample size preferably of at least **4 or 5**) must be chosen for process capability (**Cpk**) studies.

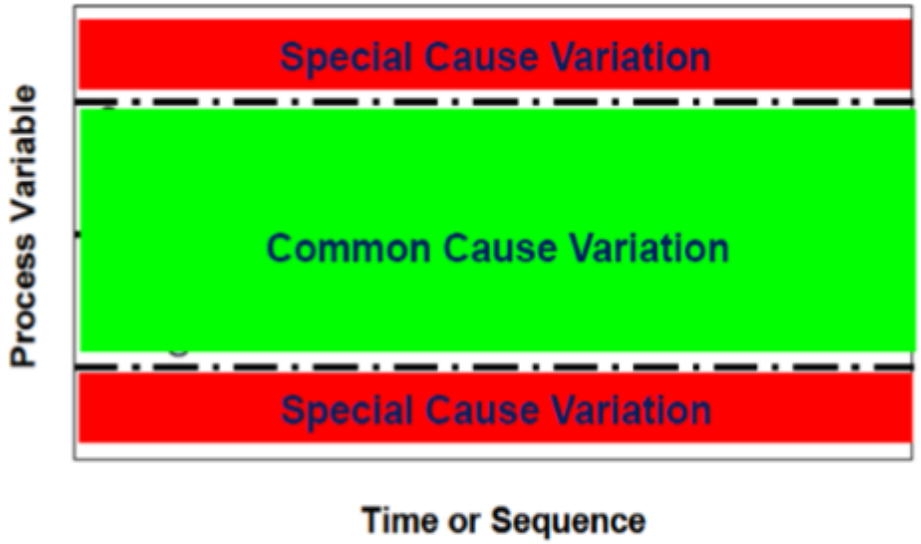
- **Ppk** for all critical product measurements considered important for CQAs should be calculated **at the beginning** of initial production to determine the general ability of the process to meet specifications. Then **from time to time**, over the life of the product, **Cpks** must be generated.

- A **control chart** must always be maintained to check statistical stability of the process before Cpk is computed.

Control Chart

Control Chart- It's a graphical display of a product quality characteristic that has been measured or computed periodically from a process at a defined frequency.

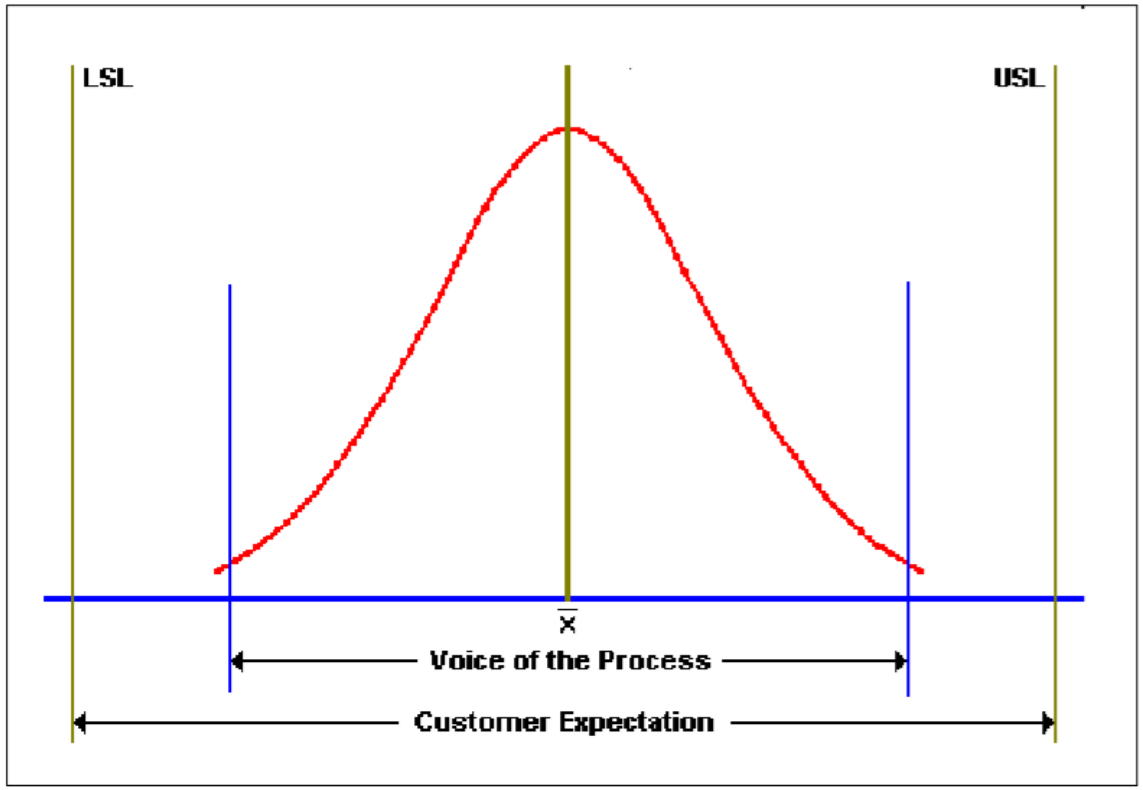




Potential Applications-

- To proactively monitor and trend a process
- To detect the presence of special cause variation
- To identify continual improvement opportunities
- To maintain the process in the state of statistical control

Case 1: Cpk > 1.33 (A Highly Capable Process)



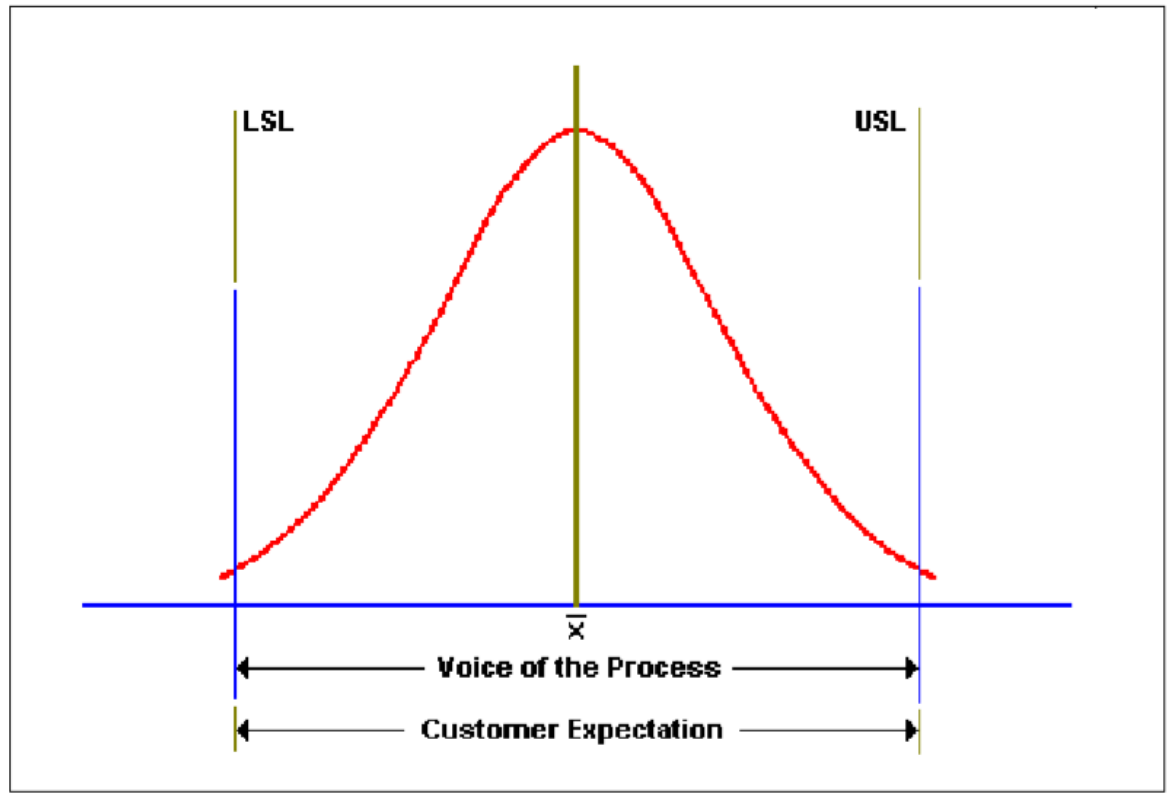
A Highly Capable Process: Voice of the Process < Specification (or Customer Expectations).

This process will produce conforming products as long as it remains in statistical control. The process owner can claim that the customer should experience least difficulty and greater reliability with this product. This should translate into higher profits.

Note: Cpk values of 1.33 or greater are considered to be industry benchmarks. This means that the process is contained within four standard deviations of the process specifications.

Case 2: Cpk = 1 to 1.33 (A Barely Capable Process)

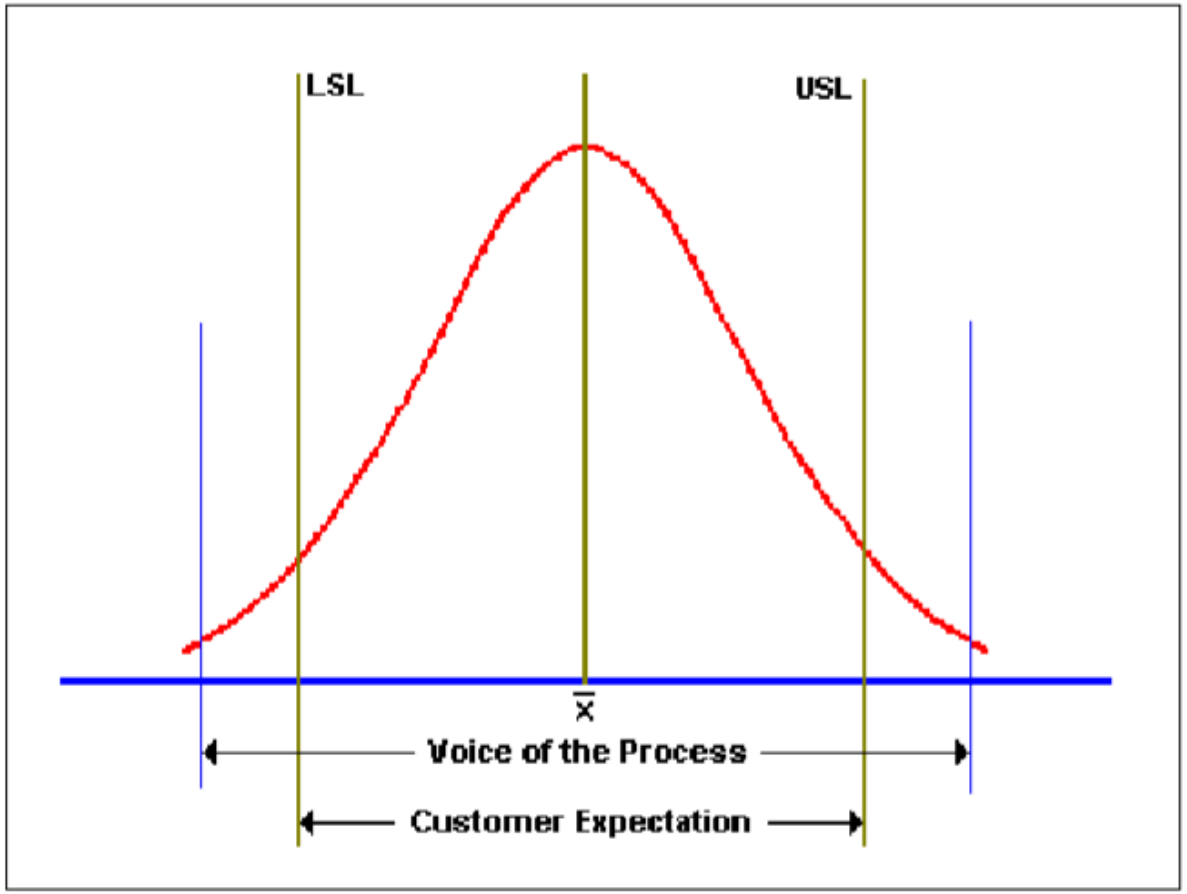
This process has a spread just about equal to specification width. It should be noted that if the process mean moves to the left or the right, a significant portion of product will start falling outside one of the specification limits. This process must be closely monitored.



A Barely Capable Process: Voice of the Process = Customer Expectations

Note: This process is contained within three to four standard deviations of the process specifications.

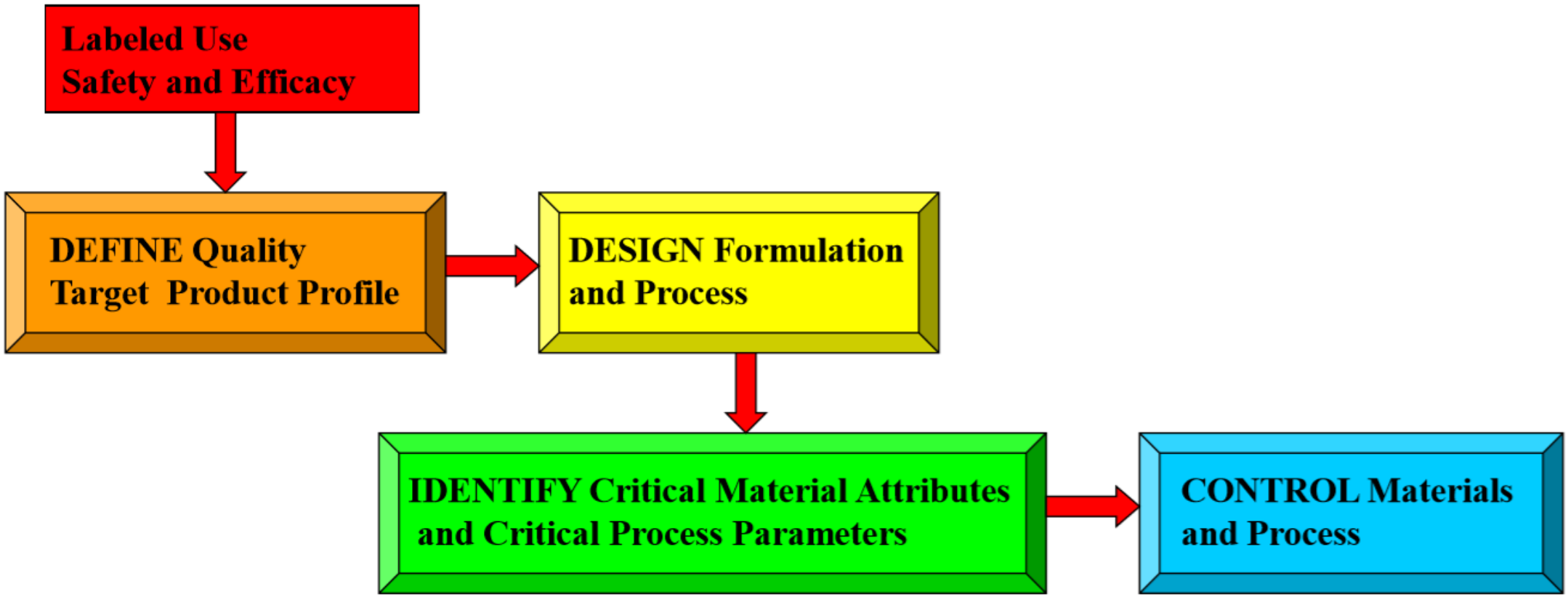
Case 3: Cpk < 1 (The Process is not Capable)



A Non-Capable Process: Voice of the Process > Customer Expectations.

It is impossible for the current process to meet specifications even when it is in statistical control. If the specifications are realistic, an effort must be immediately made to improve the process (i.e. reduce variation) to the point where it is capable of producing consistently within specifications.

Overview of QbD



TARGET → DESIGN and UNDERSTANDING → IMPLEMENTATION

Traditional

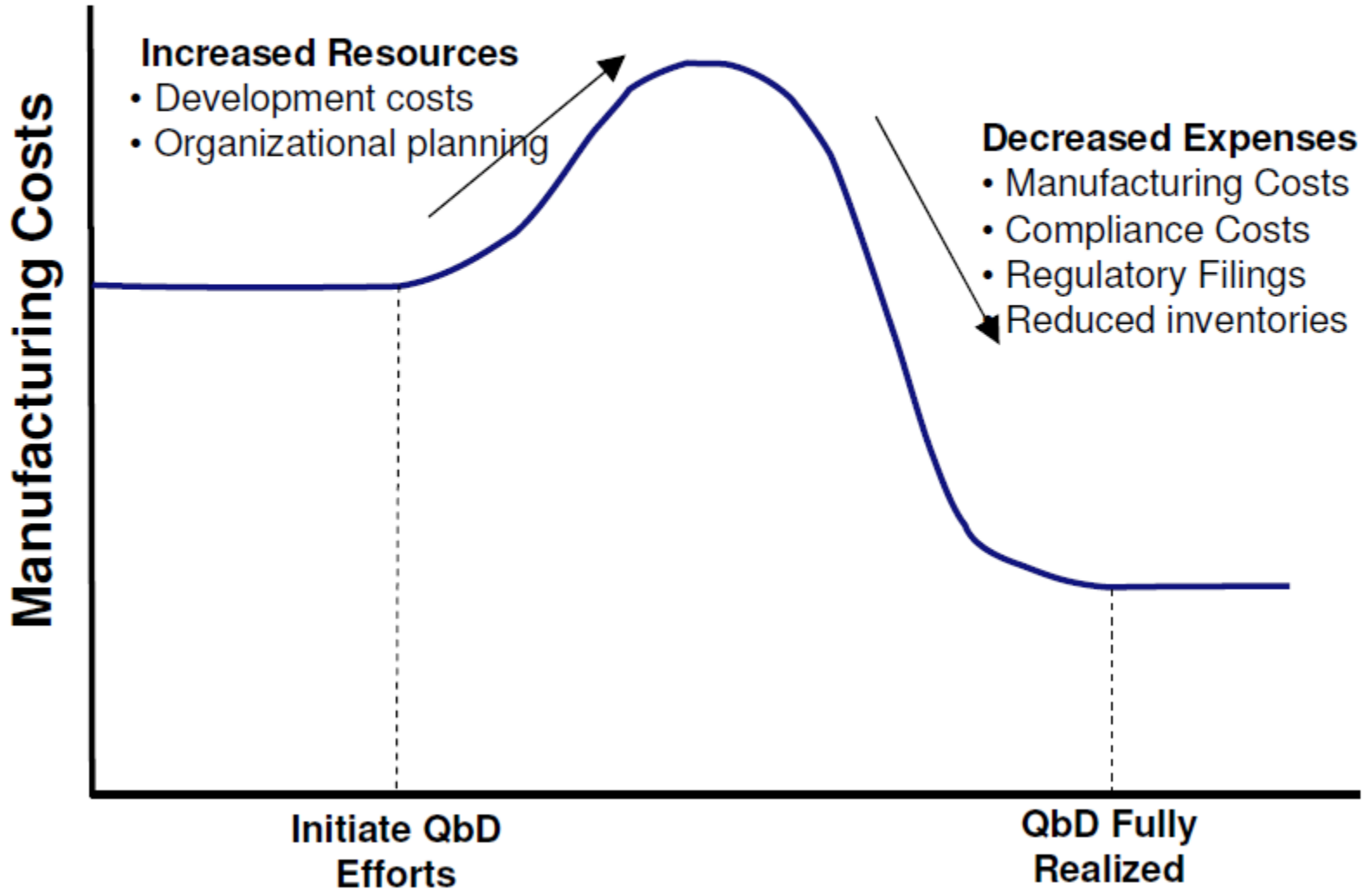
- Empirical development
- Data Driven
- Retrospective
- "Test to document quality"
- Acceptance criteria based on batch data
- Variability not understood and avoided /Focus on reproducibility

Q8

QbD

- Systematic development
- Knowledge driven
- Prospective
- Science and Risk based assurance of Quality
- Acceptance criteria based on patient needs
- Variability explored and understood (**Design Space, PAT**)

Potential Costs & Benefits of QbD



Conclusion

- The principles of Quality by Design have been proven in multiple industries including pharmaceutical.
- Pursuing Quality by Design does not require additional capital or overhead, **just good science**.
- The business benefits of improved control and greater productivity provide for a more stable and predictable business operation.

QUESTIONS

Example Product Development Cycle

Stage 1: Looking for new opportunities

- Look for new opportunities.
- Conduct initial market assessment to determine supply and demand relationship
- Determine whether to pursue further assessment.

- **Control Point to Assess (CPA)**

Stage 2: New opportunity assessment

- Assess the potential of the new opportunity through literature survey to figure out potential process and technology required as well as patents might involved.
- Self evaluate corporation capability including technology, facility, human resource, and financial factors.
- Estimate efforts required and compare to the benefit of the opportunity

- **Control Point to Refine (CPR)**

Example Product Development Cycle

Stage 3: Conduct preliminary proof of concept (POC) lab work

- Evaluate what kind of assumptions made in the previous stages need to be verified (proof of concept) before the decision for pipeline entry.
- Conduct lab work to verify the assumptions. The lab work may include small lab scale tests to evaluate feasibility of planned technology, and/or initial animal tests to evaluate assumed drug substance functions.
- Collect all POC results that are required for decision making of whether to enter pipeline.

- **Decision for Pipeline Entry (DPE)**

Stage 4: Process Development and Clinical Trials

- QbD process must be initiated early at the beginning of this stage.
- Some additional POC tasks may also needed at this stage.

- **Manufacturability Reviews (MR) before toxicity study and each clinical trials**
- **Go/No-go Decision Points (DPG) after each trial and before launch**

QbD and MR during Stage 4 Process Development

- **MR1** (before Toxicity study)
  - **Input**: information from DPE
  - **Example Deliverables**: additional POC studies not completed before DPE, preliminary quality target product profile (QTPP), preliminary risk assessment, preliminary critical quality attributes (CQA), preliminary Cost of Goods (COG) estimation and justification.
- **MR2** (before Phase I clinical trial)
  - **Input**: deliverables of MR1
  - **Example Deliverables**: preliminary design of experiment (DOE) for factors screening and preliminary critical process parameters (CPP), MSDS (SDS) and critical safety operations (HSE, HACCP, etc.) further risk assessment to finalize CQA, initial proposed specifications for raw materials and product, stability test plan, initial analytical development report with draft SOP, initial process development history report including all POC studies, and completed toxicity study report for IND submission.

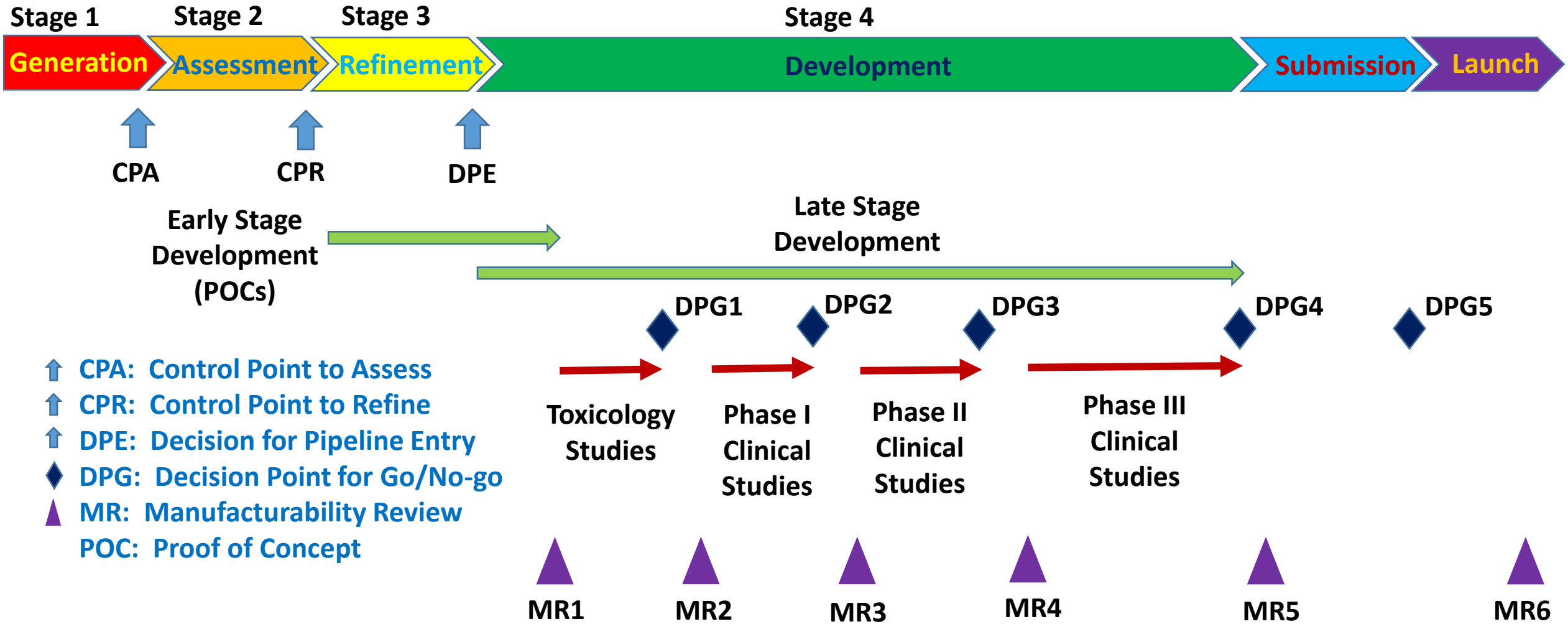
QbD and MR during Stage 4 Process Development

- **MR3** (before Phase II clinical trial)
  - **Input**: deliverables of MR2
  - **Example Deliverables**: accelerated stability test results, based on finalized CQA to finalize CPP (risk assessment), process scalability review, preliminary DOE for initial optimization and initial proposed design space, draft specifications for raw materials and product, draft plan for supply chain and other logistic issues, expanded process development history report, finalized analytical development history report with method validation plan, completed phase I clinical trial report.
- **MR4** (before Phase III clinical trial)
  - **Input**: deliverables of MR3
  - **Example Deliverables**: thorough DOE on optimizing CPP to finalize proposed design space, scale-up to larger pilot scale sufficient to support phase III clinical manufacturing, initial results for real time stability, process safety review (HSE, HACCP, etc.), draft near final process development history report, method validation report, completed phase II clinical trial report.

QbD and MR during Stage 4 Process Development

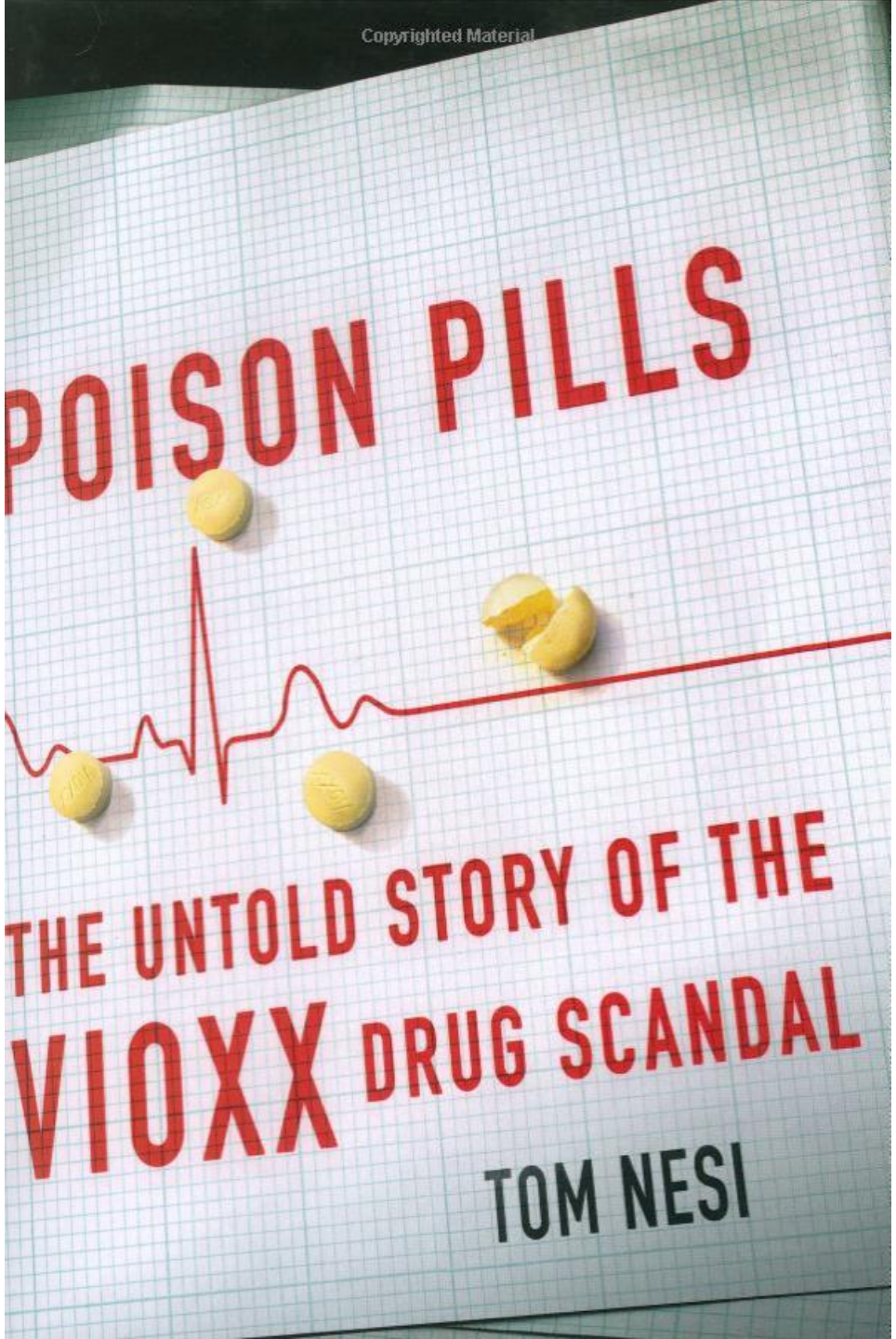
- **MR5** (before product registration submission)
  - **Input**: deliverables of MR4
  - **Example Deliverables**: finalized stability test report including complete real time stability results, finalized design space, finalized specifications for raw materials and product, finalized packaging and labeling, finalized plan for supply chain and other logistic issues, completed process development history report, completed analytical development history report, completed method validation report, completed process validation report, completed phase III clinical trials report, finalized COG/COP evaluation to propose product prize on the market.
- **MR6** (one year after commercial launch)
  - **Input**: deliverables of MR5
  - **Example Deliverables**: annual material and product review, lessons learned and feedbacks, recommendations for continuing improvement, recommendations for future new project handling.

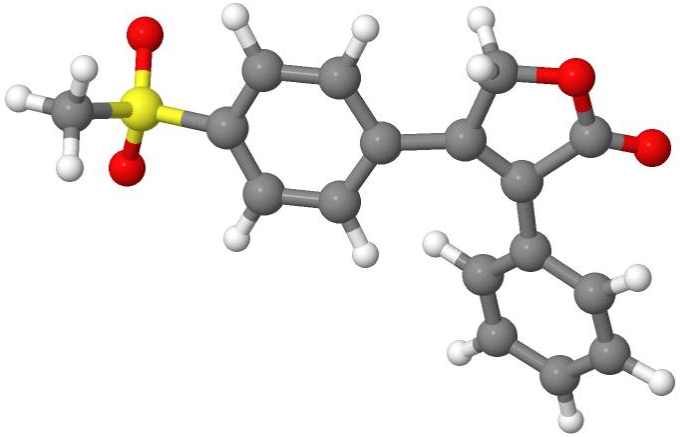
Pharmaceutical Product Development Life Cycle



Kill or Persist?

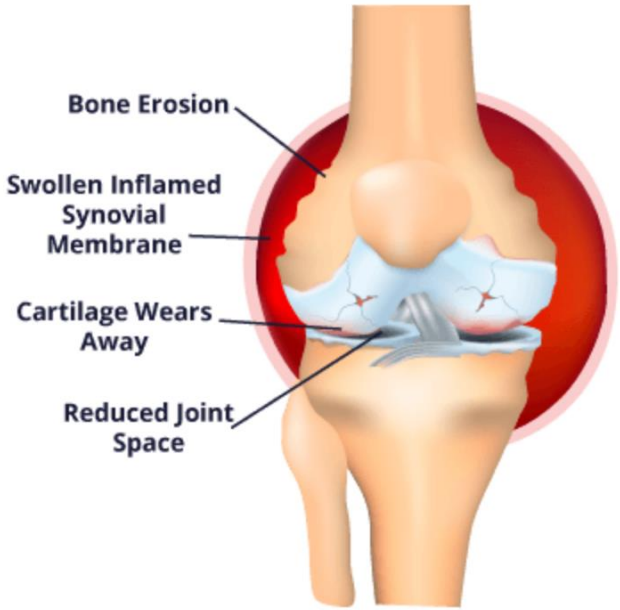
- Two Classes of decision making errors:
  - Managers ignore evidence challenging their assumption that a project will succeed
  - Organizational or personal bias against a project or because of a shortage of resources that terminate a project prematurely
- Real Example:
  - Merck's **VIOXX**
    - FDA approved VIOXX in May 1999.
    - By 2001, VIOXX became Merck's second biggest drug.
    - VIOXX linked to thousands of death, 4 heart attacks occur for every 1000 patients taking VIOXX.
    - Being taken off the market in September 2004.



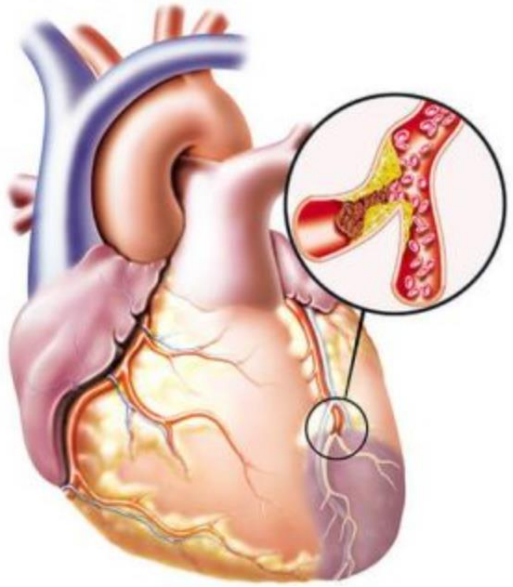


VIOXX Molecular Structure

Grey: Carbon
White: Hydrogen
Red: Oxygen
Yellow: Sulfur



Vioxx treats Rheumatoid Arthritis, pictured above

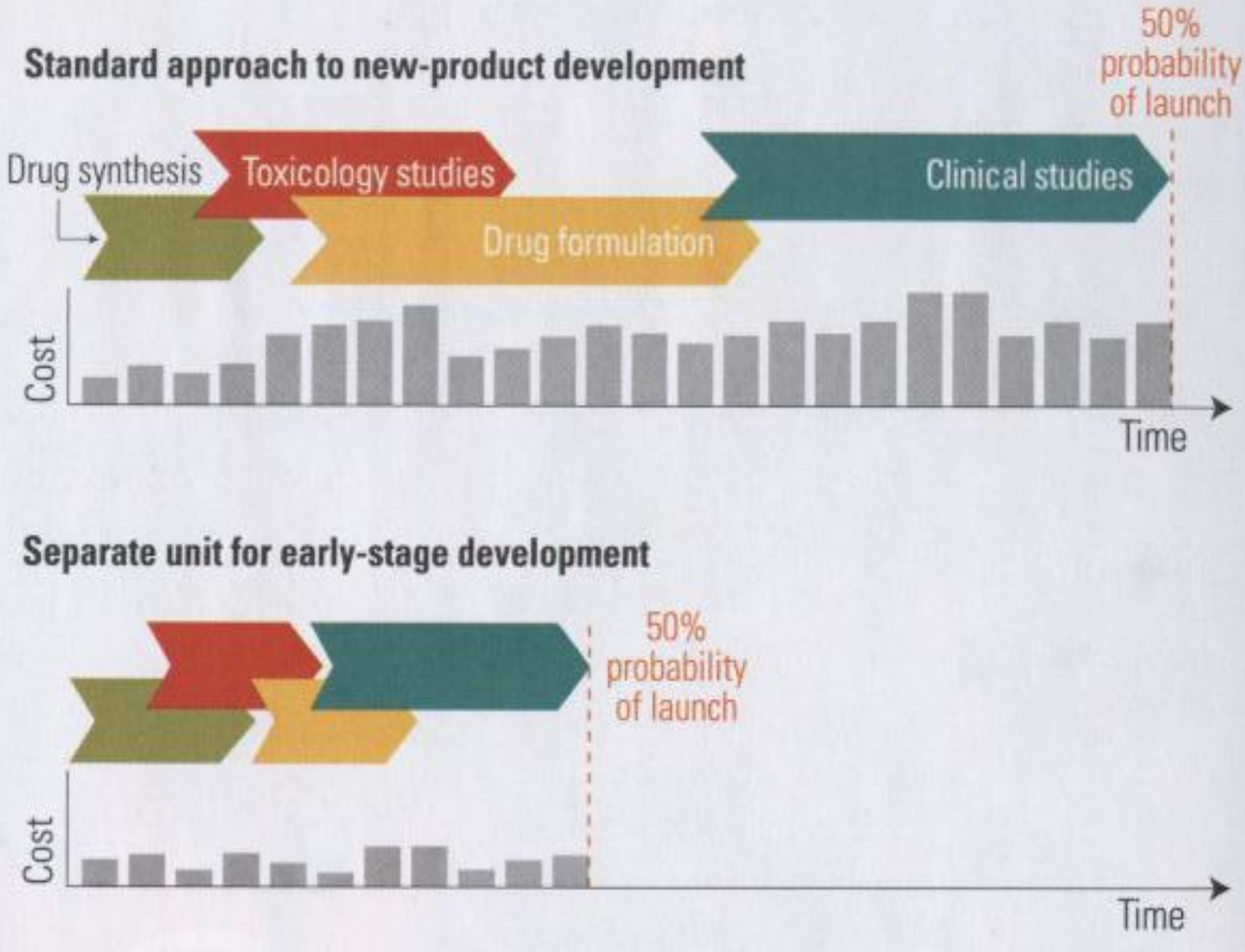


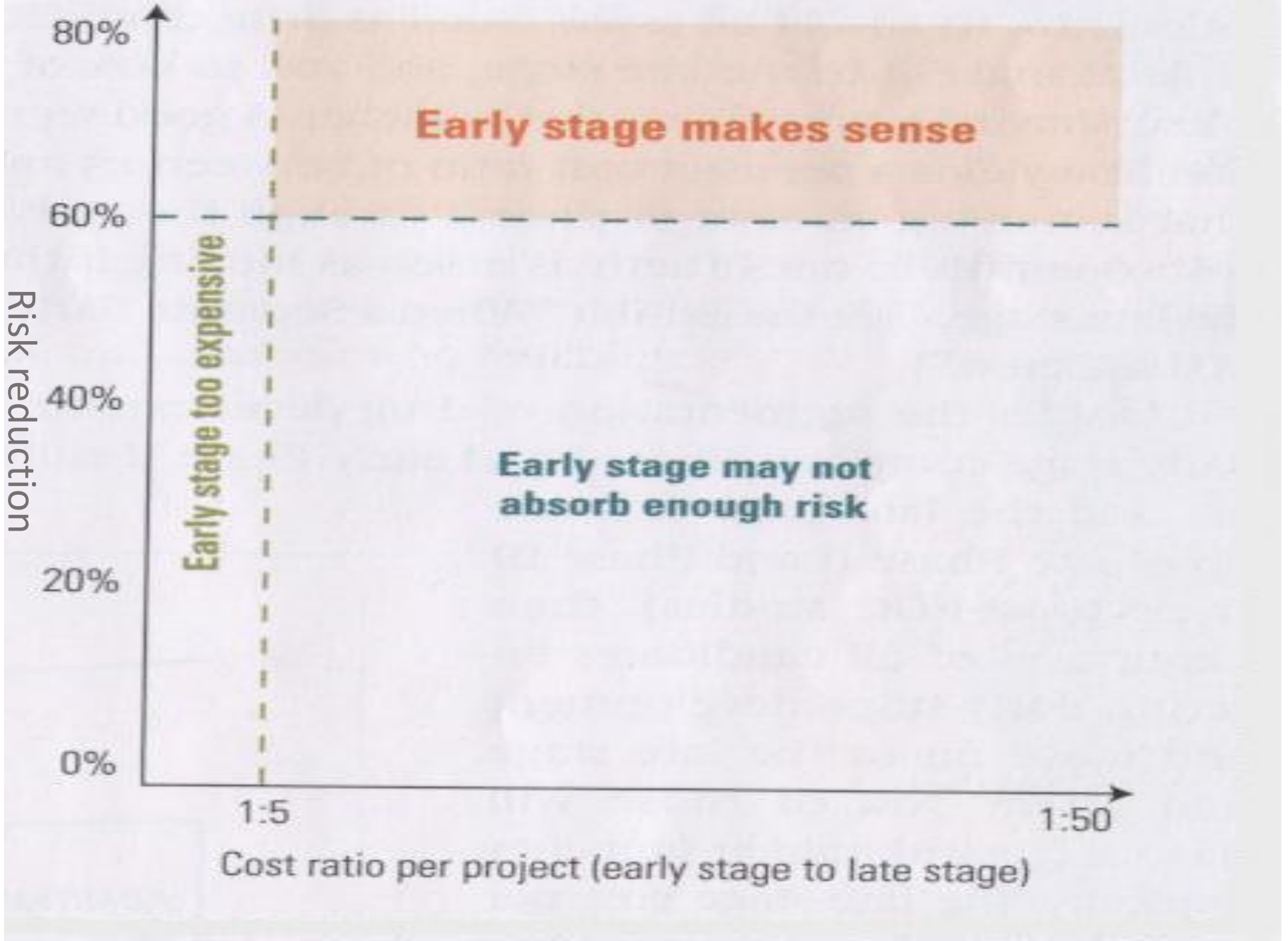
Vioxx caused cardiovascular risks by increasing thrombus formations

The Two Faces of Pharmaceutical New-Product Development

The early and late stages of new-product development require fundamentally different goals, strengths, and approaches.

Early	Late
Organizational Goal	
Seek truth	Seek success
Organizational Strength	
Establish novel products' promise or lack thereof	Take products to market
Organizational Approach	
Reduce risk	Maximize value
Maintain loyalty to the experiment	Maintain loyalty to the product
Focus on scientific method	Focus on commercialization
Operate with low fixed costs, low capital requirement	Operate with high fixed costs, high capital requirement
Work in small, experiment-based teams	Work in large, product-based teams
Emphasize testing	Emphasize refining


Standard approach to new-product development
50% probability of launch
Drug synthesis
Toxicology studies
Clinical studies
Drug formulation
Cost
Time
Separate unit for early-stage development
50% probability of launch
Cost
Time


80%
60%
40%
20%
0%
Risk reduction
Early stage makes sense
Early stage too expensive
Early stage may not
absorb enough risk
1:5
1:50
Cost ratio per project (early stage to late stage)

QbD Deliverables and Metrics Example

	QTPP	CQA	CPP	Design Space	Control Strategy
MR1	Proposed	Hypothetical	Not Available	Not Available	Not Available
MR2	Defined	Defined	Parameters Defined	Initial Proposed	Initial Draft
MR3	Refined as Needed	Refined as Needed	Target and Operating Ranges Set	Refined Draft	Refined Draft
MR4	Final	Final	Final	Near Final	Near Final
MR5	Final	Final	Final	Final	Final
MR6	Assessed after 1 year	Assessed after 1 year	Assessed after 1 year	Assessed after 1 year	Assessed after 1 year

List of Example Deliverables for MRs

- **QbD:**
  - Target product profile (TPP)
  - Quality target product profile (QTPP)
  - Risk assessment report and proposed critical quality attributes (CQA)
  - Critical material attributes (CMA)
  - DOE summary report (screening) for current CPPs confirmation status
  - DOE summary report (optimization) for CPPs and design space
  - Design Space and tolerance intervals
  - Process capability establishment
  - Quality by Design summary

- **Quality Attributes:**
  - Stability test results and property summary
  - Internal manufacturing specifications
  - Packaging specifications for product material
  - Product specifications to be registered
  - Identified commercial manufacturing site audit report and qualification status
  - If use CMO, quality agreement with external partners
  - Critical audit findings

Example Deliverables for MRs

- **Regulatory:**
  - Proposed regulatory path
  - Regulatory submission plan
  - Review of label and claims
  - Registration submission package check list
  - Global registration strategy

- **Analytical Development History:**
  - Summary of method evolution
  - Current method qualification status (accuracy and precision, before validation is required)
  - Current method assay SOP and method validation report
  - Changes to analytical methods
  - Instrumentation needs
  - Primary and secondary reference standards status
  - Analytical development history report

Example Deliverables for MRs

- **Process Development History:**
  - Current process development history include all prove-of-concept studies
  - Complete process development history report
  - Process capability and scale history
  - Process flow document (PFD)
  - Process control strategy
  - Cleaning requirements
  - Cleaning validation protocol
  - Proposed raw materials/intermediates/products specifications
  - Specifications and limit ranges data (supporting process flow document)
  - Animal test summary
  - Dose response animal trial summary
  - Starting materials classifications (medium and downstream processing additives)
  - MSDS (SDS) status (raw materials, intermediates, products)

Example Deliverables for MRs

- **Manufacturability:**
  - Technology transfer protocol
  - Scalability review/gap analysis – equipment/utilities/process
  - Assessment of pilot runs for process robustness
  - Plant permit/license assessment
  - Plant permit/license in place
  - Batch size plan
  - Bioburden control strategy
  - Facility, utility and equipment commissioning reports
  - Personnel training records
  - Manufacturing master batch records
  - Manufacturing SOPs and production records
  - Review of engineering lots for compliance
  - Engineering lots summary report
  - Summary of changes

Example Deliverables for MRs

- **Process Safety:**
  - HSE process safety summary
  - HSE process hazard review
  - Critical safety operations (risk assessment)
  - HSE process safety and hazard review update based on all changes
- **Supply Chain:**
  - Raw materials supply plan
  - Strategy of supply for trials and registration
  - Commercial supply strategy
  - Commercial supply schedule
  - Global distribution temperature profile
  - Supply chain contractors selection

Example Deliverables for MRs

- **Business:**
  - COGs/COPs estimation and justification
  - Capital projections
  - Intended market
- **Management:**
  - Project schedule
  - Project core team assigned
  - Risk assessment - MR deliverables – acceptance criteria for each stage of MR
  - Process deviation and CAPA summary
  - Change control summary
  - Release/in-process testing analytical results summary
  - Yield summary
  - Rework/reprocessed/rejected summary
  - Complaints/recalls/adverse events summary

QUESTIONS