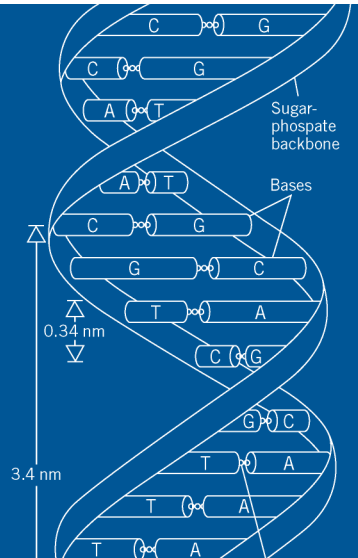
From DOEs to CPPs: Statistics in process development that begins with the end in mind

Lisa Bernstein, Genentech, Member of the Roche Group
Oana Danila, F. Hoffmann-La Roche



IABS / FDA

4th International Workshop on Statistics and Data Management Approaches for Biotechnology

The end in mind: *Bringing a reliable supply of safe & efficacious medicines to patients*

- This is a shared goal:
  - Health Authorities (HA) & Industry
  - Partnership, interactions are key

- Being mindful of this goal:
  - Helps communications
  - Brings clarity to our work
  - Brings trade-offs:
    - Appealing, less-relevant statistics vs.
    - Practical relevance (end in mind)

"DOEs to CPPs" illustrates these issues

Covey, S. (1989). New York: Simon and Schuster

Outline

- Background
- Critical Process Parameter (CPP) Identification
  - DOEs, the Impact Ratio & Thinking
- Pros, Cons and the Future

Comments about interactions & communication throughout.

Background:

Safe, efficacious medicines → Critical Quality Attributes (CQAs)

- "Desired product quality" ~ like material used in pivotal clinical trials
- Made precise in terms of Quality Attributes (QA)

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

International Conference on Harmonization, ICH Q8 R1, November 2008

Background: Typical CQAs for a biologic

Size: Variants:

- Aggregates (HMWS), Monomer, Fragments

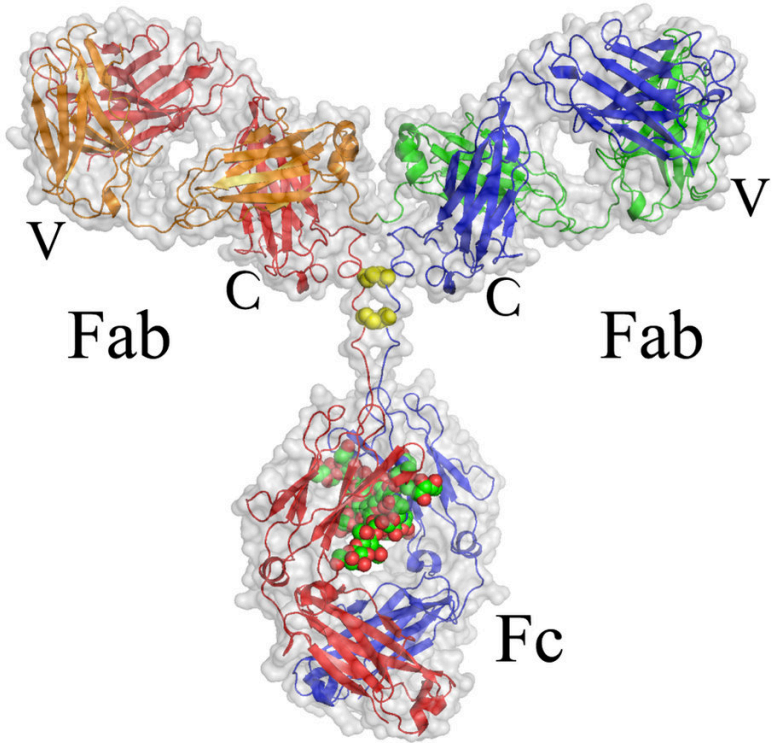
Charge Variants:

- Acidic Peak, Main Peak, Basic Peak

Deamidation

Oxidation

Glycoforms



https://www.nature.com/articles/srep22148, Stingaciu et. al.,2016

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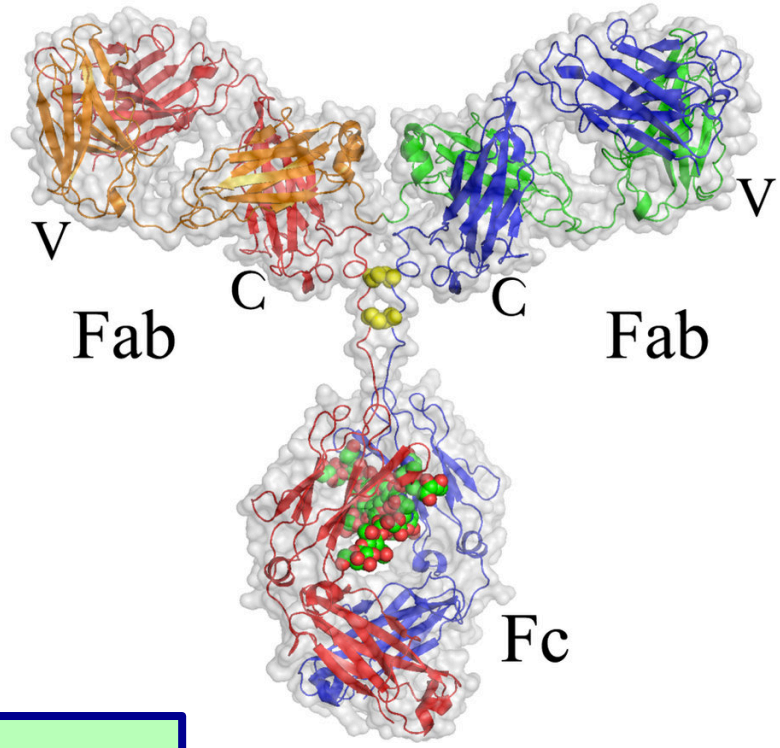
… and more …



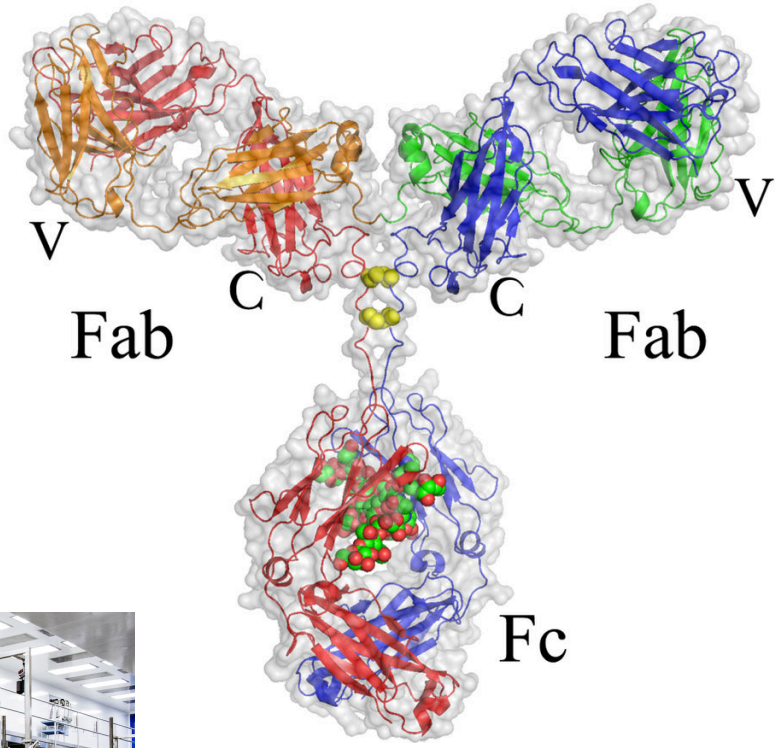
Does %HMWS (Aggregate) impact

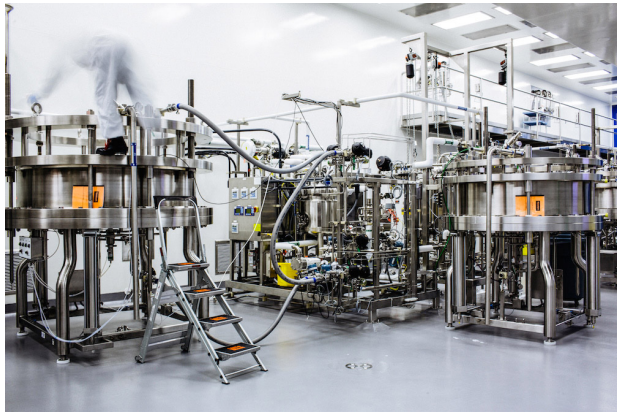
- Potency?
- Safety?
- Immunogenicity?
- Pharmacokinetics (PK)?

Background: Process Parameters (PP)

(For a process step = **“unit op”**)

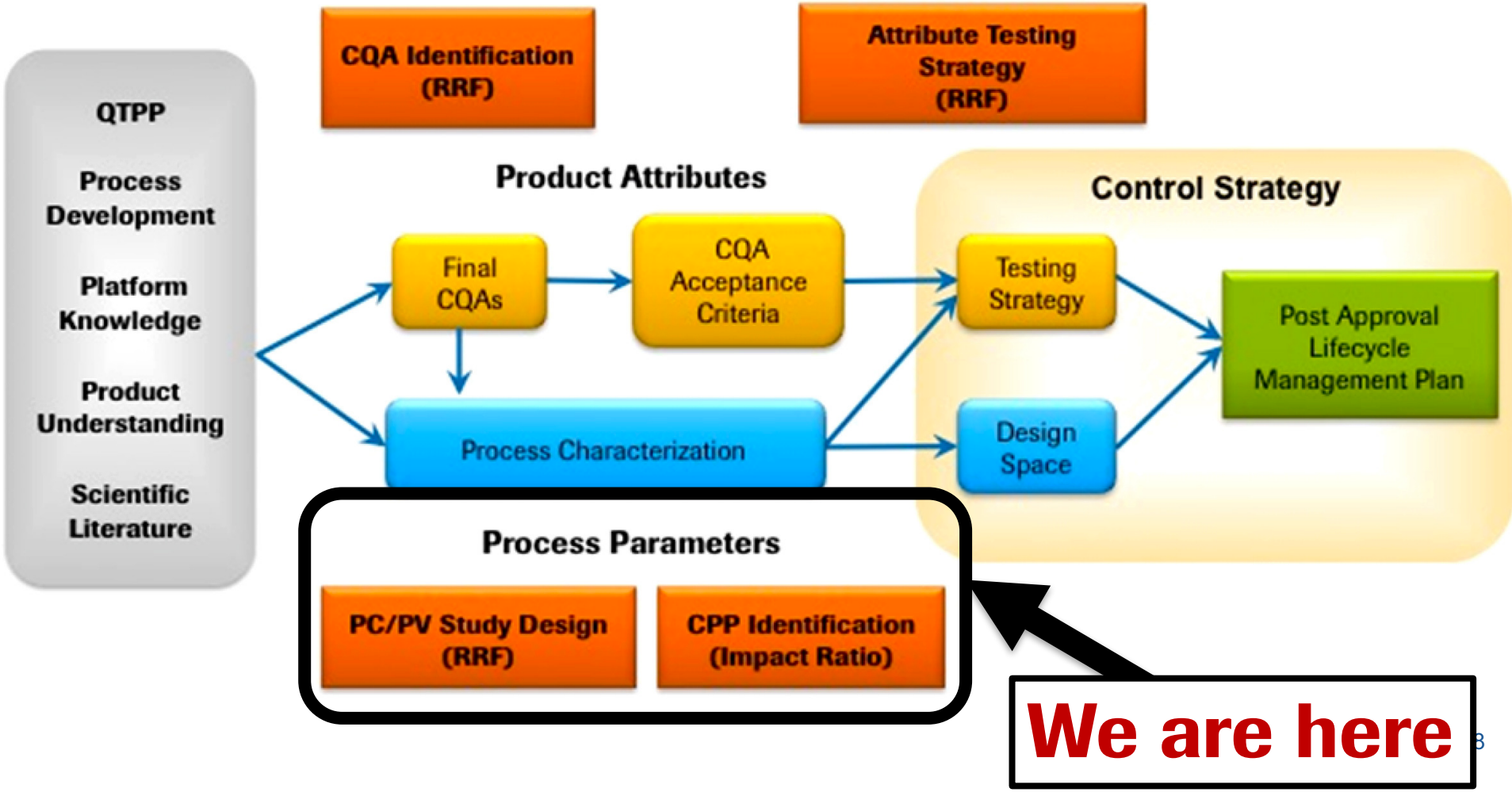
Cell culture duration - cell culture
Flow rate - chromatography step
Surfactant Conc. - formulation
Temperatures
pHs
Protein Conc.
… and many more





https://www.gene.com/stories/the-beauty-of-manufacturing?topic=manufacturing

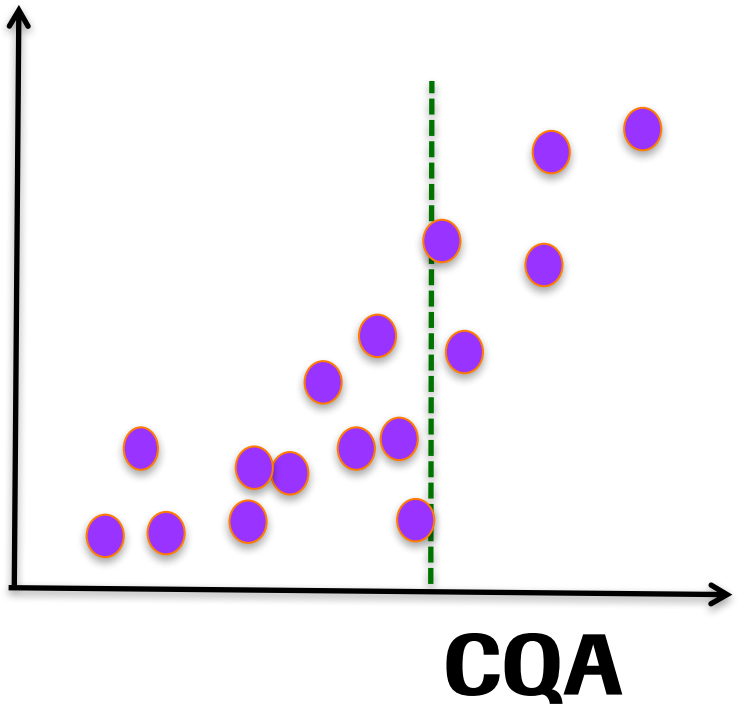
CQAs, PPs are part of a larger QbD Framework



Biologicals, 44:6, 2016 Christof Finkler, Lynne Krummen (2010)

Patient Impact vs. CQA

Data or Indicators:
Potency, Safety, PK, ATA
Clinical/preclinical data, similar molecules, bioassay, binding, …



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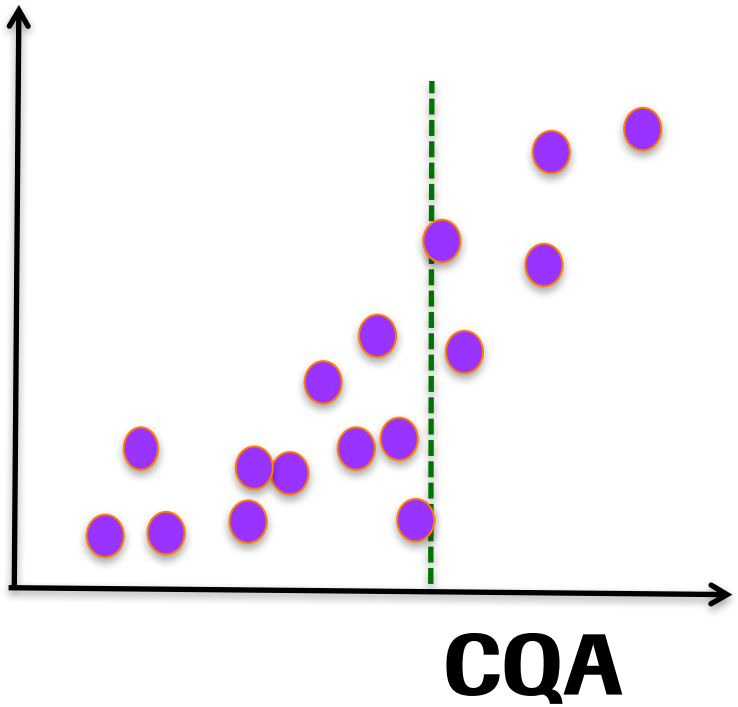
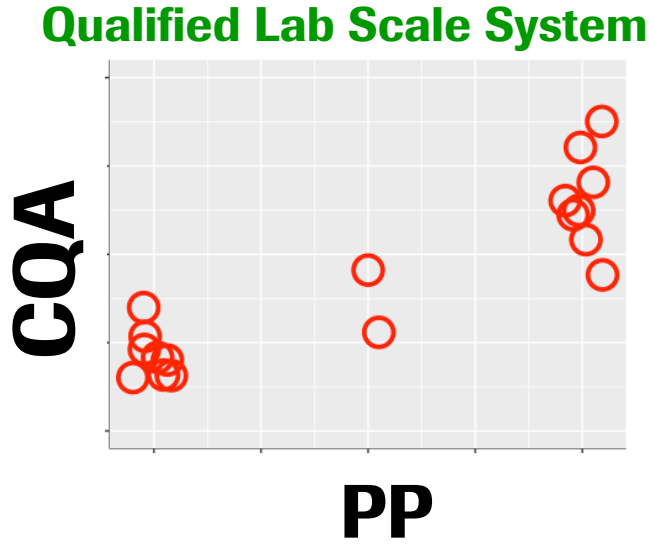


CQA vs. PP



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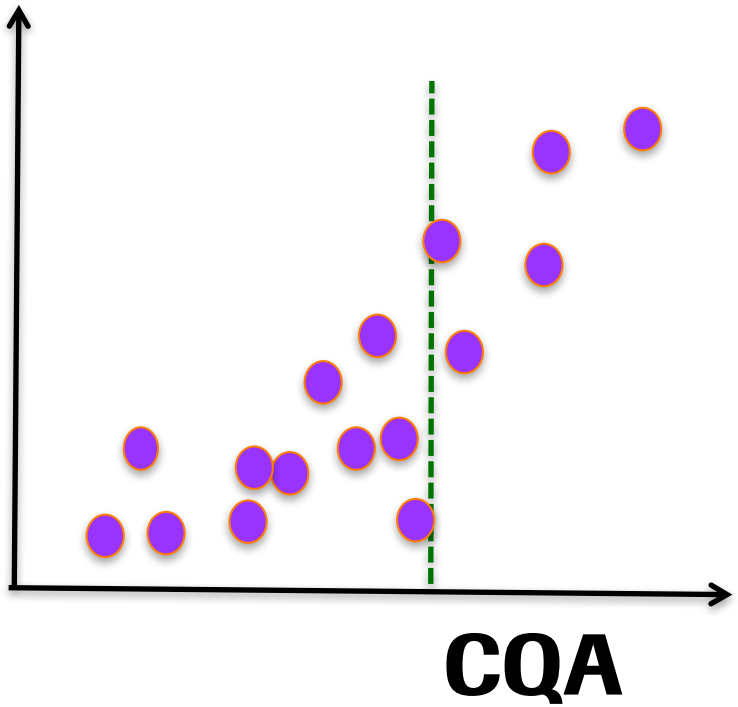
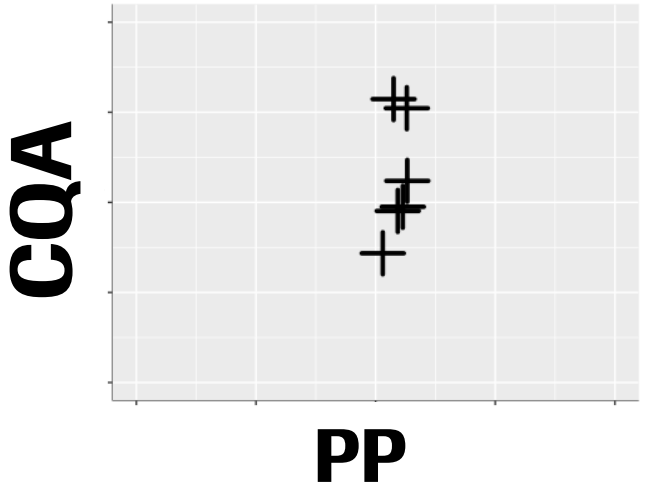
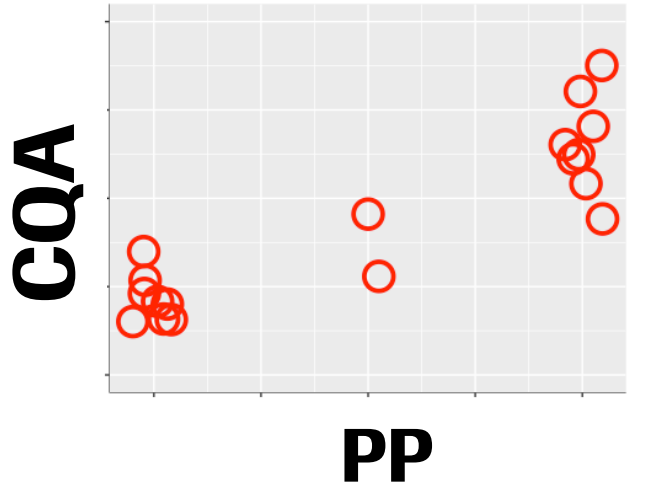


CQA vs. PP

Manufacturing Scale



Qualified Lab Scale System



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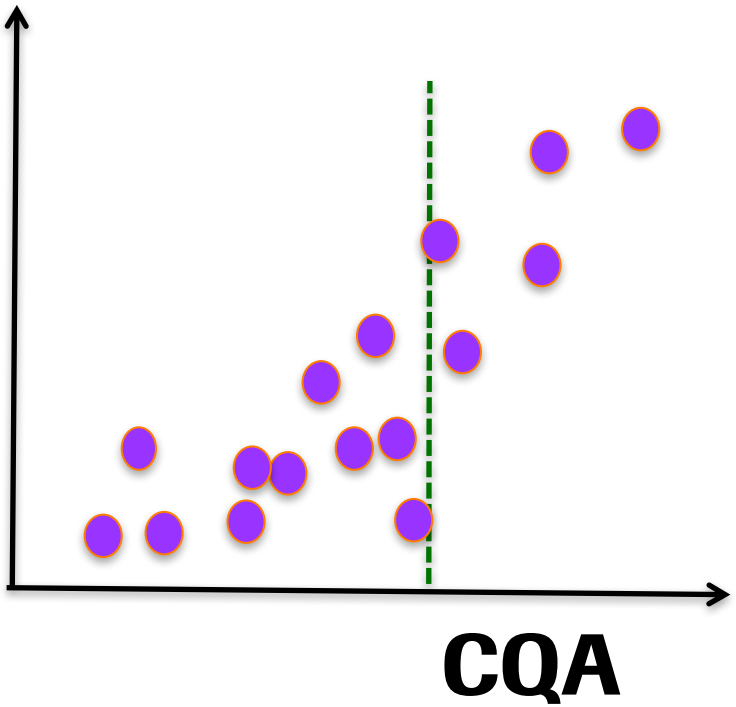

CQA vs. PP

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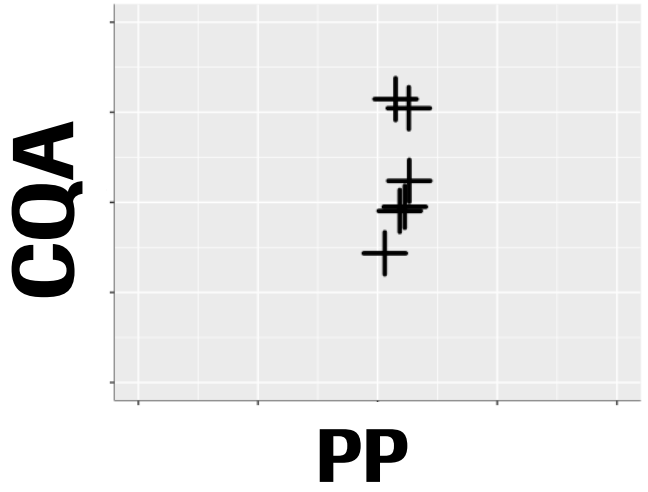

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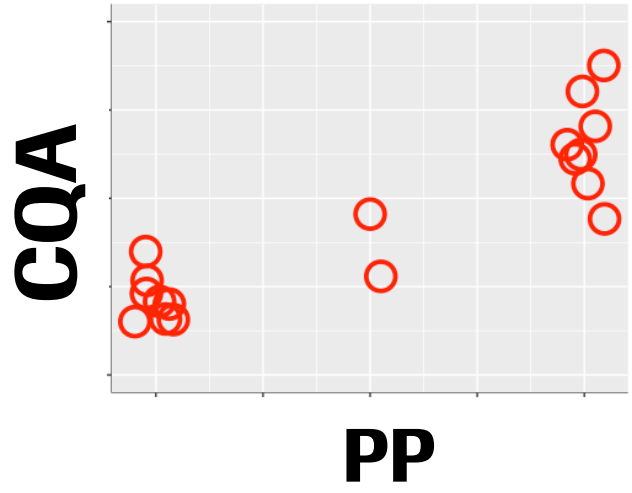

Critical Process Parameter (CPP) Identification

Critical Process Parameter (CPP):
A process parameter 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.

International Conference on Harmonization, ICH Q8 R1, November 2008

CPP Identification

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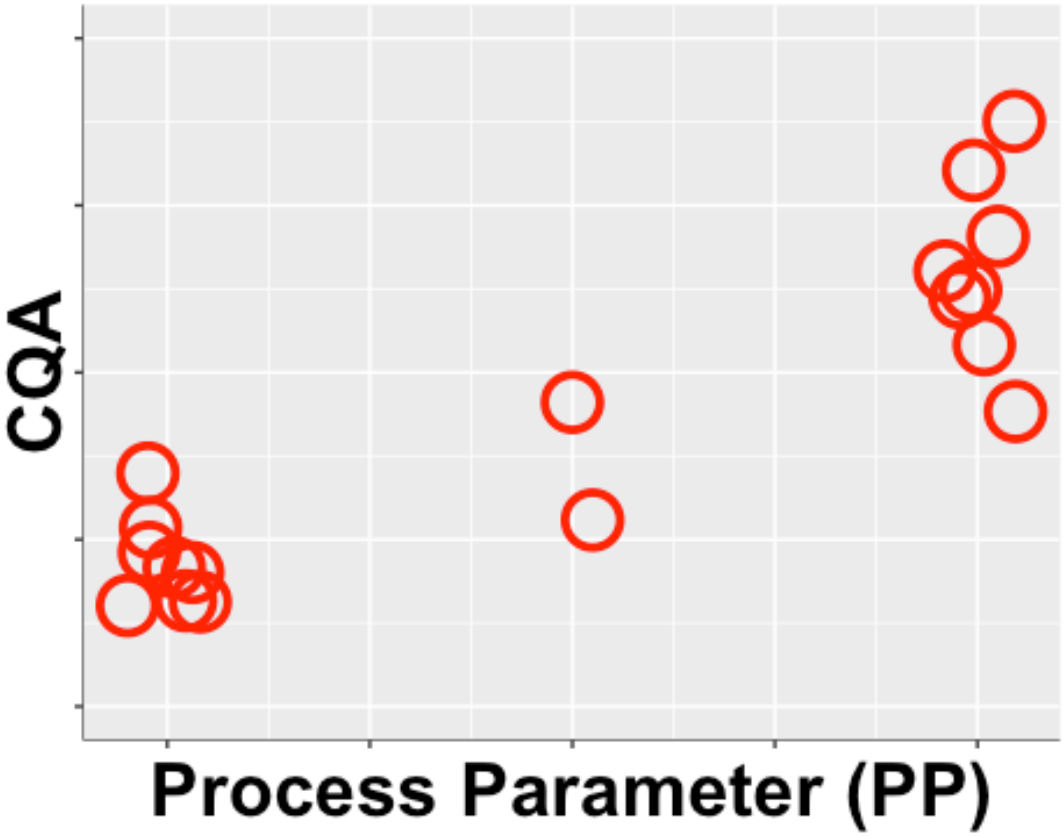
Is this PP a CPP for this CQA?

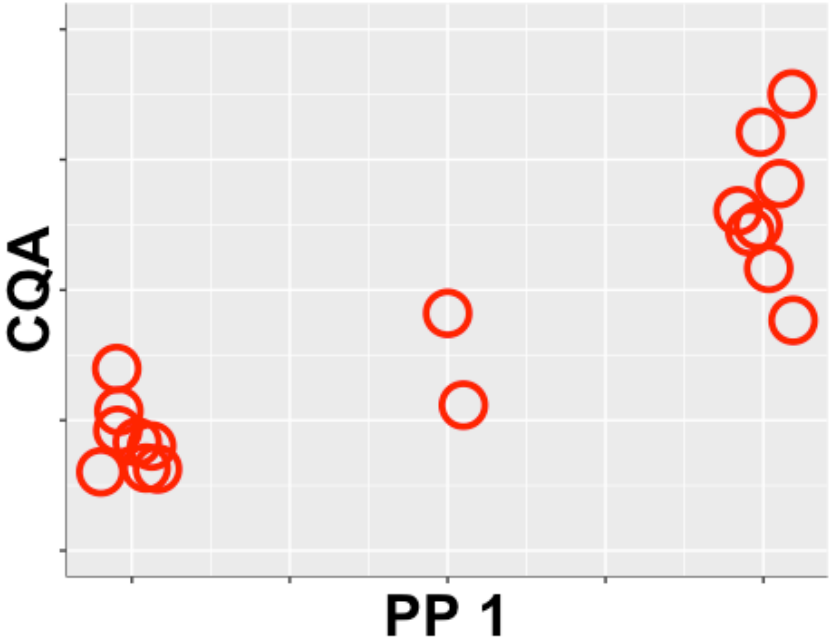


International Conference on Harmonization, ICH Q8 R1, November 2008

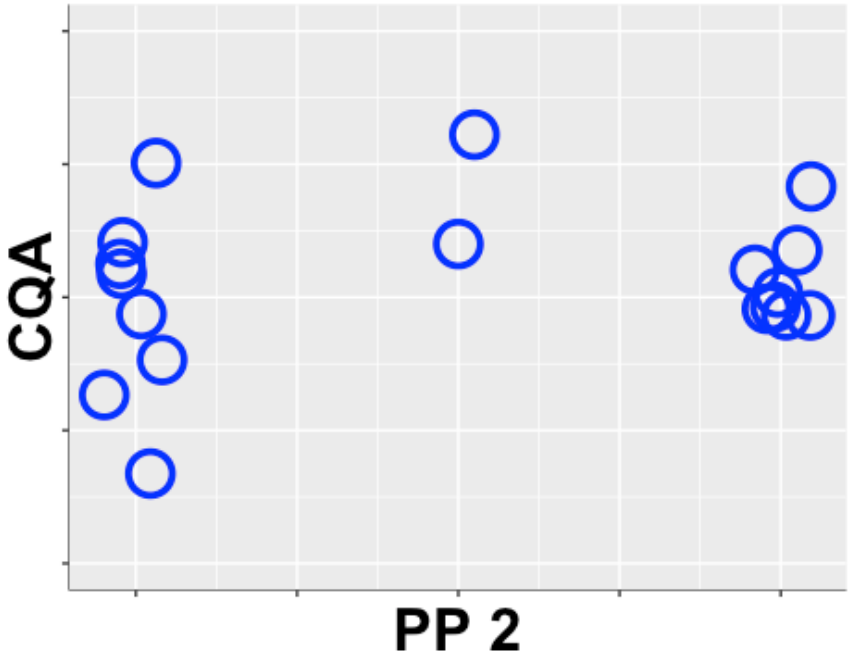
CPP Identification

Critical Process Parameter (CPP): A process parameter whose **variability** has an **impact** on a critical quality attribute …

Is this an impact?



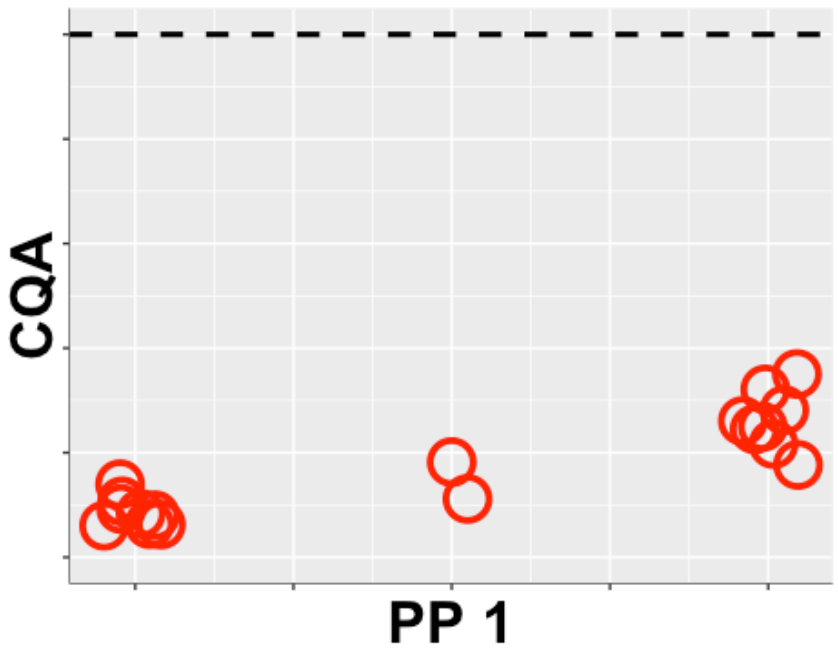
Is this?

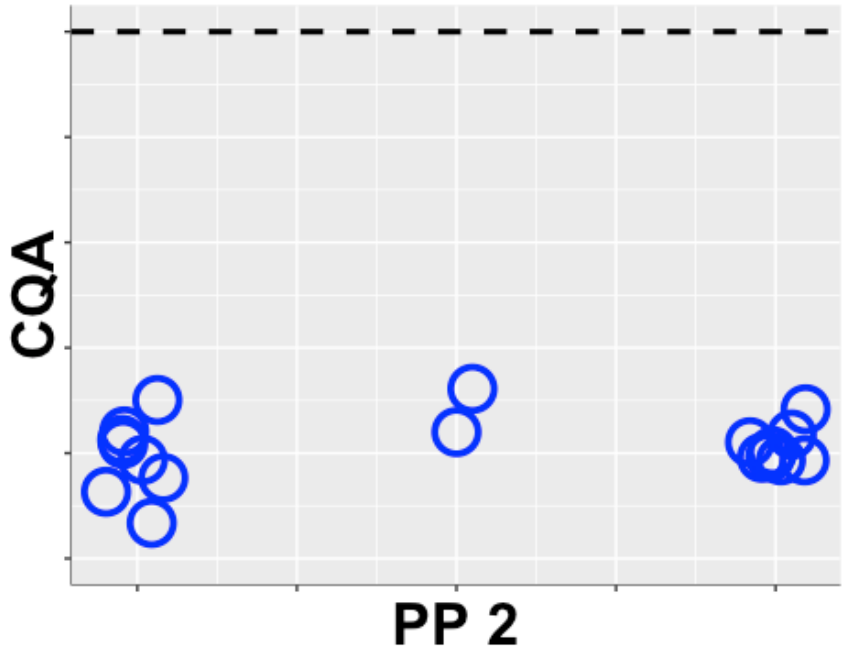


What is meant by variability?

CPP Identification

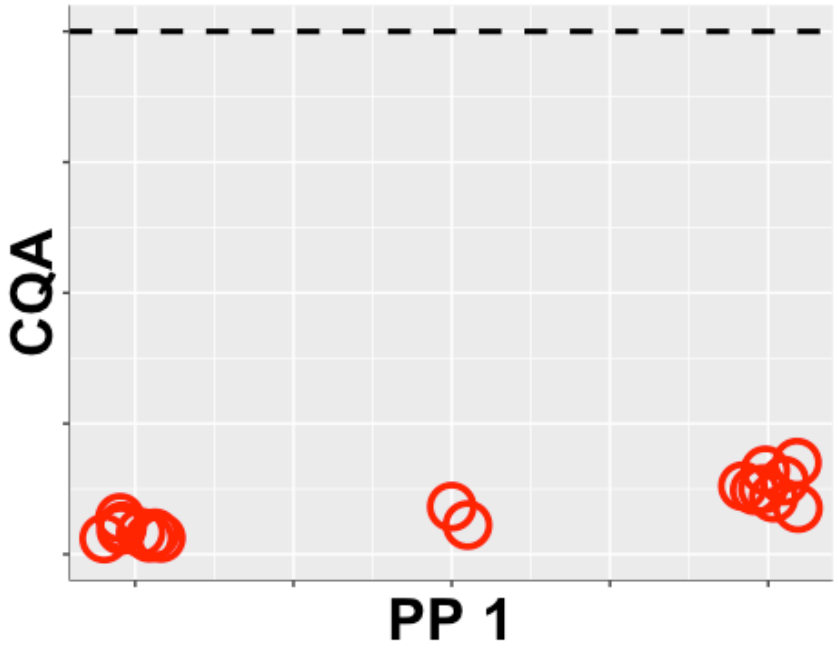
What if the limit is 5?

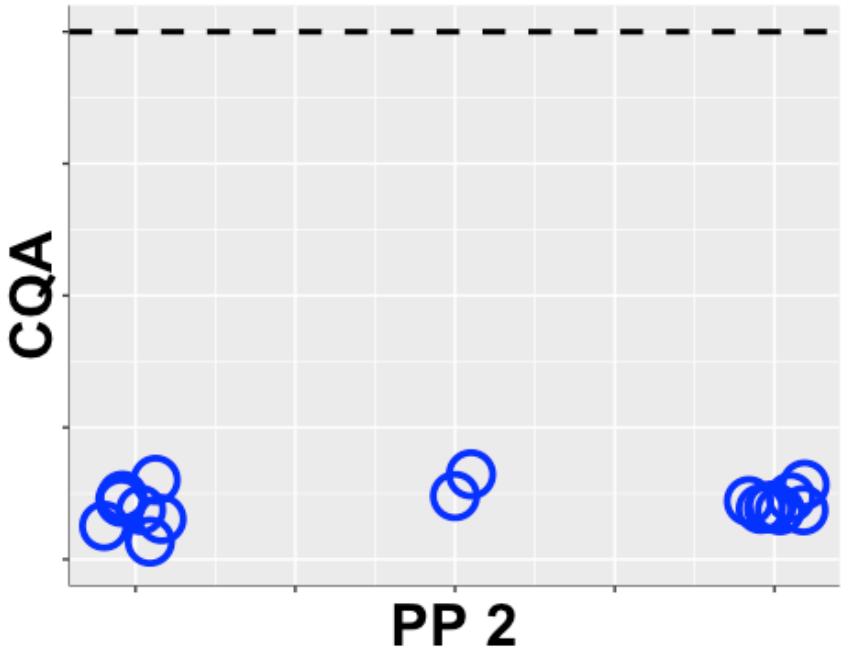




CPP Identification

What if the limit is 10?



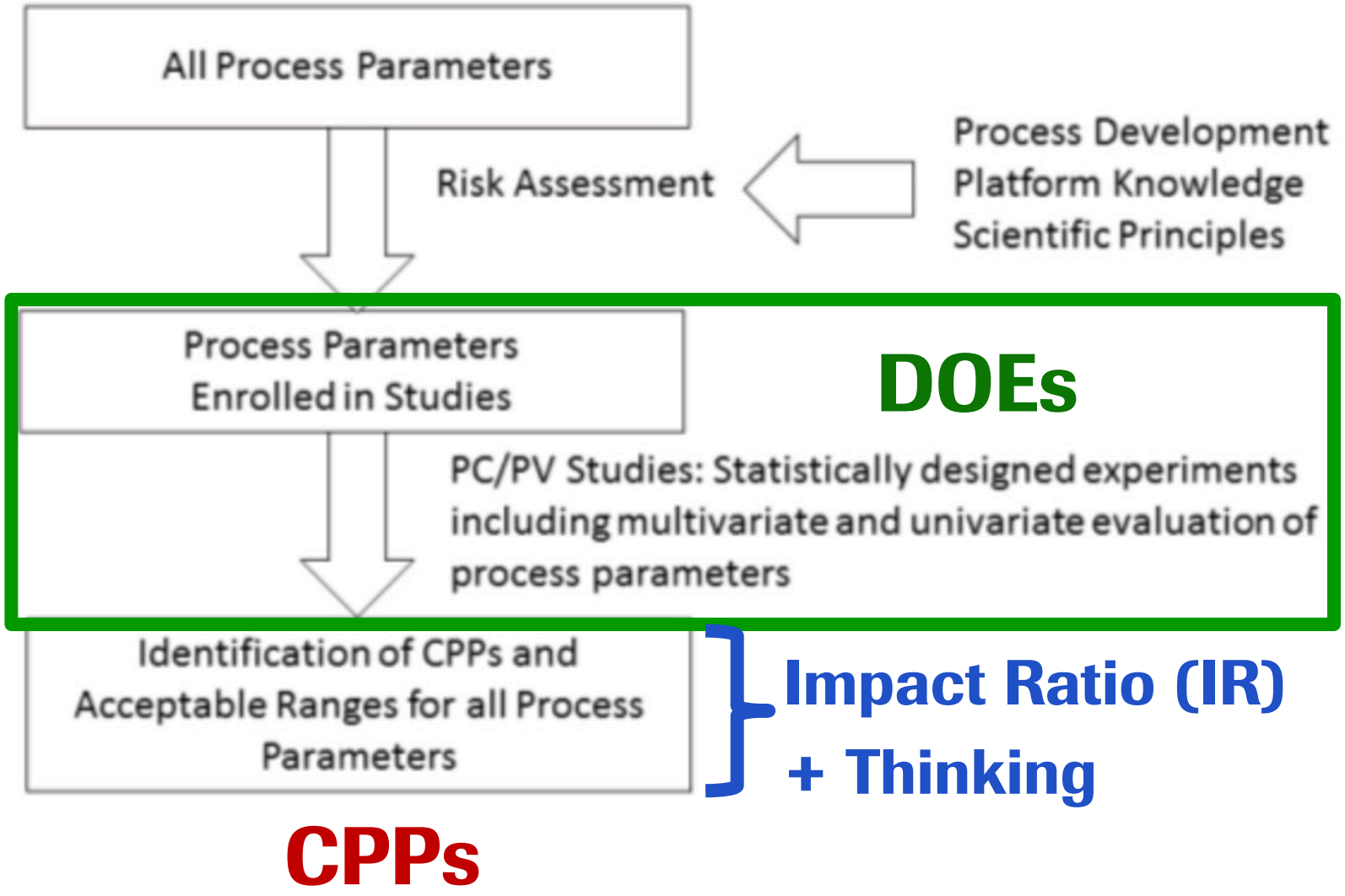


Is this a steep slope?

http://straightchuter.com/wp-content/uploads/2009/03/am_couloir_snow.jpg Photo by Brad Barlage

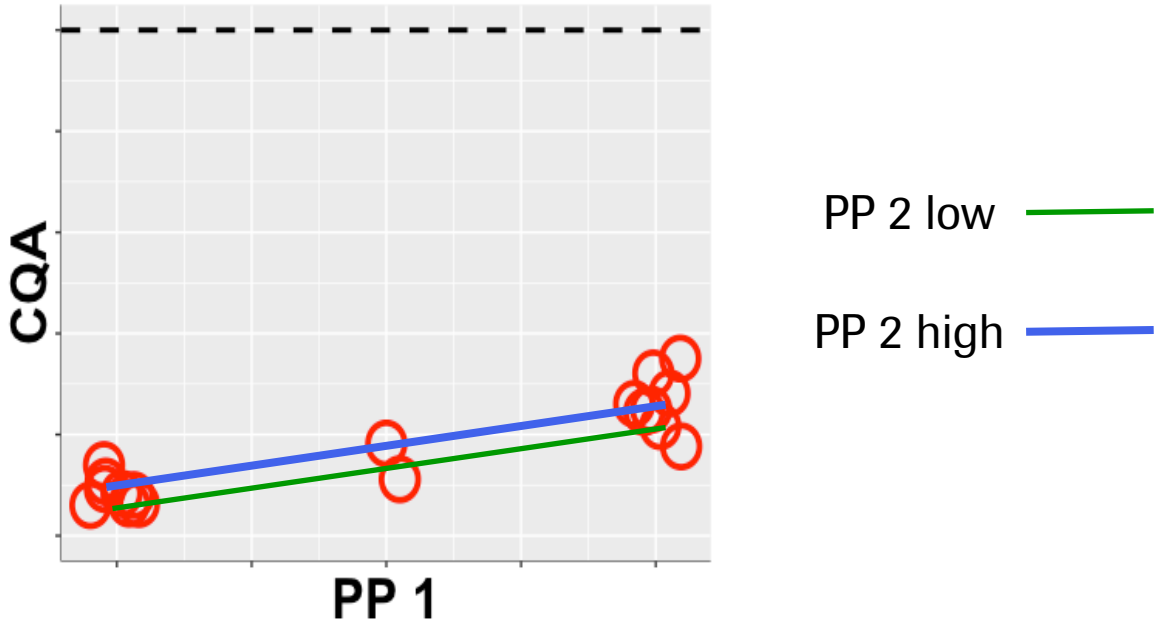
DOEs to CPPs with the end in mind

CPP Identification



Impact Ratio: Simplest Case

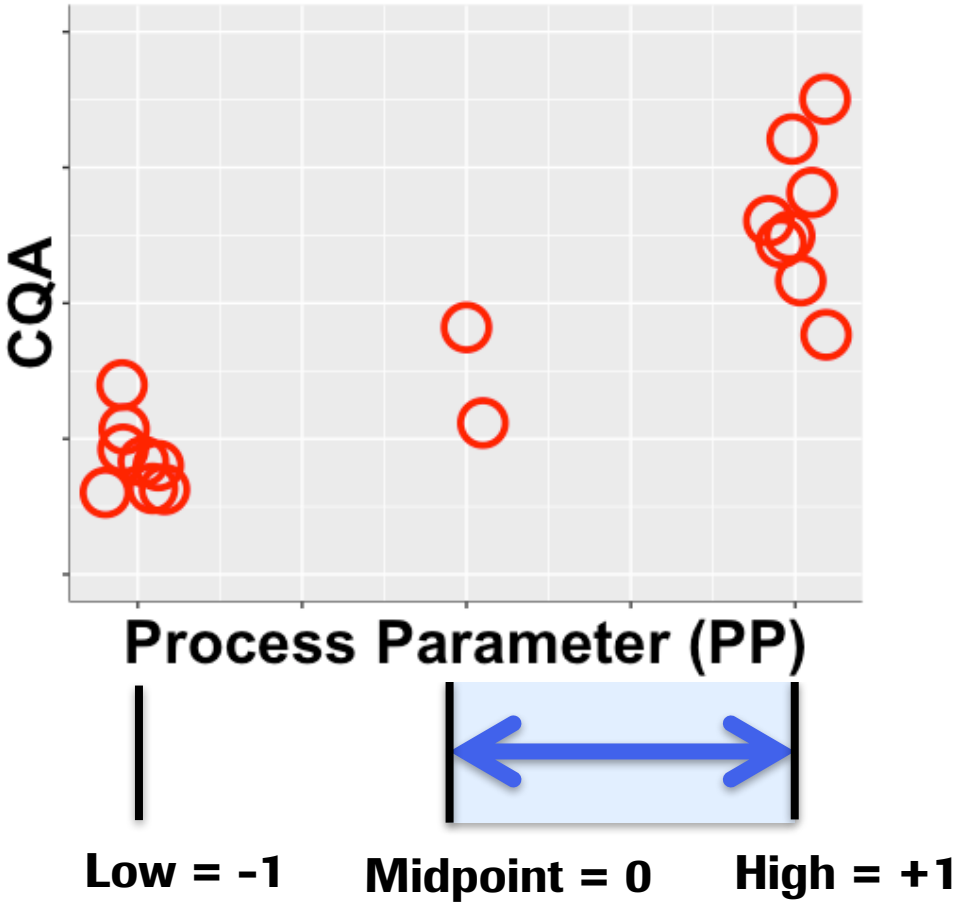
- One-sided upper limit
- No interaction, quadratic effects.



Impact Ratio: Variability

CPP: A process parameter whose **variability** has an **impact** …

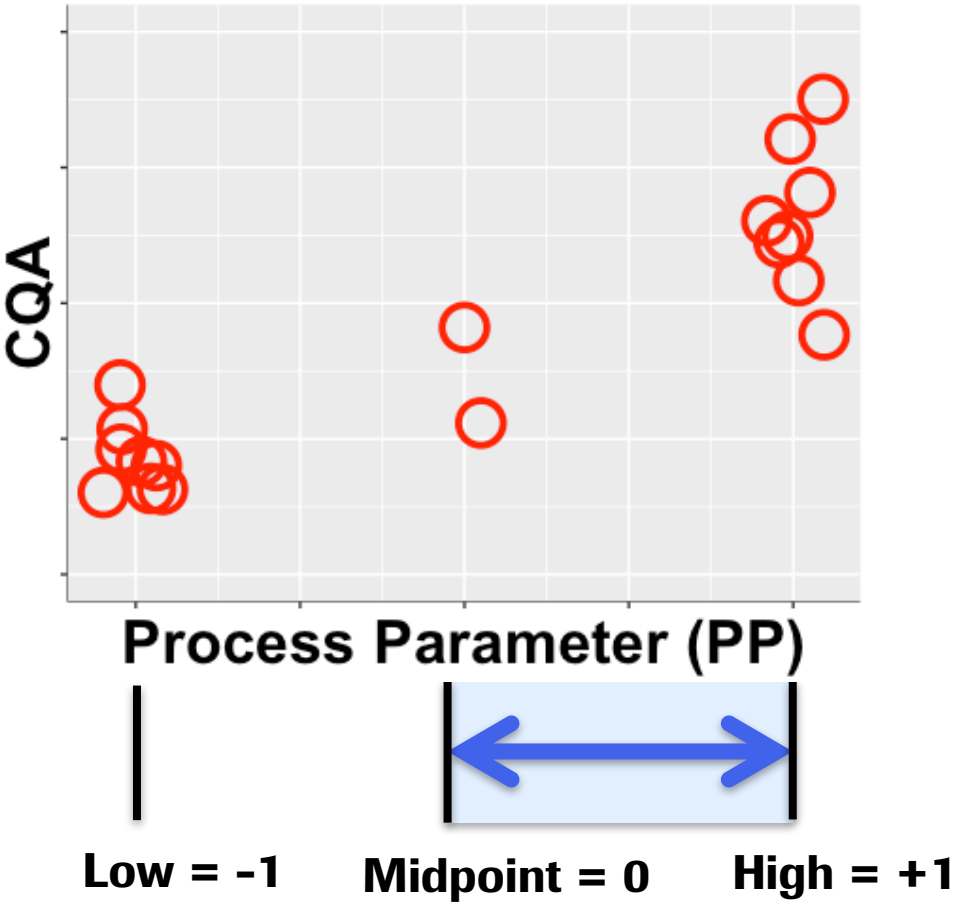
- Systematic process parameter change
- Designed experiments (often **DOE** (multifactor)
- PP range is **relevant test range** (often nominal PAR)



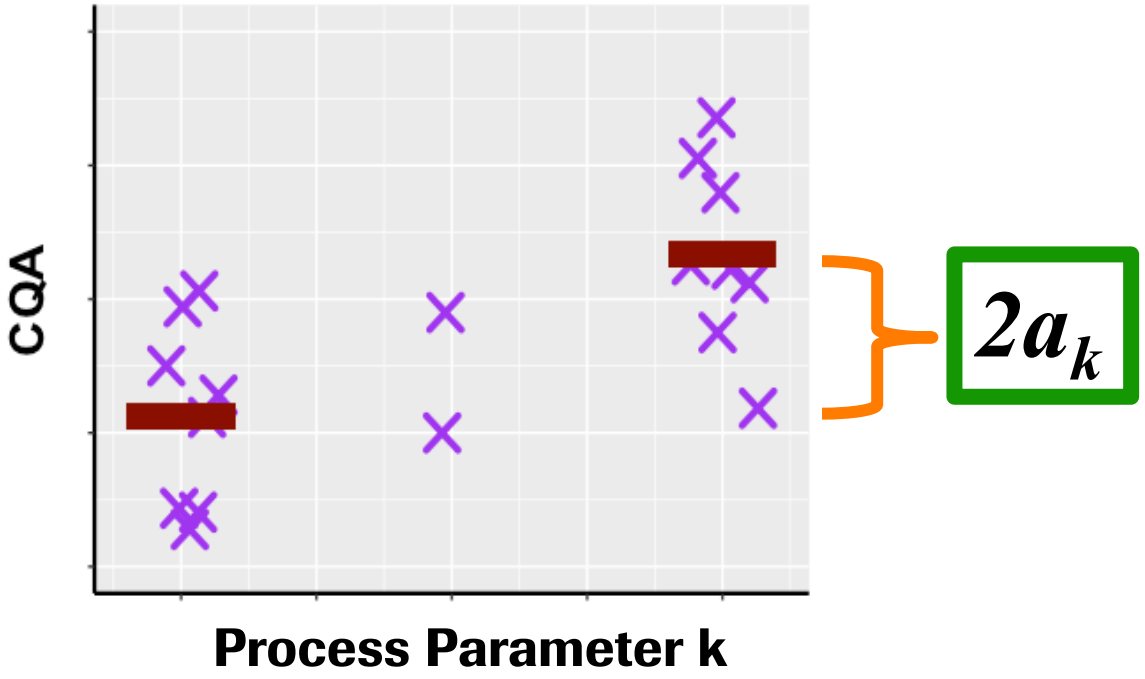
Impact Ratio: Variability

CPP: A process parameter whose **variability** has an **impact …**

- **Relevant test range** based on science, engineering
  (often: nominal PAR, wider than NOR)
- Focus on change from midpoint to the edge (**halfway across**: keeping end in mind)
- Coded -1 to 1



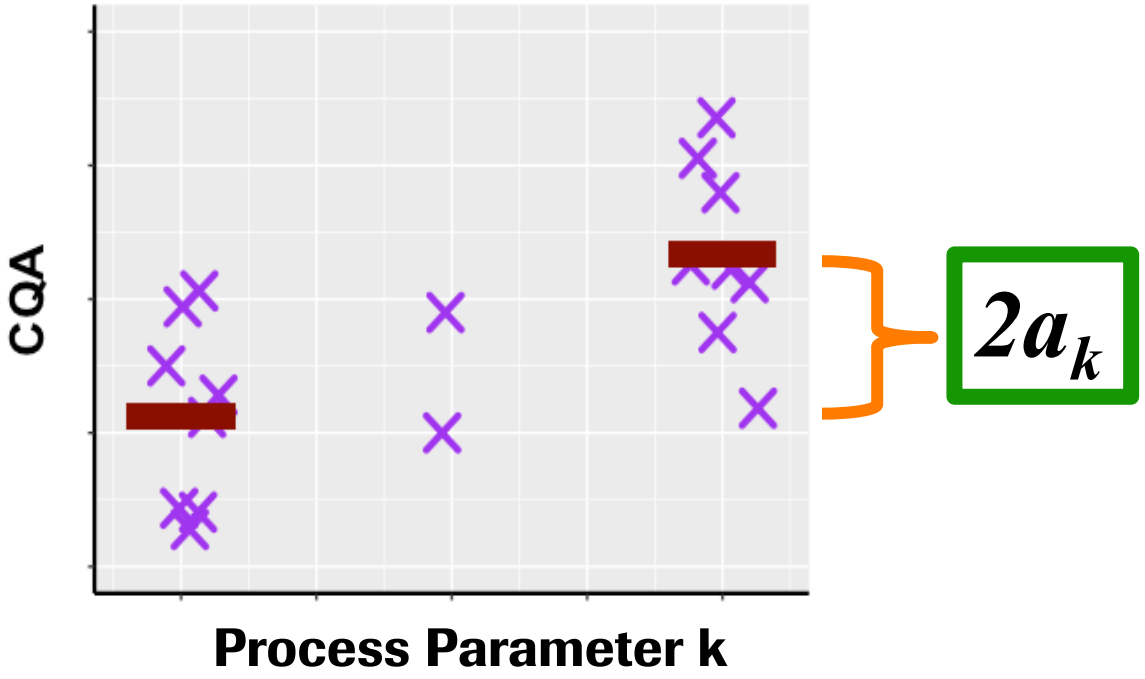
Impact Ratio: Variability → DOEs



Goals:

- **Effect Estimates**
- Confirm PP ranges

Impact Ratio: Variability → DOEs

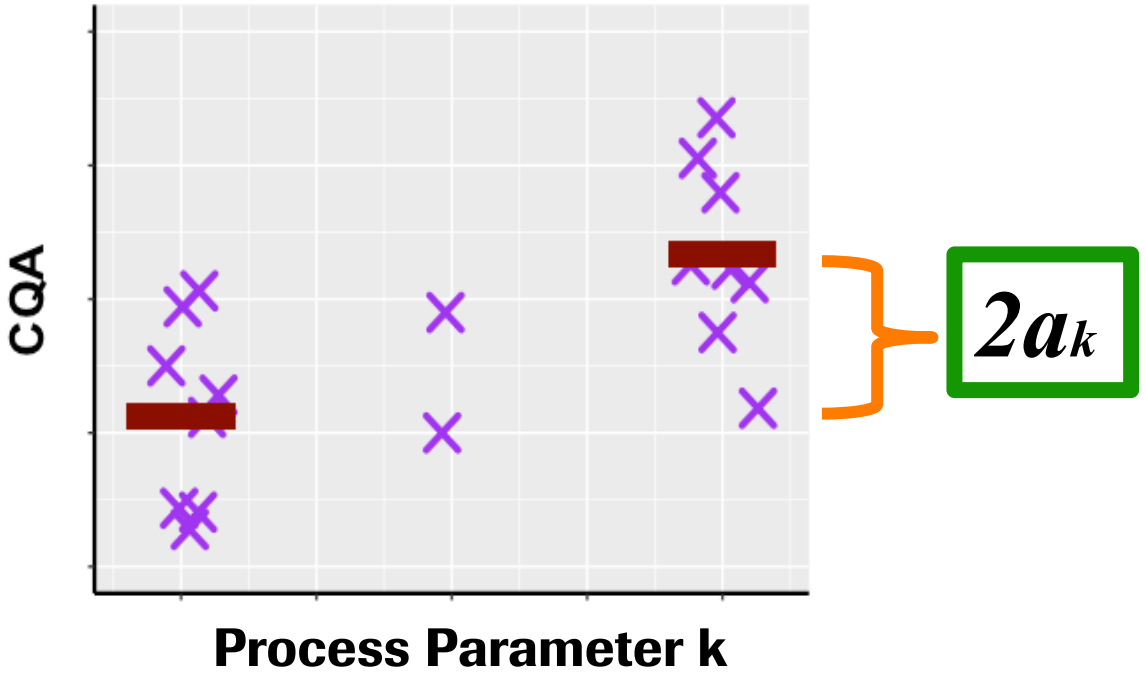


Goals:

- **Effect Estimates**
- Confirm PP ranges

- Qualified scaledown system (mostly)
- Often orthogonal, multifactor statistical DOE:
  - 10-40 runs, classicial designs
  - Full- or fractional-factorial (2^n, 2^{n-k})
  - Plackett-Burman screening PB12, PB20
  - Blocking, split plotting as needed.

Impact Ratio: Variability → DOEs



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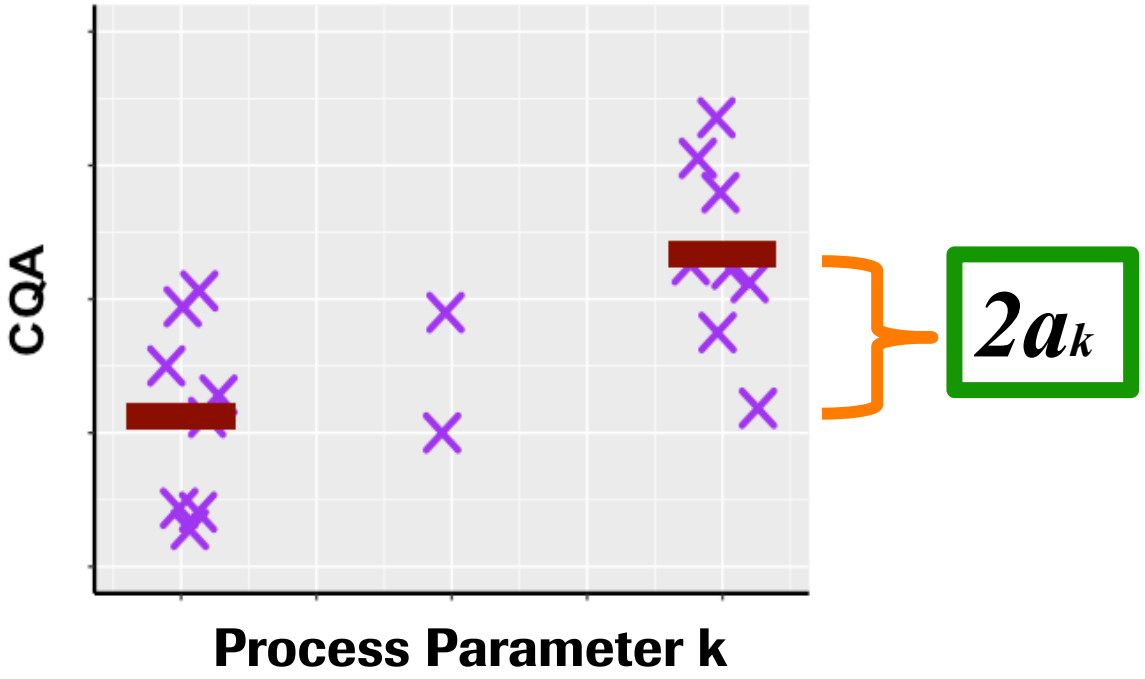
- Often 2-3 DOE per unit op
  - Sequential, parallel strategies
- 100s of DOE class alumni

Impact Ratio: Variability → DOEs



Goals:

- **Effect Estimates**
- Confirm PP ranges

What we DON'T do:

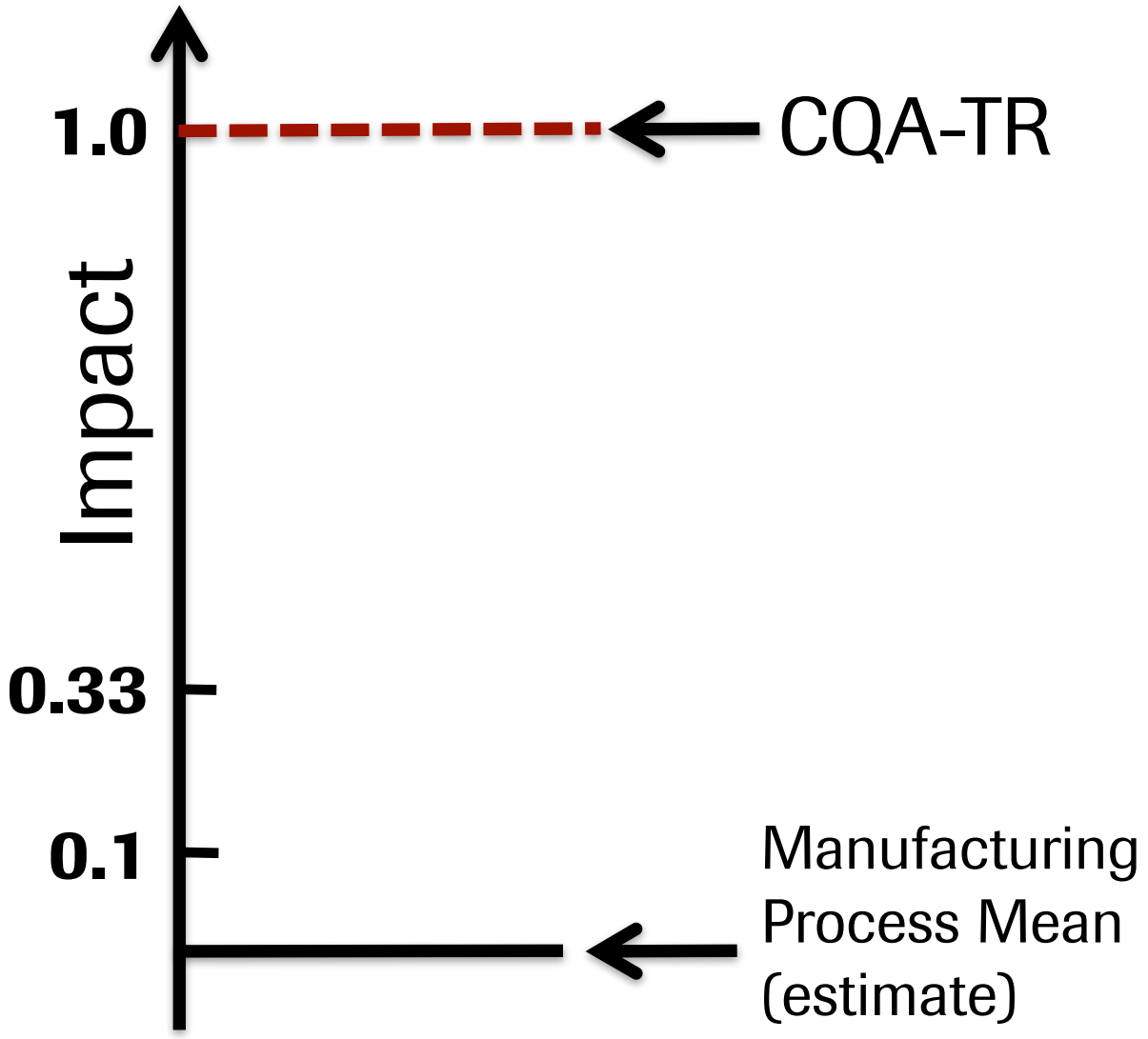
- Null Hypothesis Significance Tests (no p-value cutoffs!)
- Regression model selection
  - We use orthogonal designs, goal is effect estimates

Impact: Manufacturing reference frame defines **practical significance**

What CQA change is meaningful?

CQA frame of reference:
Manufacturing mean to CQA-TR

CQA-TR: A CQA limit for this unit operation.



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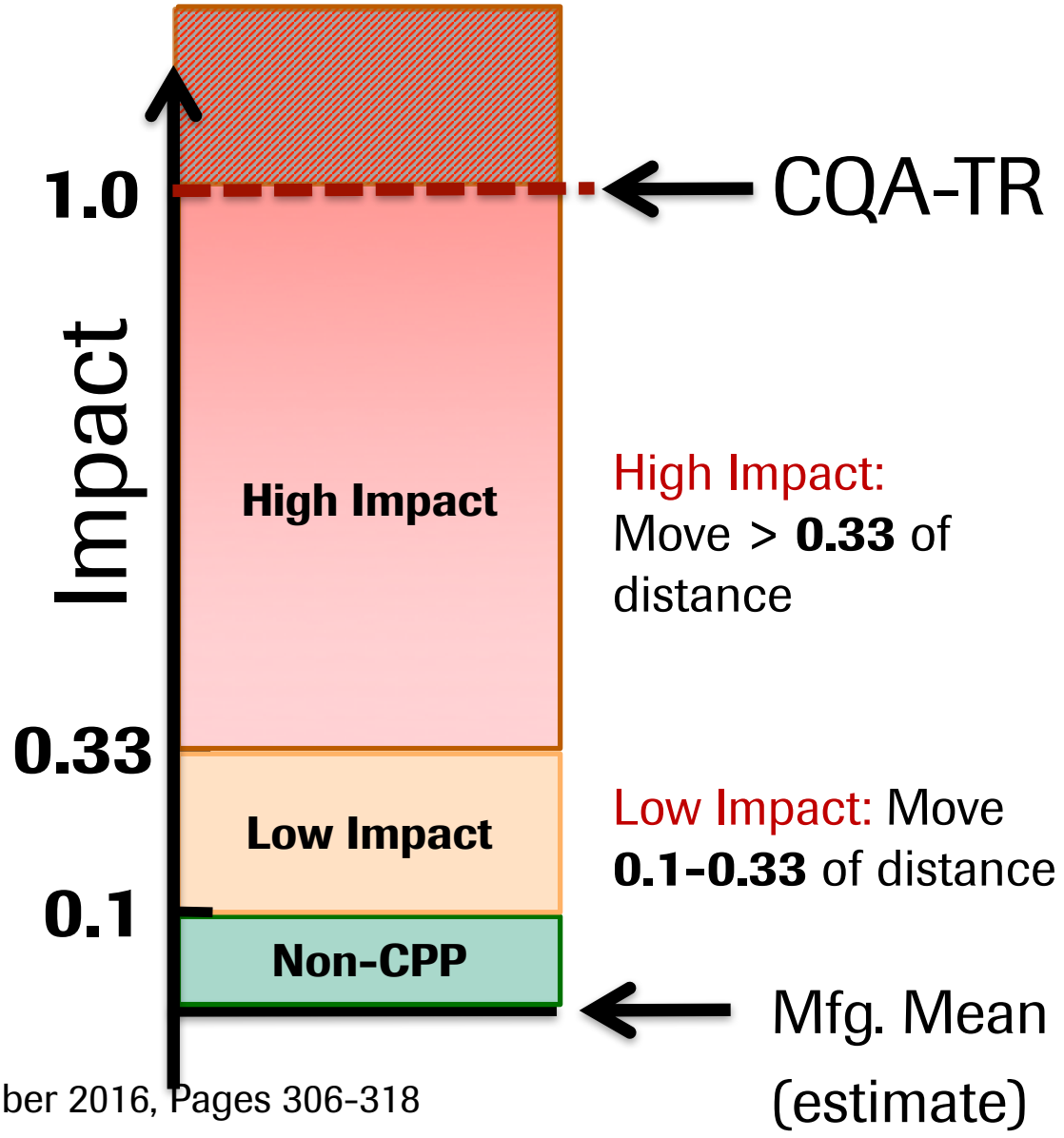

Biologicals, Vol 44, issue 5 September 2016, Pages 306-318

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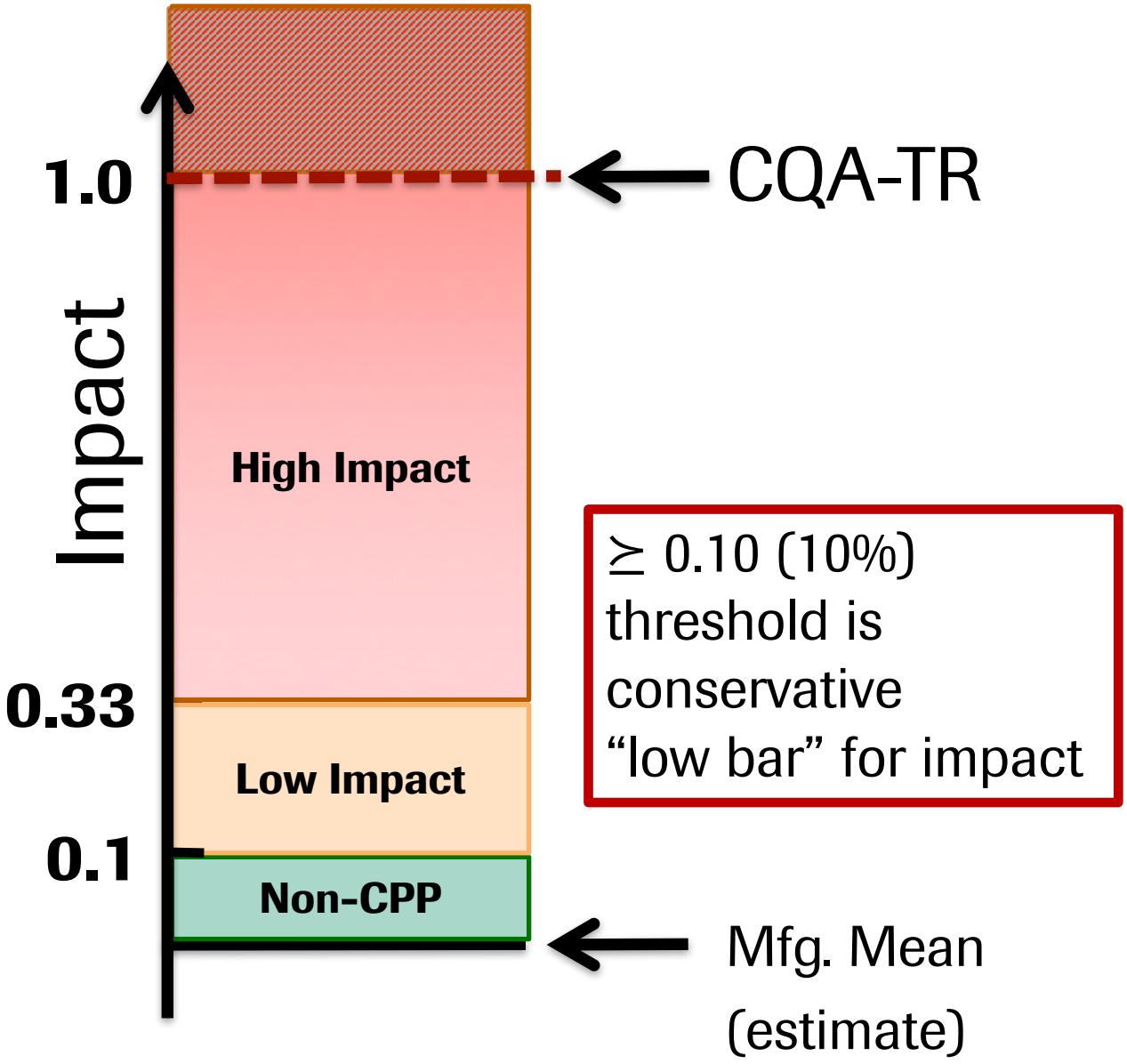

Impact Ratio Formula: Simplest Case

kth PP on a CQA, one unit op, main-effects-only DOE

$$\text{Impact Ratio} = \frac{|\ a_k\ |}{|\ \text{Process Mean} - \text{CQA}_{TR}\ |}$$

- | | means absolute value → range is [0,∞) (Usually < 1)
- a_k **effect estimate** for the main effect of factor k (kth PP)
  - Systematic factor change
  - Midpoint to edge (½) of relevant test range
  - Measured w/ **qualified scaledown system**
- **Denominator: Manufacturing Frame of Reference**
  - **Process Mean estimated from large scale data**
  - CQA_{TR} = CQA-TR is based on CQA acceptance criteria
  - Same for all PP for a unit op CQA

Impact Ratio Formula: Simplest Case

k^{th} PP on a CQA, one unit op, main-effects-only DOE

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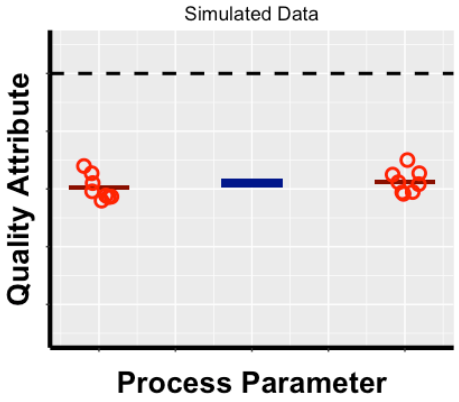
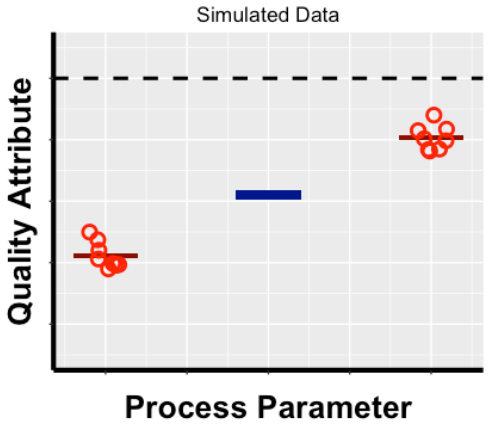
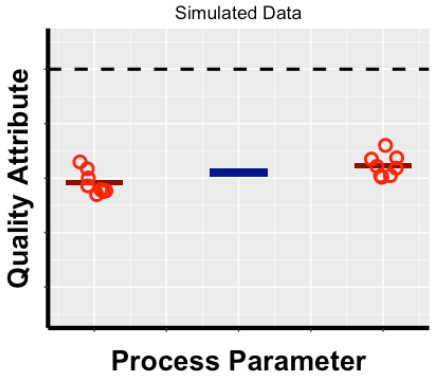


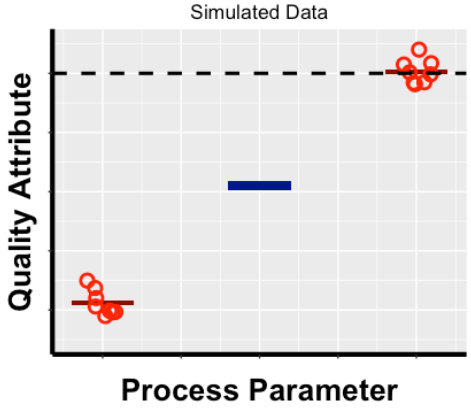
IR = 0.05
Non-CPP



IR = 0.5
High Impact
CPP



IR = 0.1
Low Impact
CPP



IR = 1.0
High Impact
CPP

Impact Ratio Formula: Simplest Case

k^{th} PP on a CQA, one unit op, main-effects-only DOE

$$\text{Impact Ratio} = \frac{|\, a_k \,|}{|\ \text{Process Mean} \ - \ \text{CQA}_{\text{TR}}\ |}$$

Standardized assessment

Typical BLA: 100s of PP impacts to assess

This IR standardizes assessment across CQA, PP, unit ops

- All IRs assessed against standard thresholds (0.1, 0.33)
- Adds efficiency, objectivity

Impact Ratio Formula: Simplest Case

For k^{th} PP on a CQA for one unit op, main-effects-only DOE

$$\text{Impact Ratio} = \frac{|\ a_k\ |}{|\ \text{Process Mean} - \text{CQA}_{\text{TR}}\ |}$$

- Quantitative metric / engineering calculation
- **Not** an appealing statistical object
- **Is** relevant, meaningful, useful
- Depends on CQA-TR, which depends on:
  - Specification, which unit op, process knowledge
  - **May change with spec negotiation!**

Impact Ratio Formula: Details

k^{th} PP on a CQA, one unit op, main-effects-only DOE

$$\text{Impact Ratio} = \frac{|\ a_k\ |}{|\ \text{Process Mean} - \text{CQA}_{\text{TR}}\ |}$$

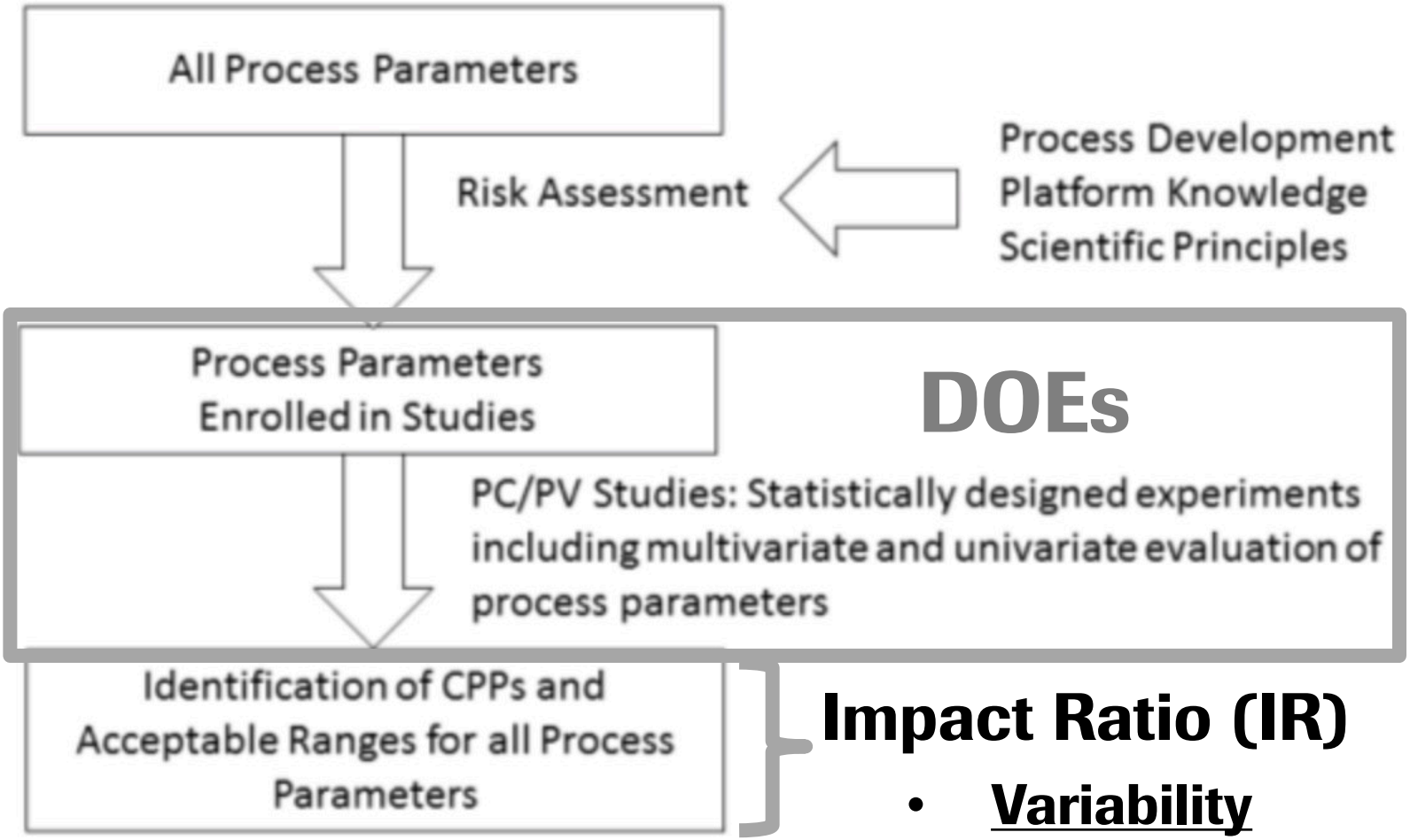
What are CPPs for a unit operation?

- Not CPP for any CQA
  - → treat as non-CPP
- Low-impact CPP for 1 or more CQA, not high-impact for any CQA
  - → treat as low-impact CPP
- High-impact CPP for 1 or more CQA
  - → treat as high-impact CPP

If N experiments for unit op: often IR ← max $\{IR_n\}$

Special cases: Hold studies, equipment constraints, off-center target … **Keep the end in mind!**

CPP ID Includes Thinking



CPP ID Includes Thinking

"CPPs may be added or the designation changed to high-impact by subject matter experts to provide additional process control and monitoring or based on process knowledge beyond the process parameter acceptable range."

Identification of CPPs and Acceptable Ranges for all Process Parameters

CPPs

Impact Ratio (IR)

- Variability
- Impact

+ Thinking

IR Calculation: Beyond the Simplest Case

Increased complexity when the DOE and regression model include interactions and/or quadratic effects.

$$CQA = a_0 + a_1(x_1 - m_1) + a_2(x_2 - m_2) + \cdots + a_{11}(x_1 - m_1)^2 + \cdots + a_{12}(x_1 - m_1)(x_2 - m_2) + \cdots$$

$$\text{Impact Ratio} = \frac{|a_j| + |a_{1j}| + |a_{2j}| + \cdots + |a_{mj}| + \cdots}{|\ \text{Process Mean} - \text{CQA–TR}\ |}$$

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$$\text{Impact Ratio} = \frac{|a_j| + |a_{1j}| + |a_{2j}| + \cdots + |a_{mj}| + \cdots}{|\ \text{Process Mean} - \text{CQA–TR}\ |}$$

- **No intuitive practical interpretation** of numerator as "max CQA change due to moving PP"
- **No simple statistical interpretation**
- Only larger coefficients are included (use IR thresholds)
  - Not intuitive, complicated to compute

IR in CPP ID

Advantages

- Leverages robust experimentation (DOE, replication) to measure impact
- Standard assessment across CQA, PP and unit operations
  - Adds efficiency, objectivity
- Conservative CPP threshold of IR > 0.1 (10%) provides assurance
- **Keeps the the end in mind**
  - Manufacturing reference frame - practical significance - no p-values!

    Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold."

    - ASA Statement on p-values
  - Thinking – can add/upgrade PP

    "There is no substitute for thinking"

    - Mrs. L. Swaggerty, Palo Verde Elementary School

IR in CPP ID

Disadvantages (of current IR formula(s))

- With off-center target, two-way interactions, curvature:
  - Can't interpret IR as "max CQA change due to moving PP"
  - Lacks clear statistical interpretation
  - Not intuitive & complicated to compute
- Even in the simple case, IR depends on CQA-TR (and so to specification) that may change
  - PP status change → control system change ("pain point")

Looking back & ahead

- Impact Ratio used in multiple BLA filings
  - With and without design space claims
- Changes coming – QbD tools will adapt:
  - Goals to improve, simplify tools
  - ICH Q12 “Established Conditions”
  - Shorter timelines & development strategies
- IR formula revisions under discussion…
  - One level, instead of “Low/High impact”
  - Knowledge sharing with small molecule specialists

CPP identification by DOE, IR & Thinking

- Looking ahead to **simplify, adapt** but retain strengths:
  - **Robust DOEs** measure relevant factor effects
  - Impact Ratio (IR) gives **standardized assessment**
  - **Meaningful frame of reference**
  - **Thinking**: subject-area, business knowledge complements IR

HA Communications

- Statisticians can & should get involved
  - We can bring clarity to work and the interactions
- Partnership with shared goal:

Safe, efficacious and reliable supply of medicines for patients

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