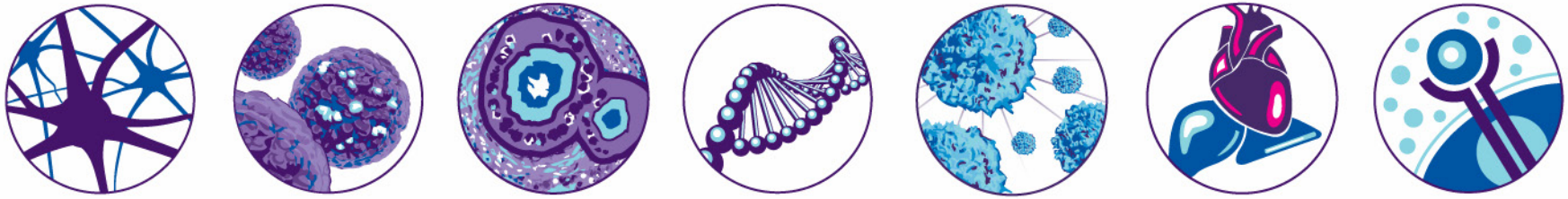

A Structured Statistical Approach to Aid the Assessment of Process Parameter Criticality

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WORLDWIDE RESEARCH & DEVELOPMENT
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Criticality Designations and Control Strategy

- Assessing Criticality of Quality Attributes and Process Parameters is an Important Part of the Overall Control Strategy for Drug Substances and Drug Products.
- Definitions from ICH Q8(R2):
  - 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.*
  - 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.*
- In Practice, Assessing CQAs is Relatively Straightforward, but Assessing CPPs Can be Challenging.

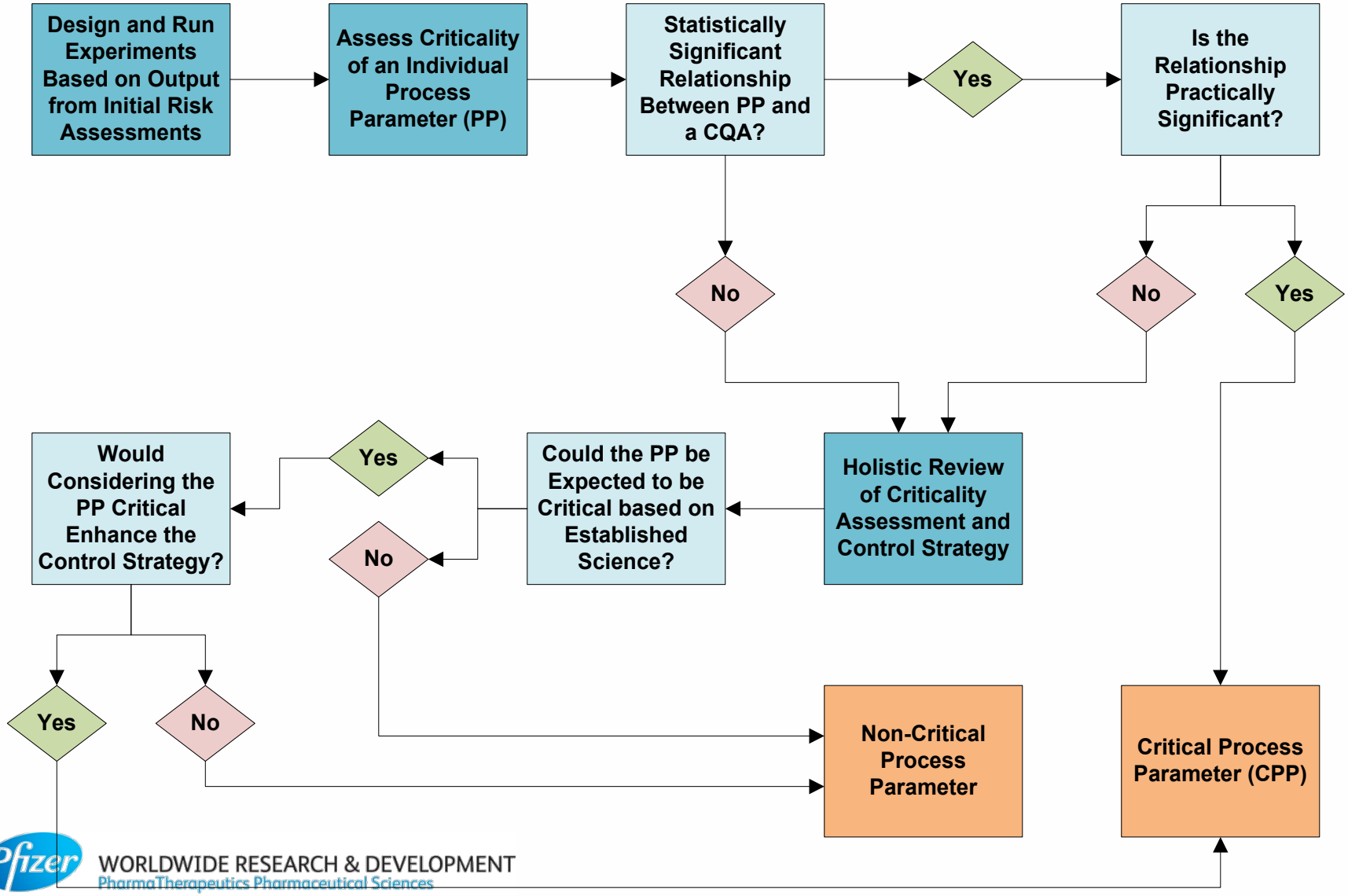
Challenges with Assessing Parameter Criticality

- Parameters Need to be Viewed Individually but also Within the Entire Control Strategy.
  - Overly Aggressive Approaches Can Ignore Important Parameters.
  - Overly Conservative Approaches Can Bury Important Parameters in a Large Group of Relatively Unimportant Parameters.

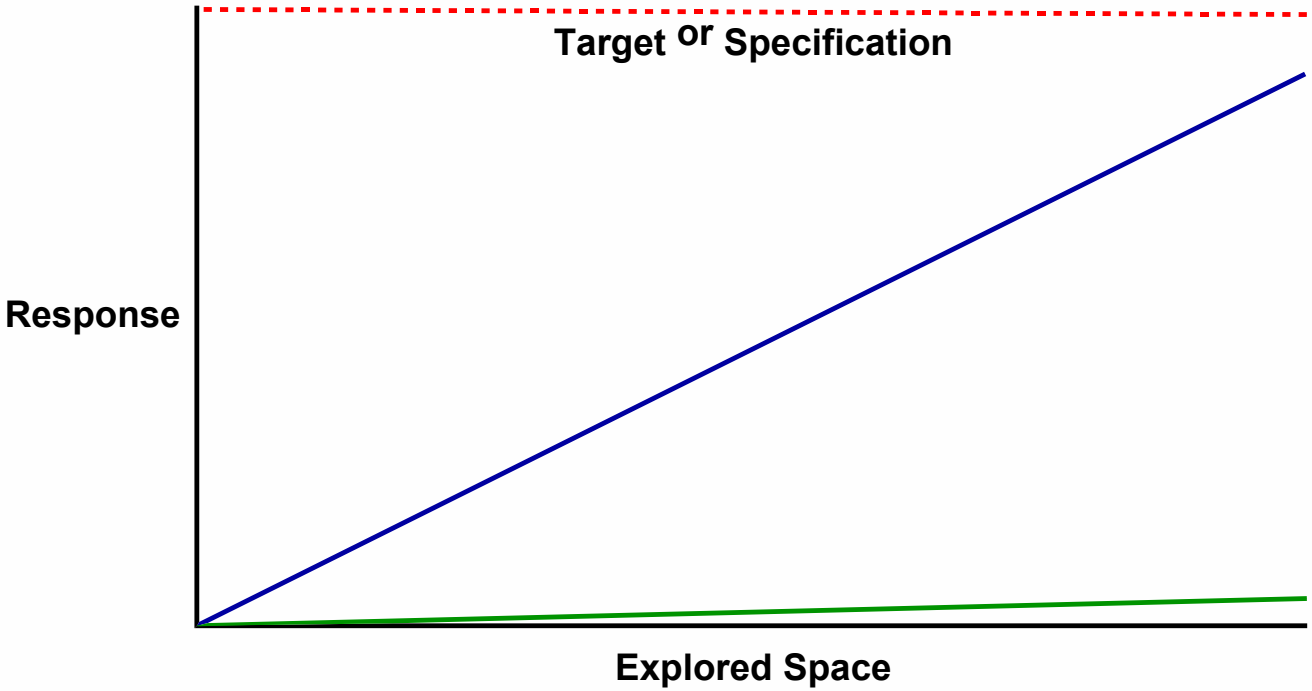
- Parameter Criticality is Determined using Risk Assessment, Experimental Investigation, Established Science or a Combination of these.
  - Approaches that Rely Too Heavily on Risk Assessments (i.e. Numerical Rankings) Can be Inconsistent from Team to Team.
  - Approaches that Rely on Rigid Statistical Evaluations Might Ignore Important Scientific Knowledge.
  - Statistical Approaches Also Require Decisions on Thresholds for "Significance".

- Can We Develop an Approach that Utilizes Statistical Tools for Consistency, While Still Incorporating Scientific Judgment and a Holistic View of the Control Strategy?

Criticality Assessment Decision Tree



Challenges with Statistics and Criticality



- Green and Blue Lines are Both Statistically Significant
- Blue Line is Practically Significant - Green Line is Not
- Simply Assessing Statistical Significance is Not Adequate
  - Does Not Consider the Strength of the Relationship
  - Some Assessment of Practical Significance (Impact) is Required

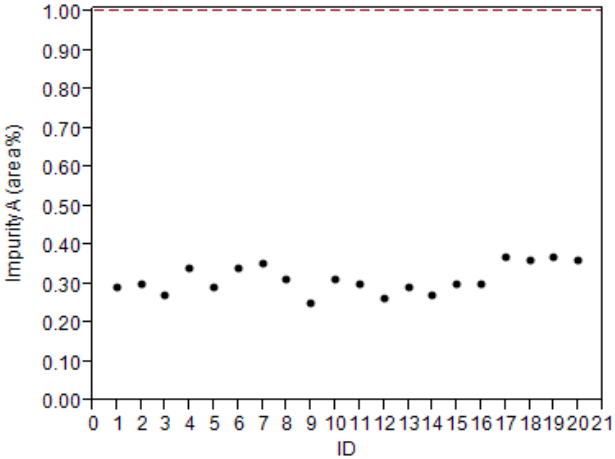
Statistical Tools
- Assessing Practical Significance

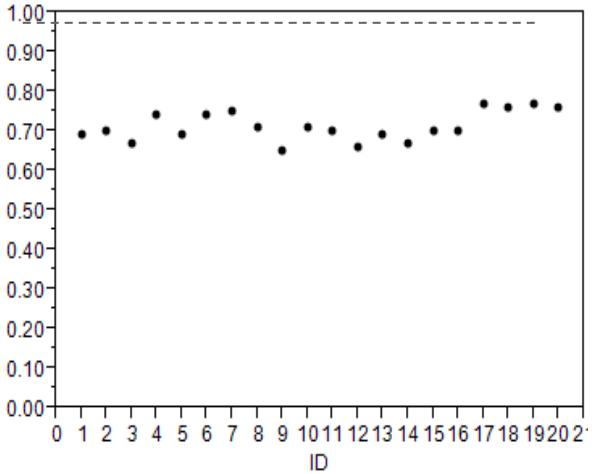
- Process Risk Evaluation (step1)
  - Evaluate a Multivariate Data Set Without Focusing on a Single Parameter
  - Determines How Close Results are to a Target/Specification
  - **Z Score Assessment**
  - Conceptually Similar to a Process Capability Index

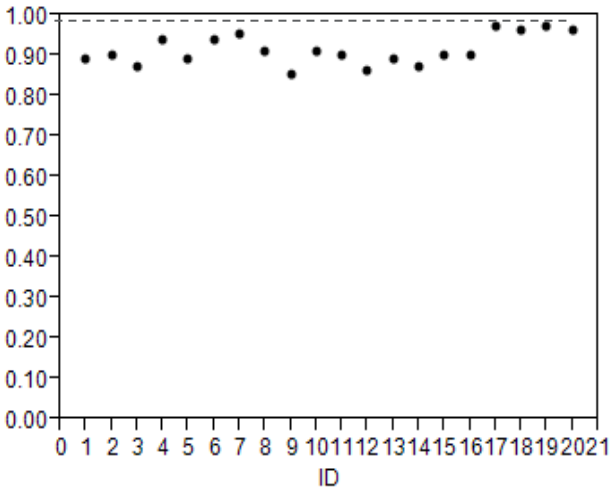
- Parameter Effect Size Calculation (step2- if Necessary)
  - Uses the Fitted Statistical Model to Quantify Individual Parameter Effects
  - Quantifies the Effect Size - Impact of a Parameter on a Response
  - Compares the Effect Size to the Specification (**20% Rule)**

- This Approach
  - Can Be Used with Univariate or Multivariate Experiments
  - Can Be Used with One-Sided or Two-Sided Specifications/Targets

Why Consider Process Risk?





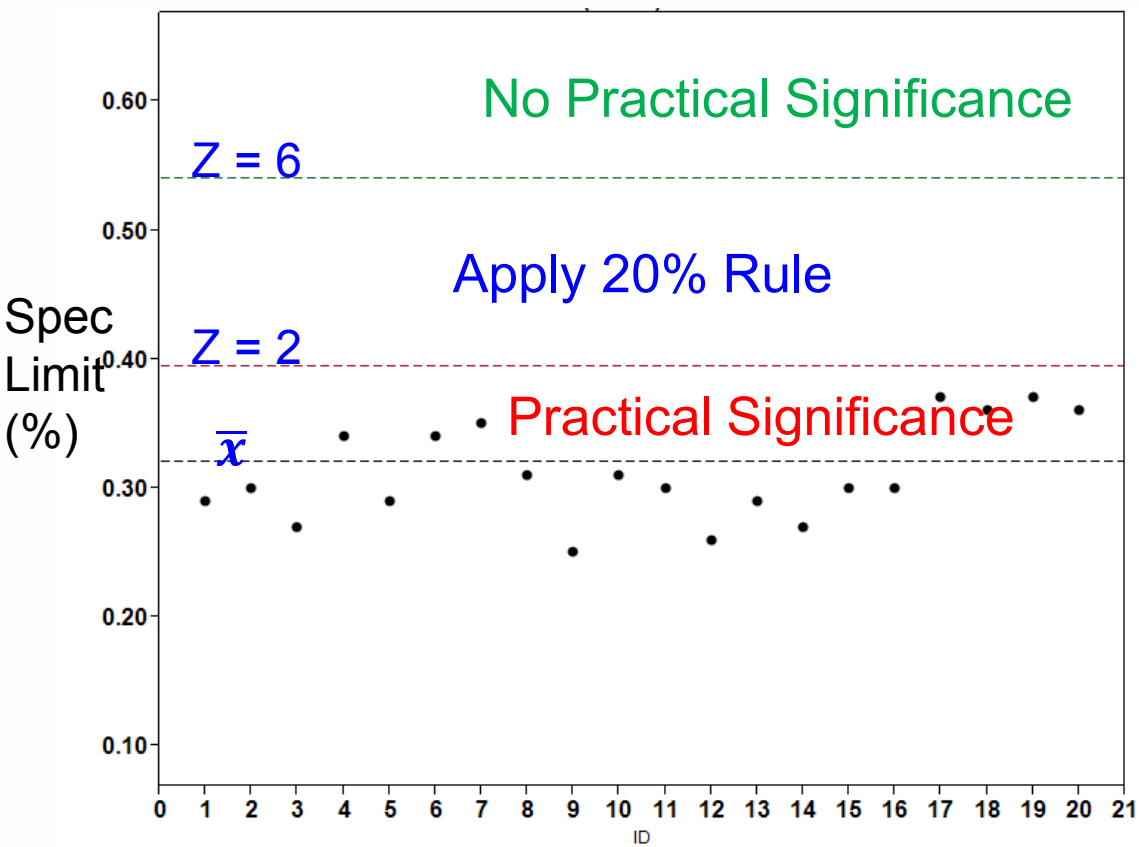


- Data Tight and Far Away from Specification/Target.
- Process is Low Risk.
- **No Parameters are Practically Significant.**

- Data is Neither Close to or Far Away from Specification/Target.
- **Additional Analysis Required (20% Rule).**

- Data Close to Specification/Target.
- Process is at Higher Risk.
- **Every Statistically Significant Parameter is Practically Significant.**

Introduction to the Z Score



$\bar{x}$ = Average of DoE Data
s = Standard Deviation
U = Target or Specification.

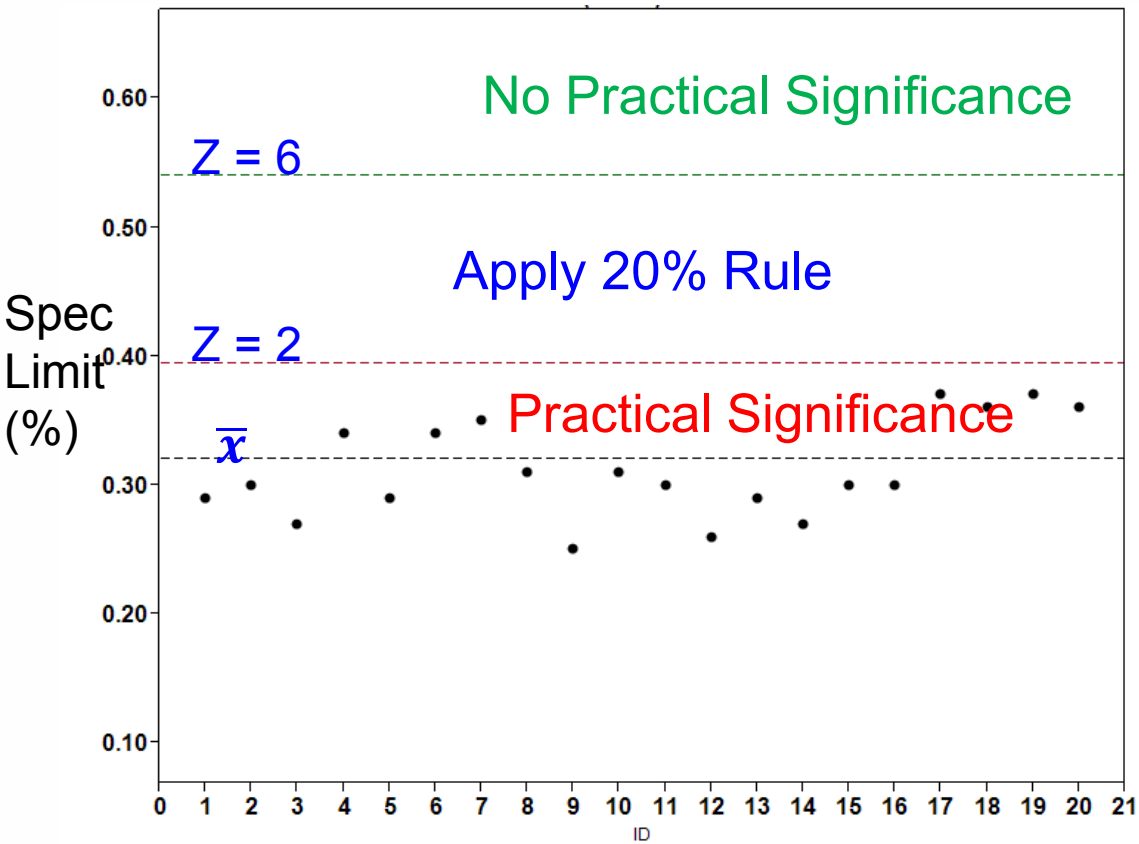
$$Z^* = \frac{U - \bar{x}}{s}$$

Z* = Distance of a Specification to the Data Average in Units of Standard Deviation

Example: $\bar{x}$ = 0.32%

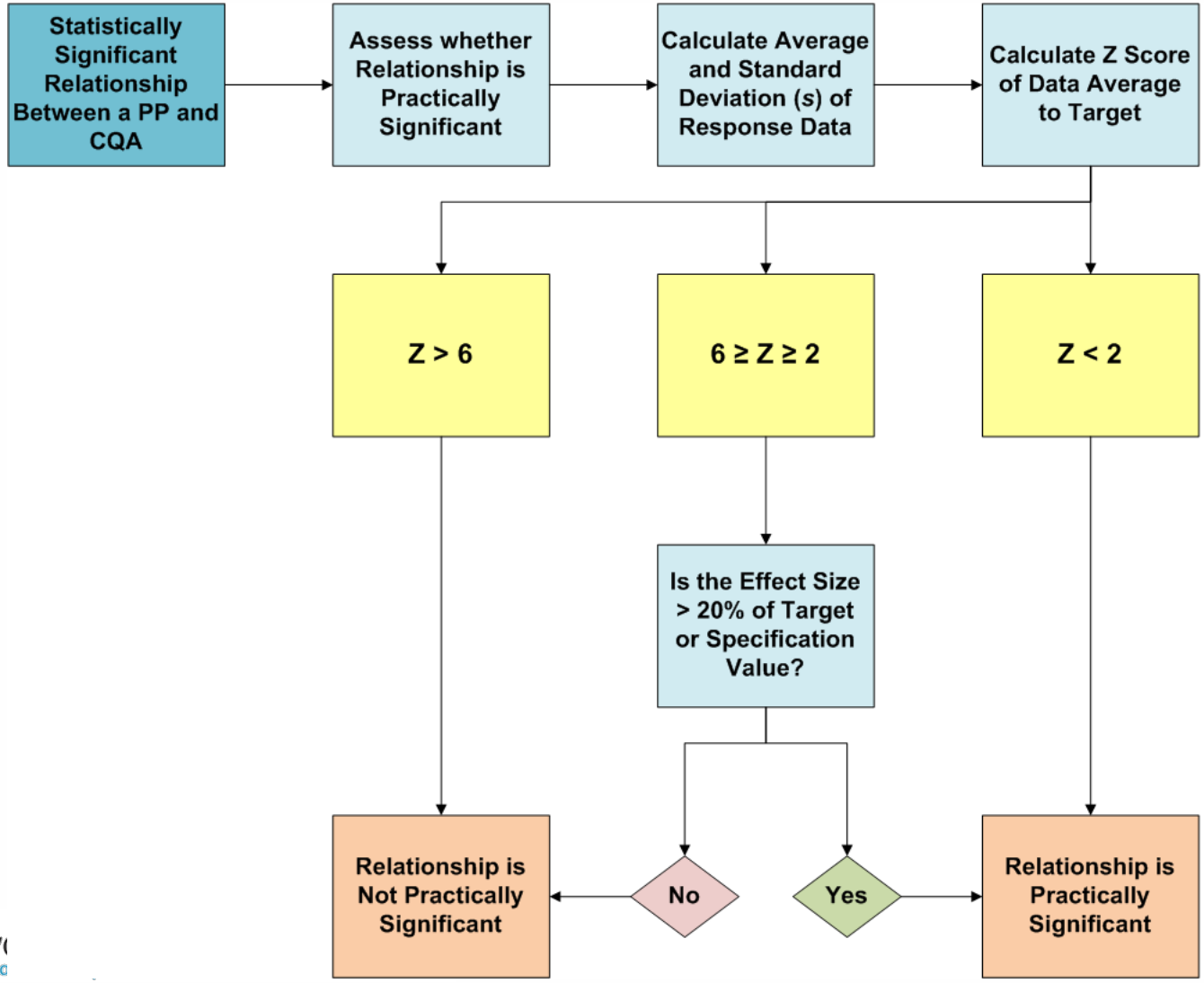
s = 0.037%

Introduction to the Z Score

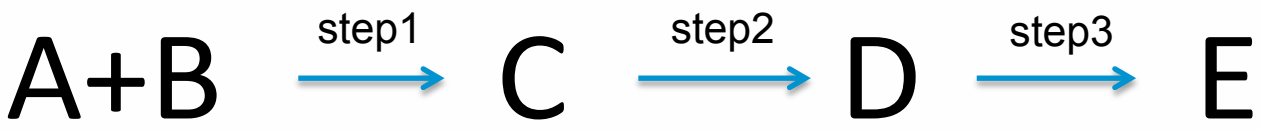


Process Capability	Defect Rate
2σ (95.45%)	1 in 20
3σ (99.75%)	1 in 400
4σ (99.995%)	1 in 20,000
5σ (99.99995%)	1 in 2,000,000
6σ (99.9999998 %)	1 in 500,000,000

Practical Significance Decision Tree



An API Example



- Taken from an approved product (small Molecule API), a 3-step process.
- A second generation route was developed and was being transferred to the manufacturing division (Pfizer Global Supply) for validation.
- The tool was applied prior to validation to assess process parameters for criticality.
- 1st example of using the tool prospectively for criticality assessment.
- Bound to the initial specifications which were tight and had to assess to the QA's from the initial submissions as well as additional QA's unique to the second generation process.

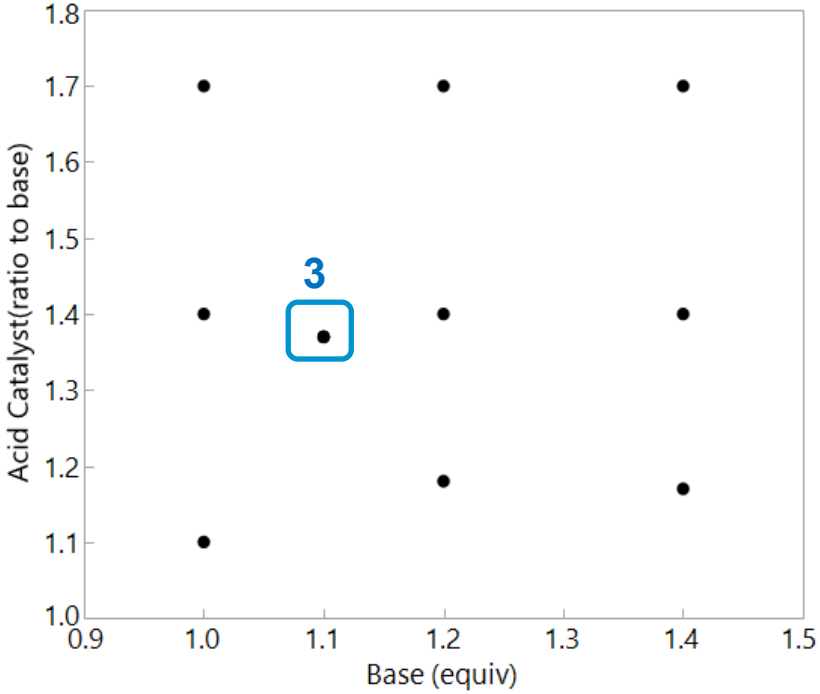
Example DoE - Design

Parameters

- Base equiv
- Acid catalyst/base

Optimization DoE:

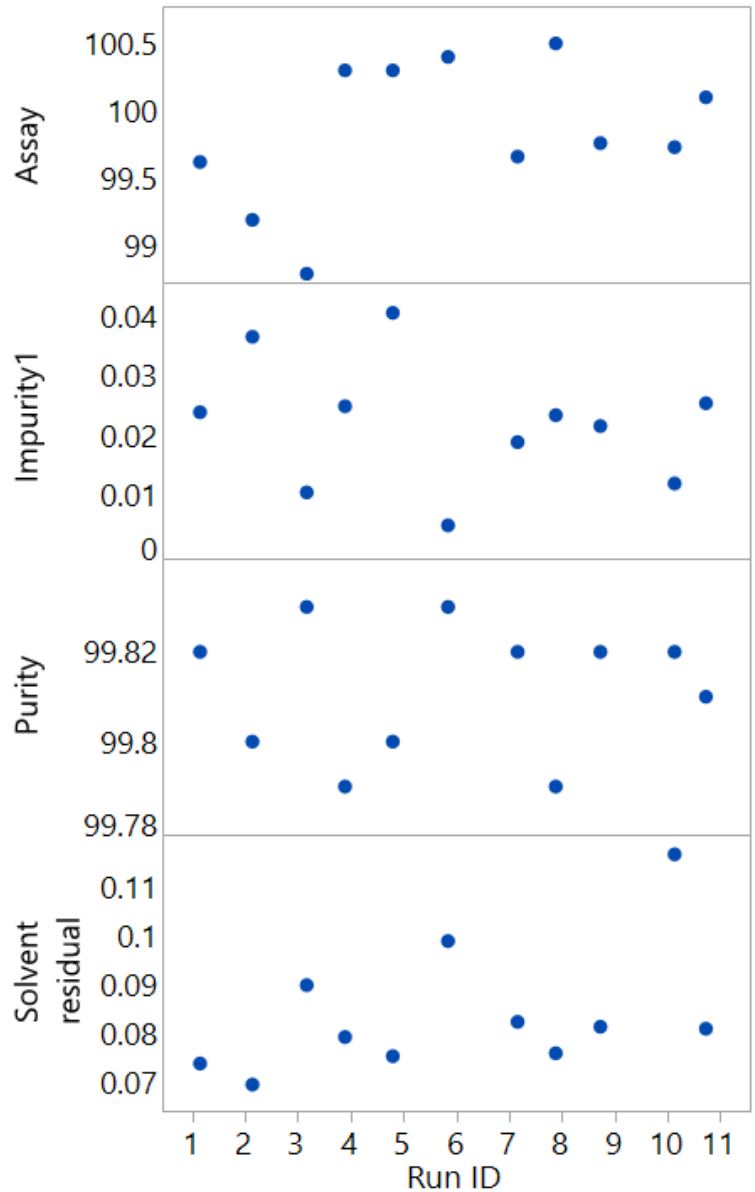
- Response Surface Design (CCD)



Responses:

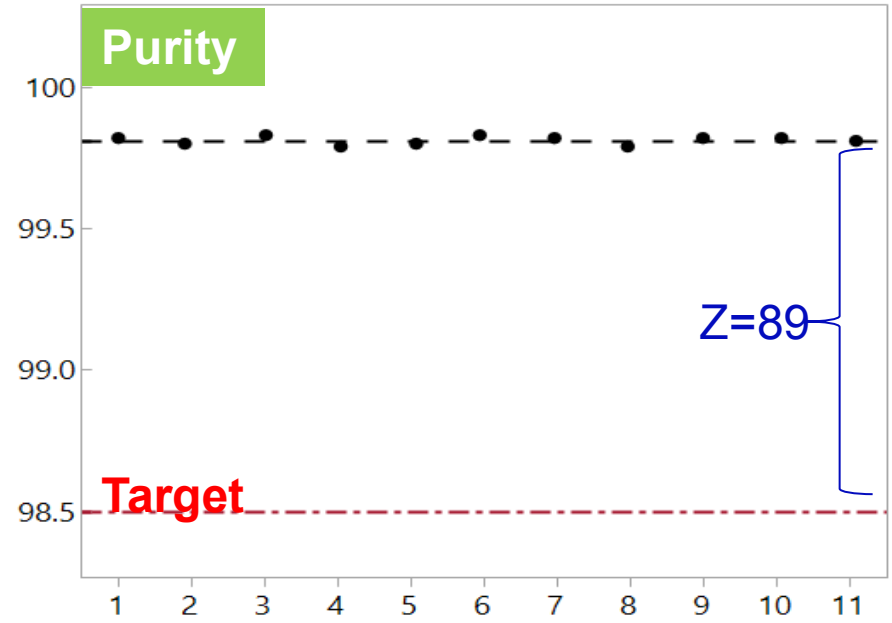
- Purity (NLT 98.5%)
- Impurity 1 (NMT 0.15%)
- Assay (98% - 102%)
- Residual Solvent (NMT 0.089%)

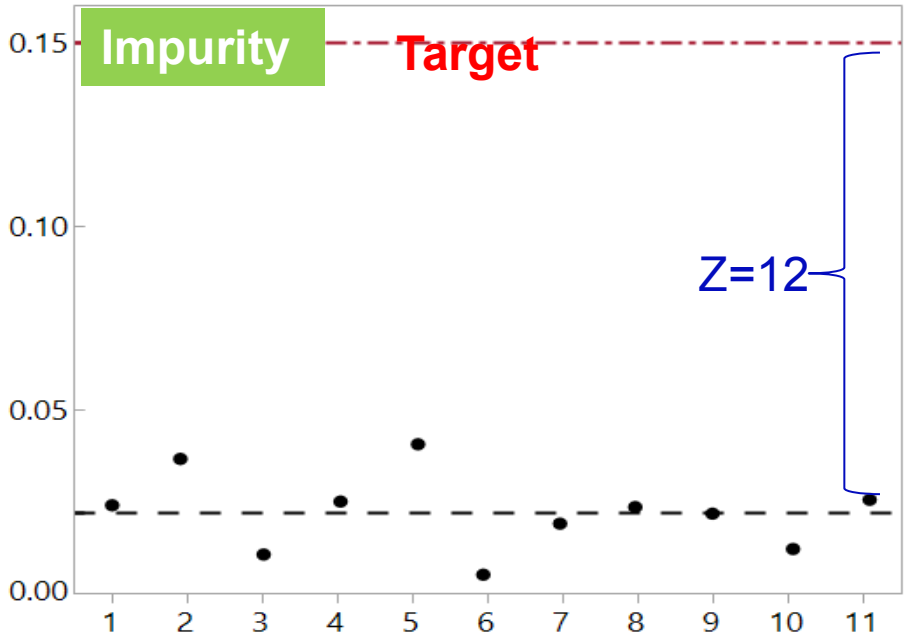
DoE CQAs, Statistically Significant Parameters

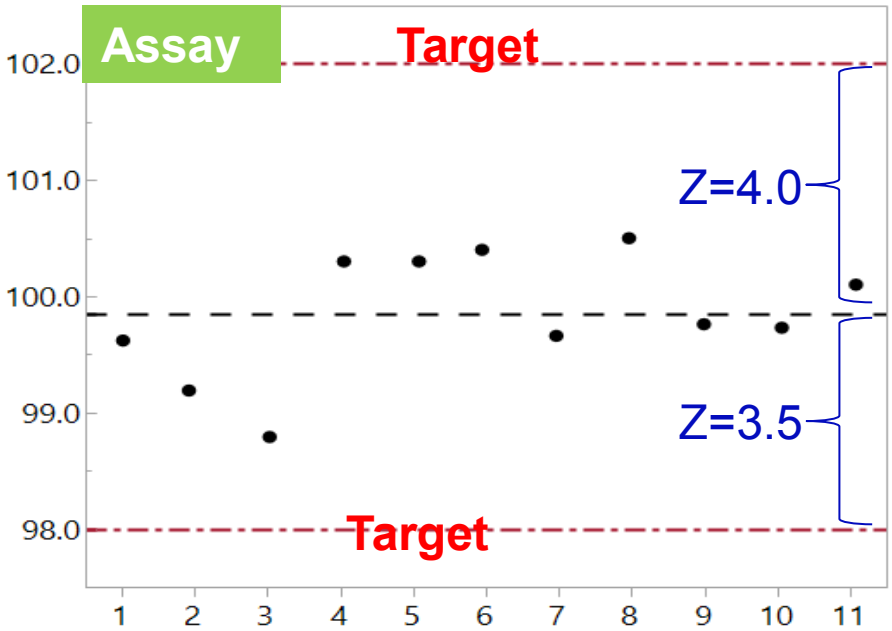


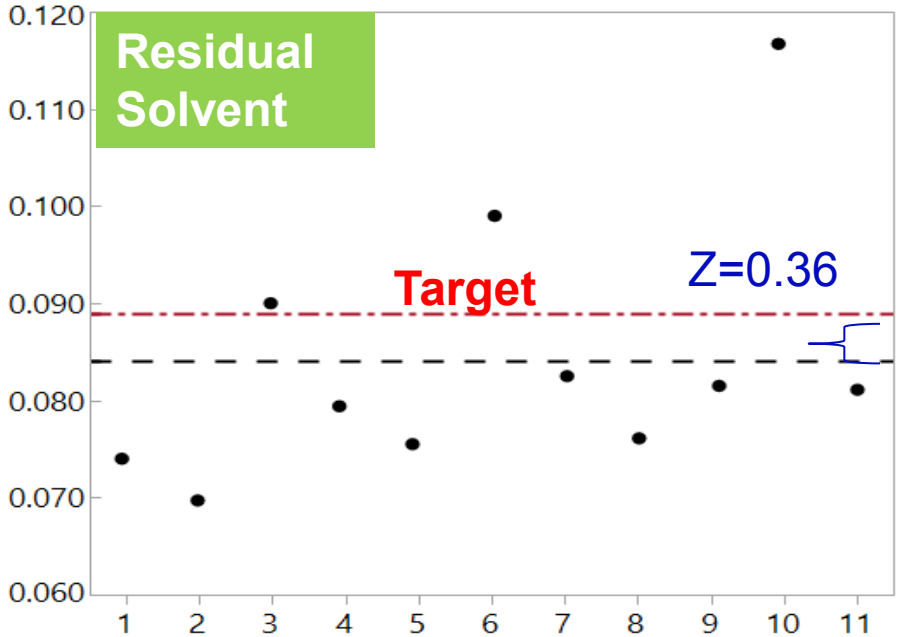
CQAs	Statistical Significance PP
Assay	Base, Ratio
Purity	Ratio
Residual Solvent	Base, Ratio
Impurity1	None

- Are these Statistically Significant Relationships Practically Significant?


Purity
100
99.5
99.0
98.5
Target
Z=89
1 2 3 4 5 6 7 8 9 10 11


Impurity
Target
0.15
0.10
0.05
0.00
Z=12
1 2 3 4 5 6 7 8 9 10 11


Assay
Target
102.0
101.0
100.0
99.0
98.0
Z=4.0
Z=3.5
Target
1 2 3 4 5 6 7 8 9 10 11


Residual Solvent
0.120
0.110
0.100
0.090
0.080
0.070
0.060
Target
Z=0.36
1 2 3 4 5 6 7 8 9 10 11

Determine Practically Significant Parameters

CQAs	Statistically Significant Process Parameter	Practically Significant Process Parameter	Rationale
Assay	Base, Ratio	Yes	Z=3.5, every parameter effect size is greater than 20% spec (0.8%)
Purity	Ratio	No	Z=89 > 6, low risk region
Residual Solvent	Base, Ratio	Yes	Z=0.36 < 2, higher risk region
Impurity	None		No statistically significant parameter and Z=12 > 6

$$Assay = 99.23 - 0.72 \bullet Base + 0.68 \bullet Ratio + 0.61 \bullet Base \bullet Ratio + 0.51 \bullet Base\text{^}2 + 1.11 * Ratio\text{^}2$$

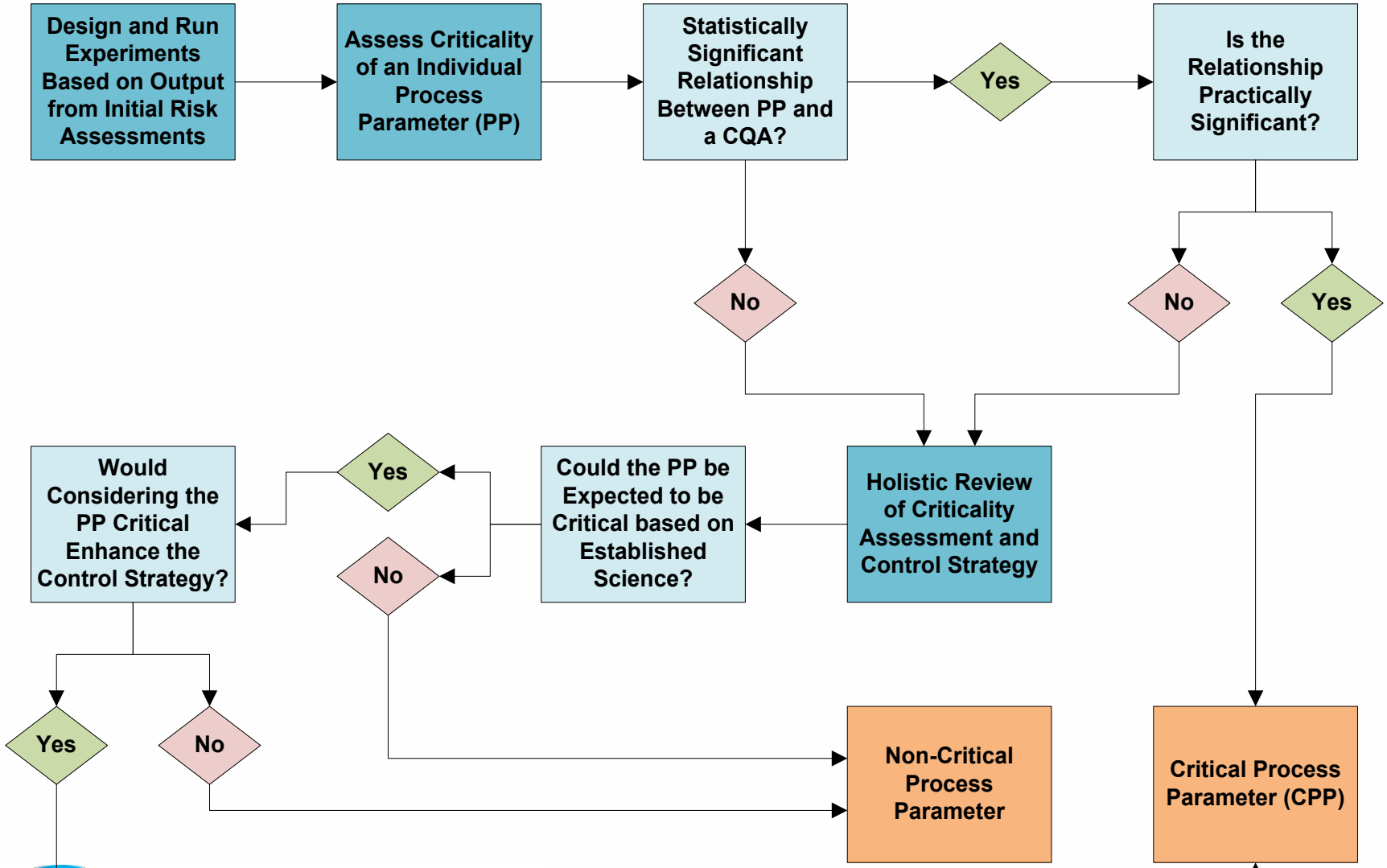
$$Purity = 99.81 - 0.019 \bullet Ratio$$

$$Solvent = 0.078 + 0.005 \bullet Base - 0.022 \bullet Ratio + 0.0065 \bullet Base\text{^}2 + 0.014 \bullet Ratio\text{^}2$$

Parameter	Parameter Effect Size on Assay
Base	2.4% > 0.8%
Ratio	1.8% > 0.8%

Both Parameters are Practically Significant and Critical.

Criticality Assessment Decision Tree



Summary

- An Approach has been Developed, for the Assessment of Critical Process Parameters, that Attempts to Balance the Use of Scientific Rationale, Risk Assessments, and Statistical Tools.

- In Practice, the Approach Allows Teams to Rapidly Assess Criticality and Produce Results that are More Consistent from Team to Team.