Enhanced Process Characterization study with Monte-Carlo Simulation

From a static to a dynamic understanding of a manufacturing process

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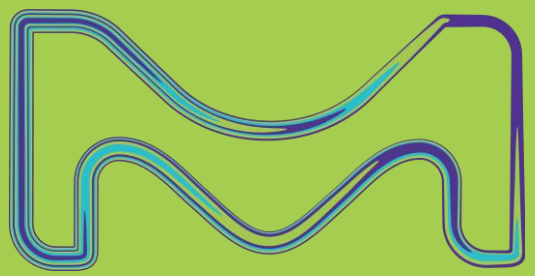

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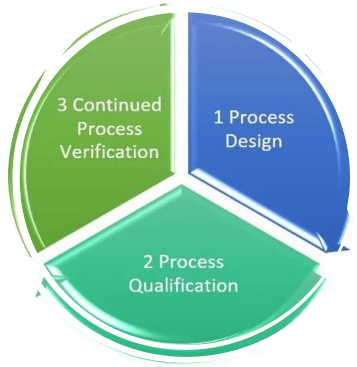
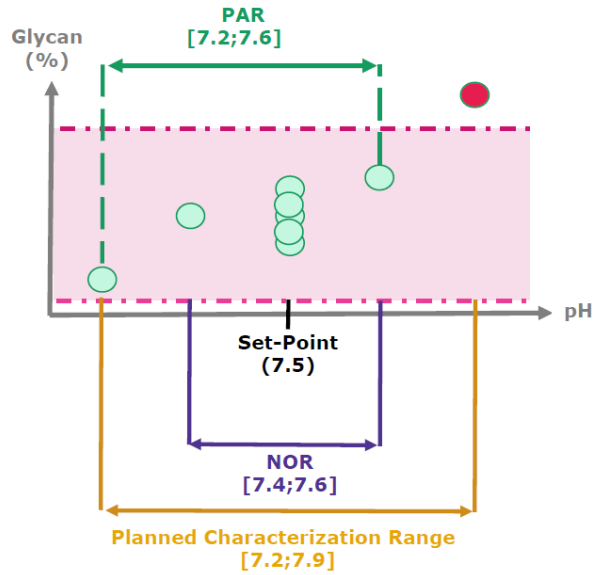
Introduction
Purpose of Stage 1 Process Design / Process Evaluation

- Generate product understanding (CQAs)
- Generate process understanding
  - Understand the impact of variations of process input variables (CMAs & pCPPs) on process output variables (CQAs, performance attributes and process indicators)
  - Establish an appropriate control strategy
    - Limits of CQAs in process intermediates
    - Limits of CMAs
    - Specification (end-product)
    - Set-points, NOR and PAR of CPPs

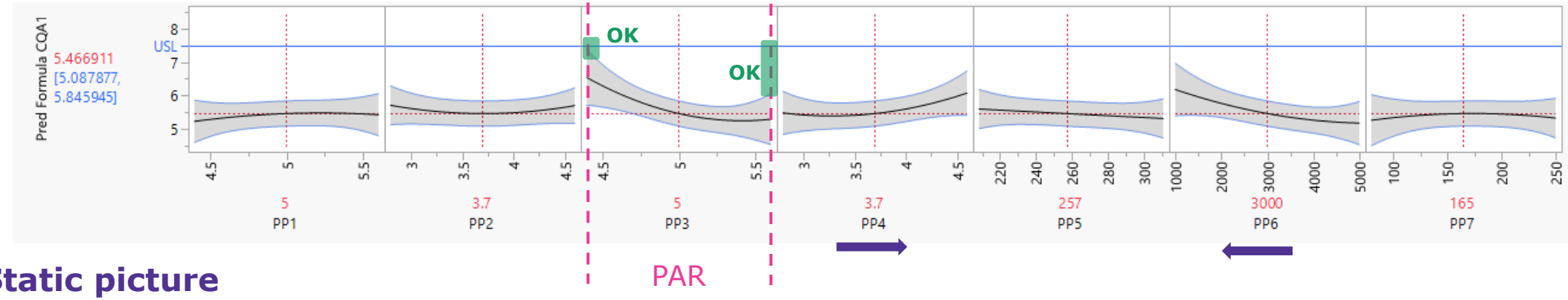
How to operate the process to ensure delivering a product with desired performance and safety profile



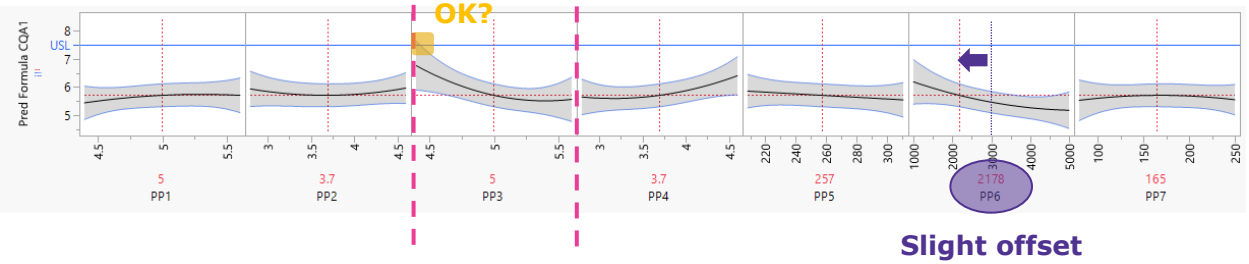


Introduction
Starting from a definition: Proven Acceptable Range

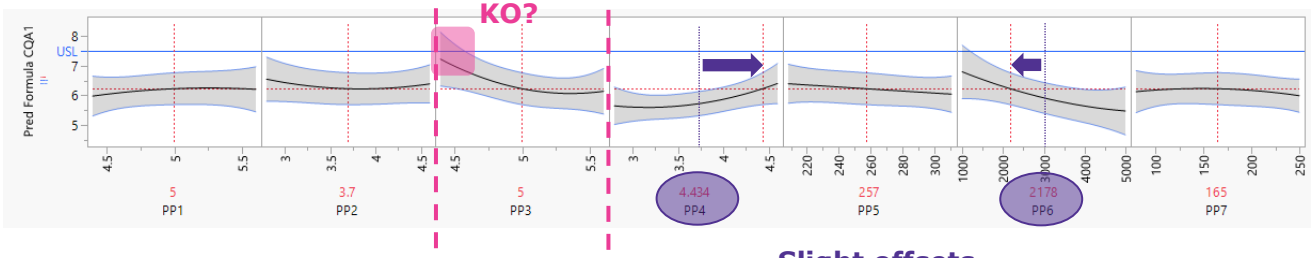
Proven Acceptable Range (PAR) - "*A characterized range of a process parameter, for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.*" (ICH Q8 R2)



- **Static picture**
- **Process is dynamic: variations of Process Parameters (PPs) are expected**



Slight offset (within NOR)



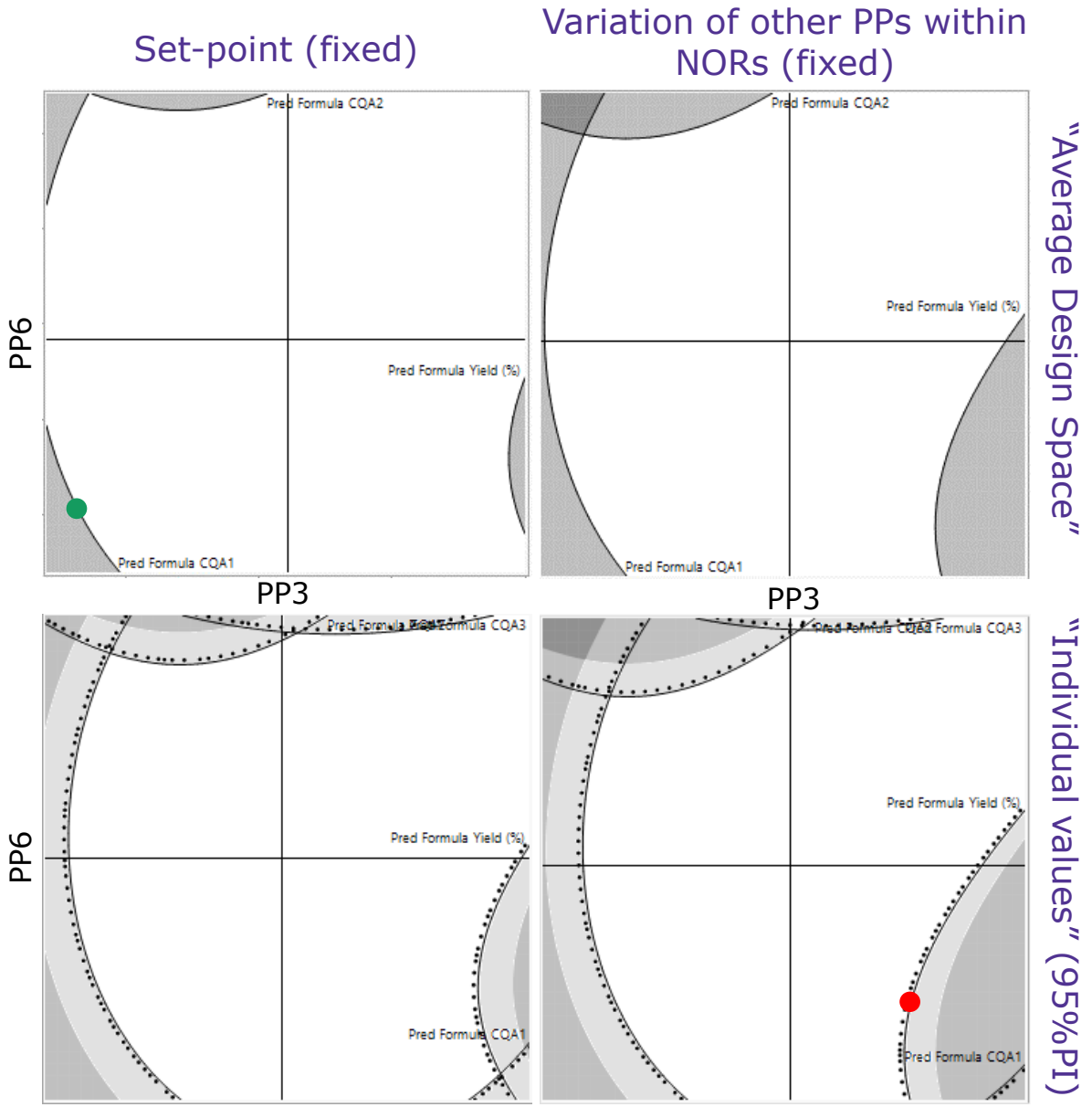
Slight offsets (within NORs)

Still confident with the "PAR"?

Introduction
Multiple CQAs: Design Space ?

"The multidimensional combination and interaction of input variables […] that have been demonstrated to provide assurance of quality. […]" (ICH Q8 R2)

- Several responses can be considered
- Visual assessment of interaction/combination effects of 2 factors
- **Still a local picture**
  - Variations of other PPs not considered
- **Effect of variation of CPPs could be introduced**
  - Limits reflect a mean = by definition, 50% chance of being out-of-limit
- **Interval can be added (e.g., prediction interval)**
  - 50% chance of being out-of-limit at X% confidence



Monte-Carlo Simulations
Integrate Process Dynamics

- Process is dynamic not static
  - Normal variations of operational process parameter are expected (NOR)
  - Cumulative and interacting effects are part of the equation
- Variability (error) is part of process (model)
  - Process/analytical variabilities
  - "All models are wrong […]"
- Answer is not "black or white"
  - Probability (of success) is of interest
- Process outcome is multidimensional
  - Several CQAs and CPPs
- Lab experiments are expensive
  - *in silico* simulations are (almost) cost-free
  - Knowledge is already available

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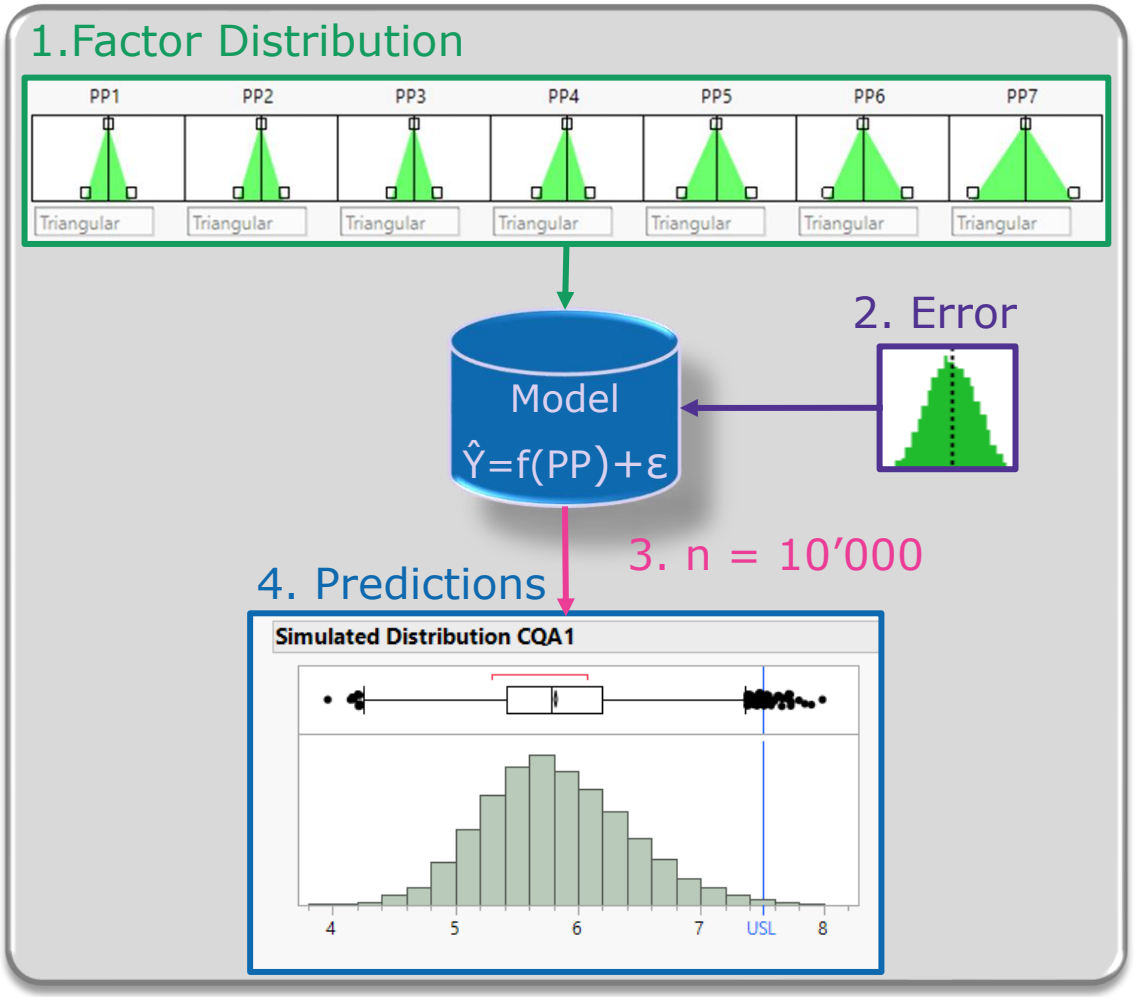
Monte-Carlo Simulations

Basic concept

Use the prediction models to **simulate a very large number of process outcomes** depending on random variations of the factors (process parameters)

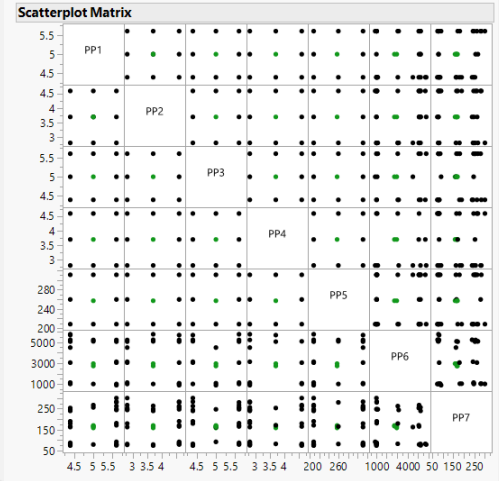


1. **Factor Distribution**
   - Range of variation: NOR, PAR with
     - max distribution = set-point
     - lower and upper limits = expected [NOR] (most frequent) or proven acceptable range [PAR] (less frequent)
   - Every type of distribution possible: usually triangular or normal, truncated, uniform, etc.
2. **Random error** Typically, model error (RMSE) Additional error can be added (→ Prior knowledge)
3. **Number of simulations** Typically, ≥ 10'000
4. **Response prediction**
   - Process understanding
   - Success / Defect rate

Case-Study
Context & Pre-requirements

Study: process characterization

- Unite-operation: 1 DSP step (micro-scale)
- 7 potential CPPs
- pCPP tested ranges: ≈ 3-fold the NORs
- 31 terms evaluated: 7 main effects, 7 quadratics, 17 2nd order interactions
- Response: 3 CQAs + yield



- DoE: "Custom Design" (D-optimal)
- 40 runs (including control runs at setpoints)

Pre-requirements*

- Qualified SDM
- CQA affected by the unit operation are known and acceptance criteria are defined (+ yield)
- Analytical methods with appropriate characteristics (specificity, accuracy, precision, linearity)
- Process characterization completed (interactions between input and output process variables, alone or in combination known)
  - Individual mathematical models for each CQA with adequate "goodness of fit"
    - High enough R^2, Q^2
    - Residuals randomly distributed (within Xs & Ys ranges, experiments order etc.)

** Out of presentation's scope*

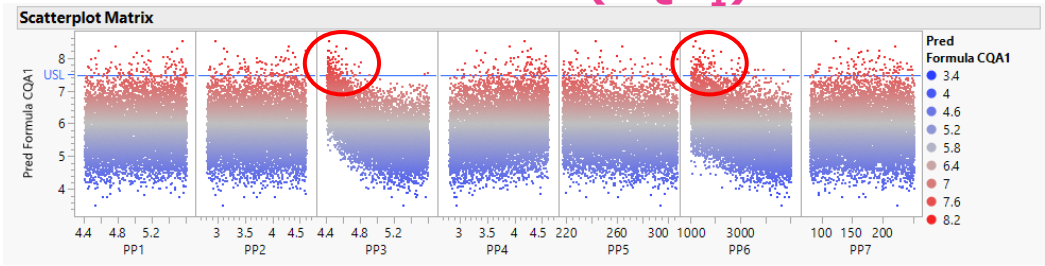
Monte-Carlo Simulations: potential applications
Visualization of Process Understanding

- Understand process outcomes within the multivariate tested ranges: uniform PP distribution
- Consider the uncertainty of process outcome: Add random noise

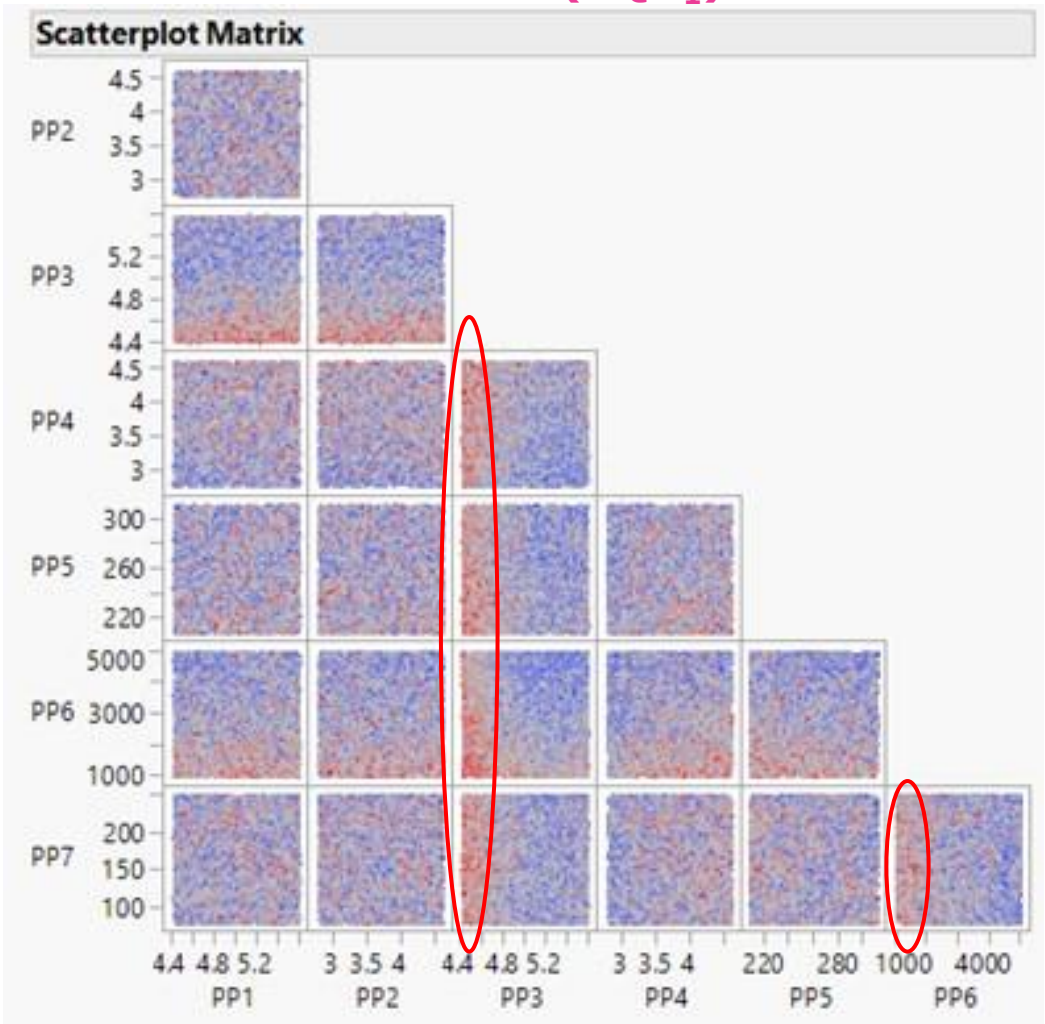
Model (one CQA only: CQA_1)

⬇ Monte Carlo Simulation

Univariate visualization (CQA_1)



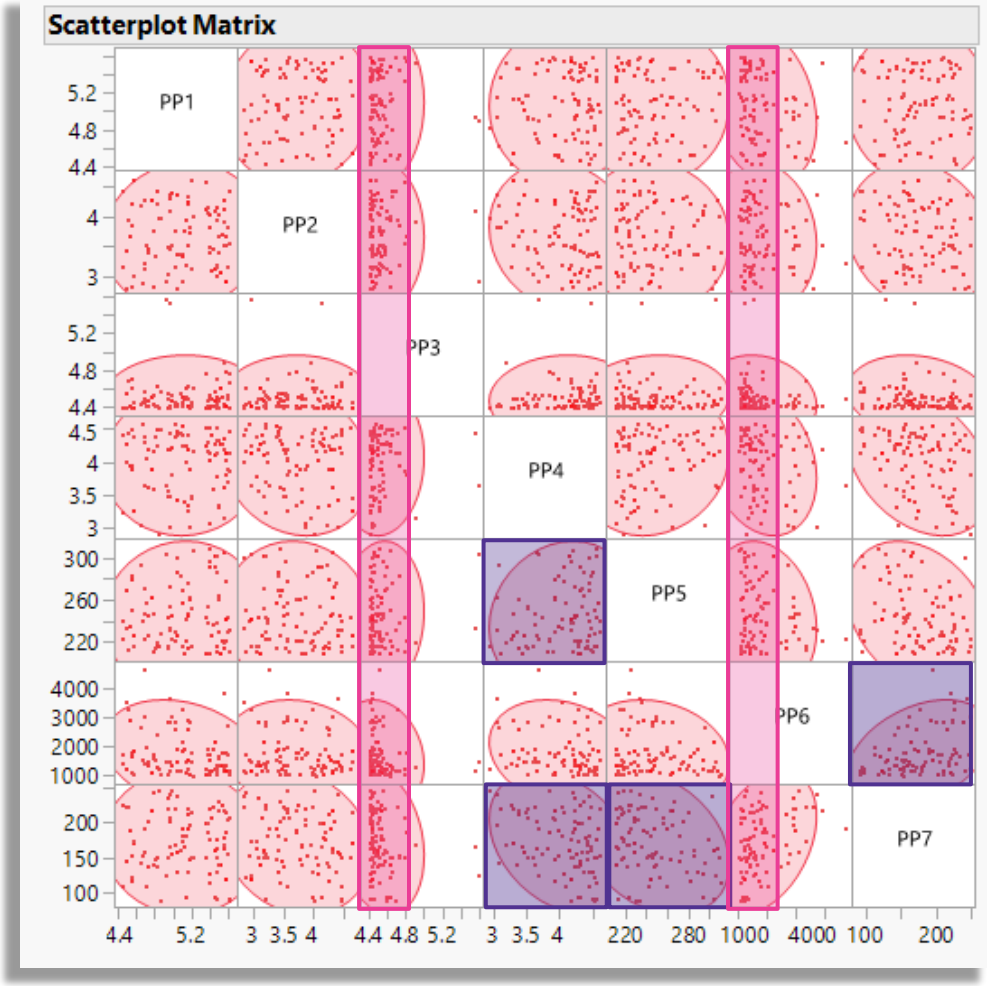
Bivariate visualization (CQA_1)



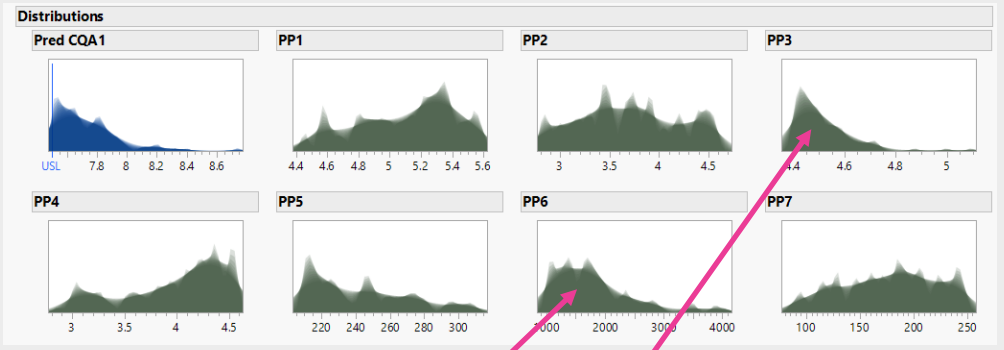
Monte-Carlo Simulations: potential applications

Visualization of risk of Out-of-Limits (CQA_1 only)

OoL for CQA_1 (> 7.5) – [out of 10000 runs]



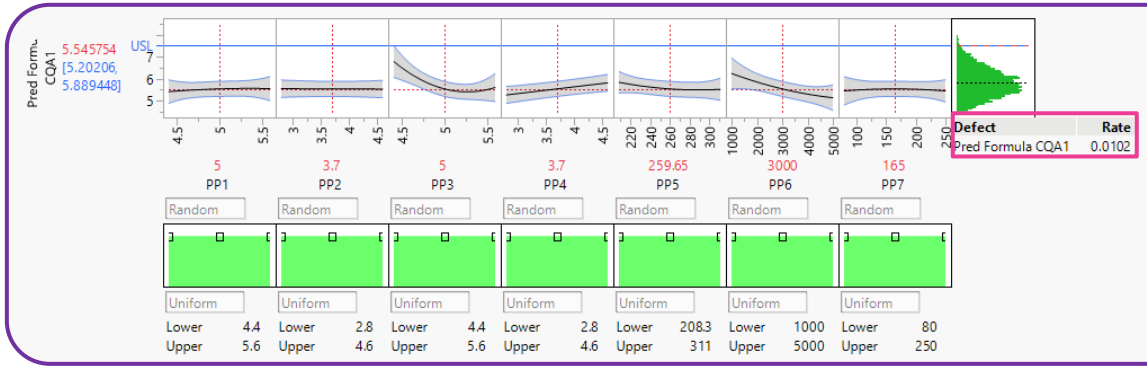
- Distribution of OoL (CQA_1 > 7.5) vs PP



- Visual interpretation of risk :
  - Low levels of PP6 and PP3
- Ellipses = interactions of risk factors
  - PP4 & PP5; PP4 & PP7; PP5 & PP7; PP6 & PP7

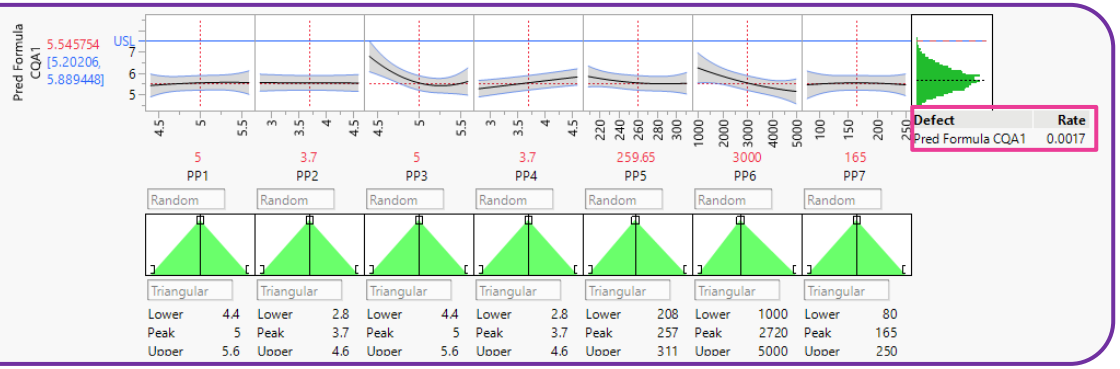
Monte-Carlo Simulations: potential applications

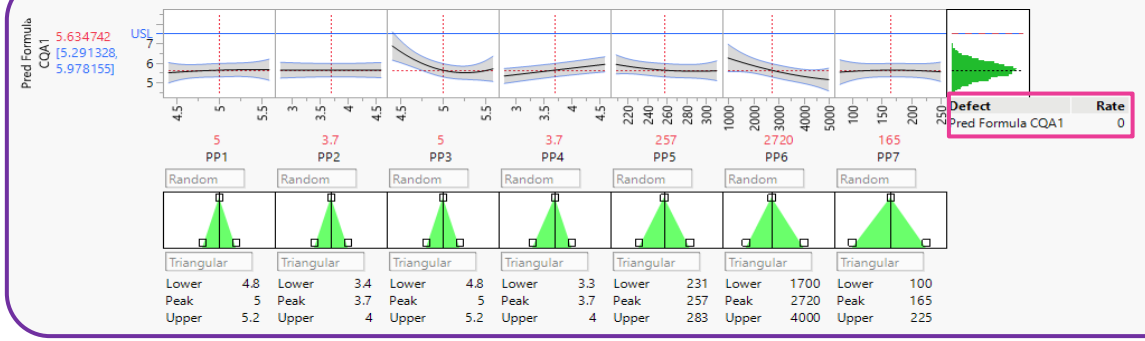
Evaluation of risk of Out-of-Limit (CQA_1 only)



- Distribution of PPs: **Uniform within PAR**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000
- Risk of OoL [CQA_1]: **~1%**

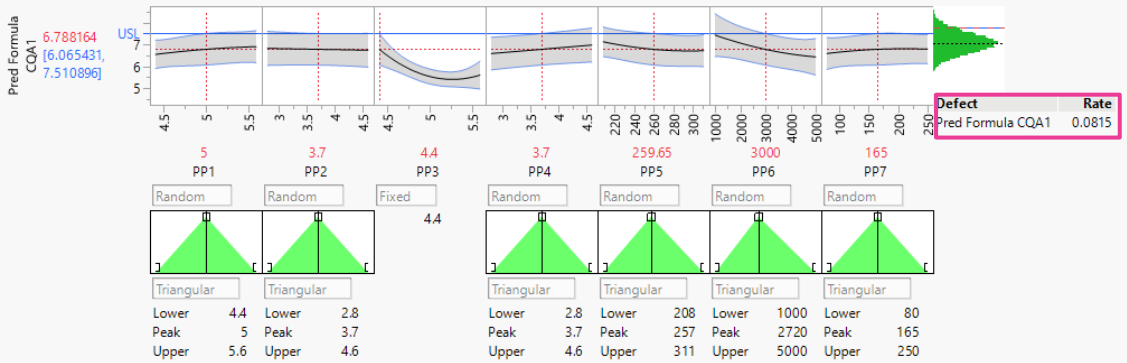
- Distribution of PPs: **Triangular within PAR**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000
- Risk of OoL [CQA_1]: : **~0.2%**



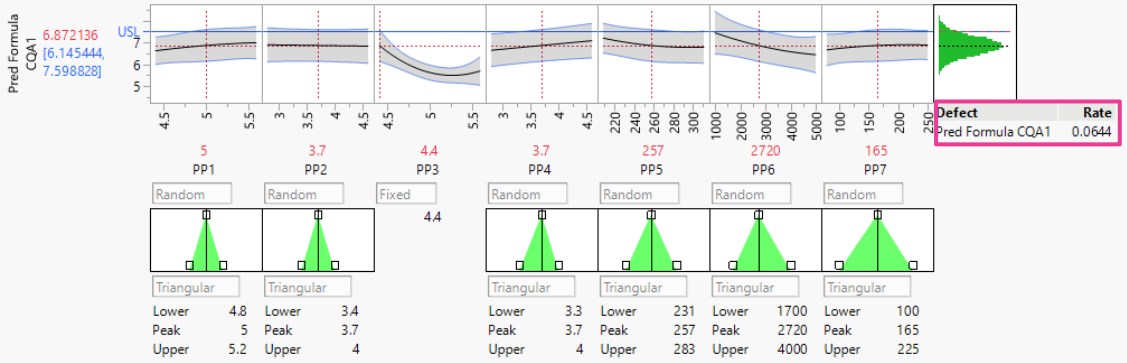


- Distribution of PPs: **Triangular within NOR**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000
- Risk of OoL [CQA_1]: **~0%**

Monte-Carlo Simulations: potential applications
Evaluation of risk of Out-of-Limit (CQA_1 only)



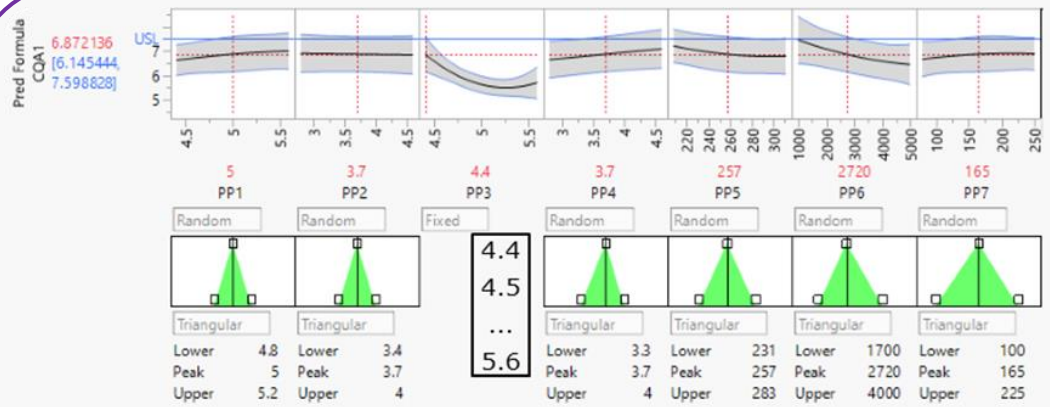
- **PP3 set at 4.4** (lower level of tested range)
- Other PPs: **Triangular within PAR**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000
- Risk of OoL [CQA_1]: **~8%**



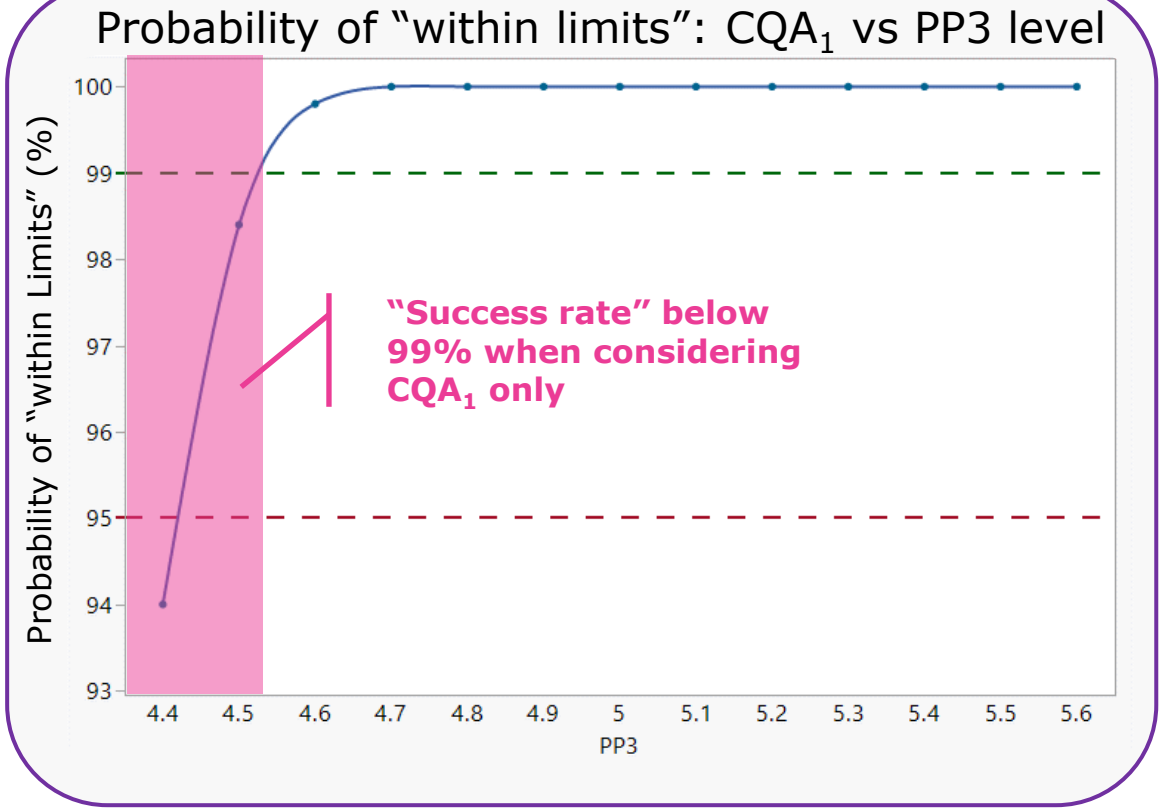
- **PP3 set at 4.4** (lower level of tested range)
- Other PPS: **Triangular within NOR**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000
- Risk of OoL [CQA_1]: **~6%**

Monte-Carlo Simulations: potential applications

Evaluation and visualization of risk of Out-of-Limit (CQA_1 only)



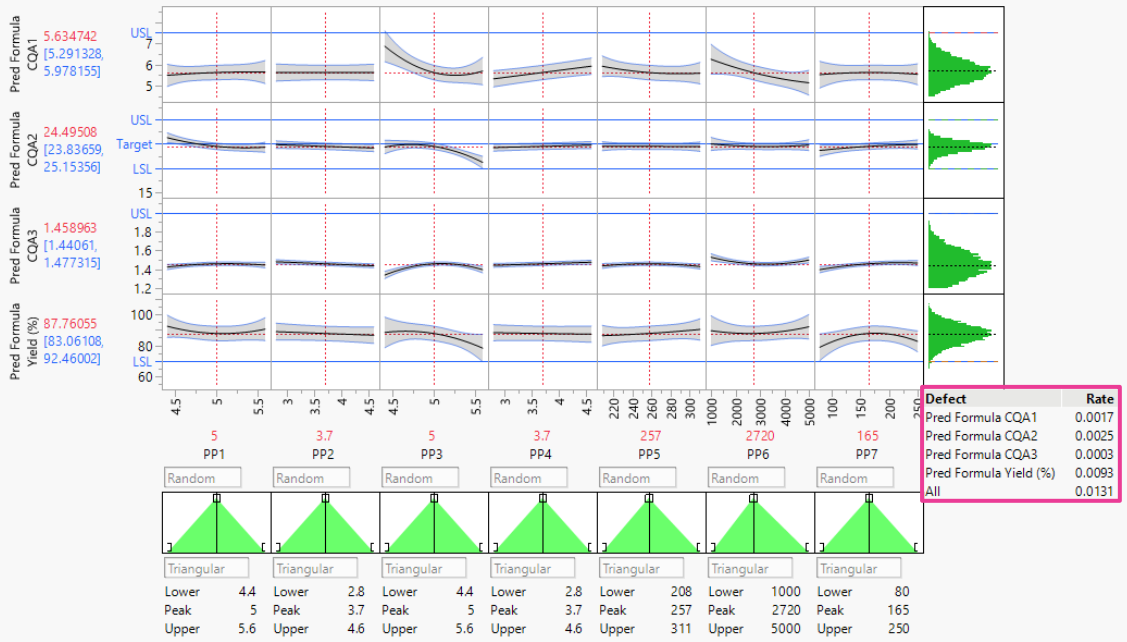
- PP3: **fixed from 4.4 to 5.6** (tested range)
- Distribution of other PPs: **Triangular within NORs**
- Random error: 0.404 (RMSE)
- n Simulation: 10’000 * number of PP3 levels



Monte-Carlo Simulations: potential applications

Same approach but considering 3 CQAs + yield

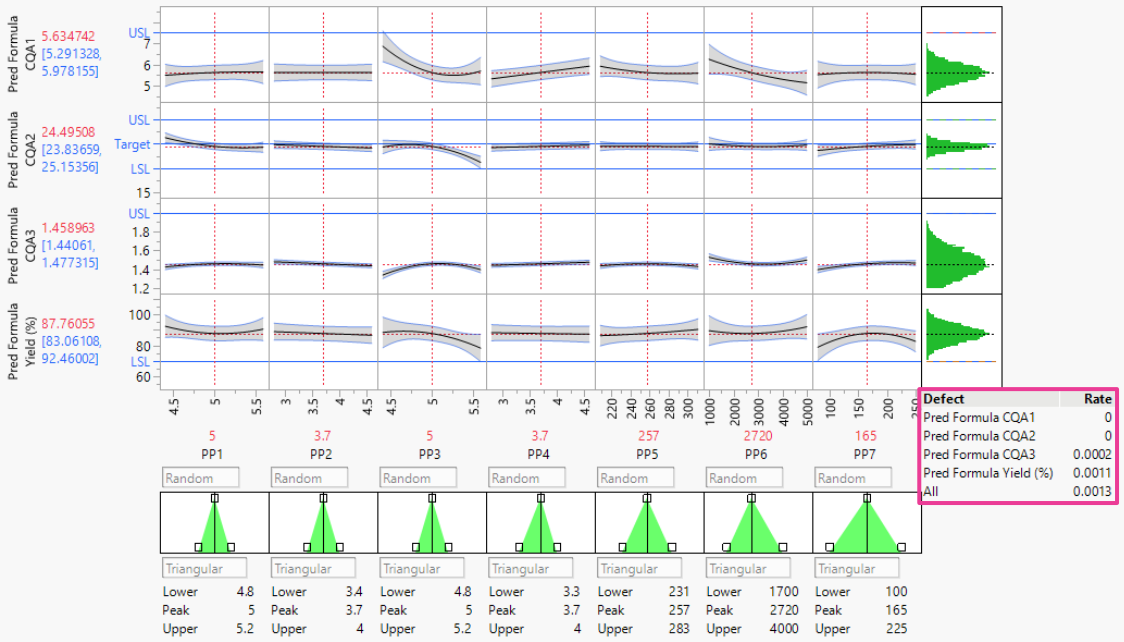
Triangular within PAR



Random error

- Overall risk of OoL: **~13%**
- Mostly driven by Yield: **~9%**

Triangular within NORs

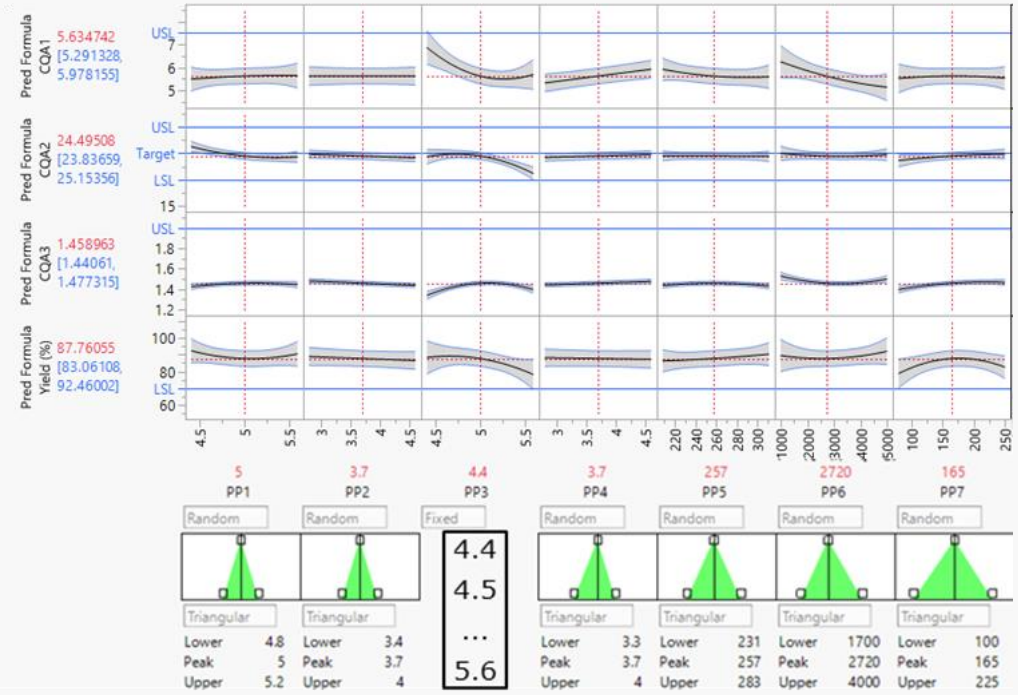


Random error

- Overall risk of OoL: **~1%**

Monte-Carlo Simulations: potential applications
Visualization of the overall risk of out-of-limits

Triangular within PAR

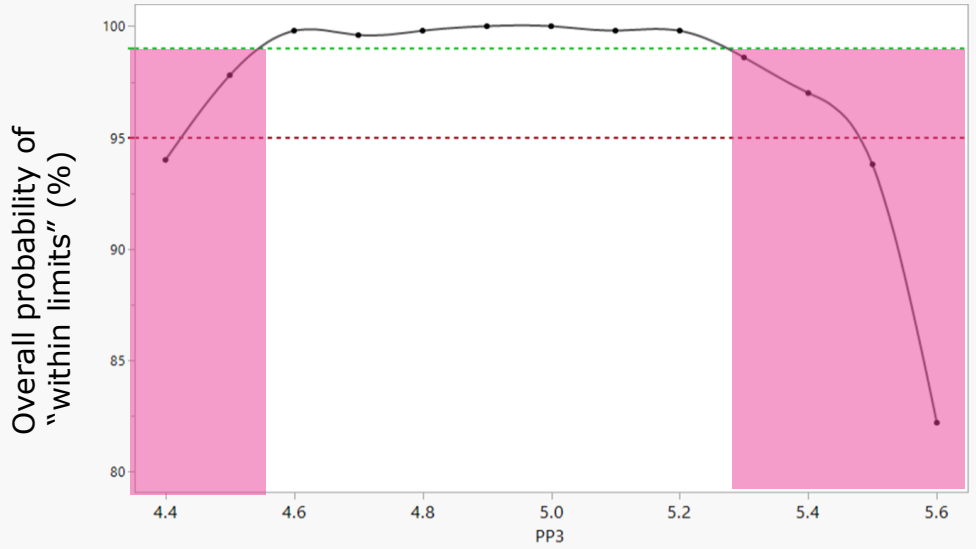


Random error

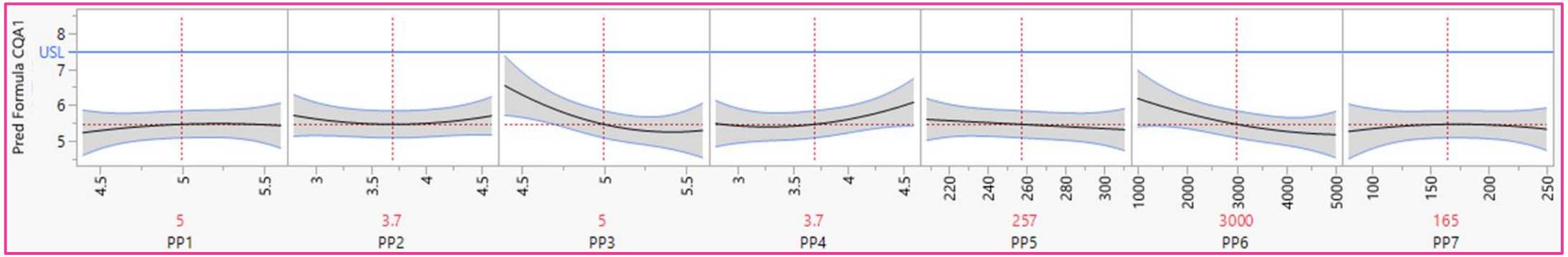
Probability of "within limits" vs PP3 level

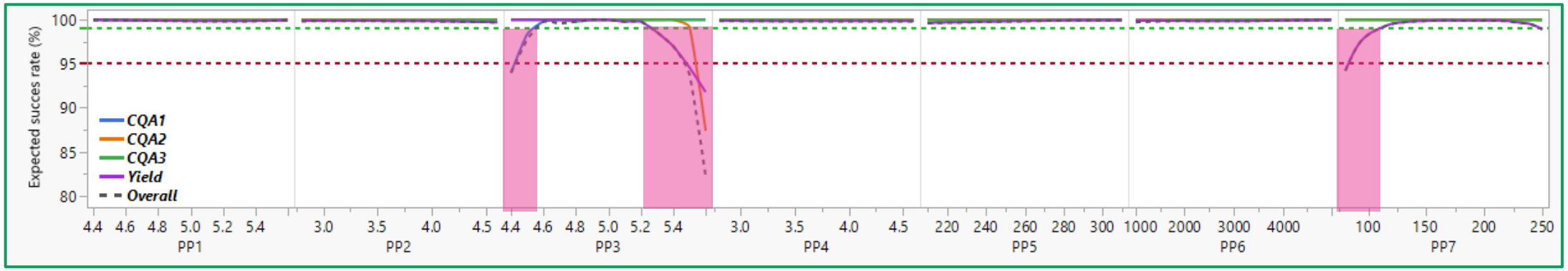
For each Response

Overall



Monte-Carlo Simulations: Summary
From a local to a global process understanding





From Monte-Carlo Simulations To

	Factors consideration	Process outcomes	Process Knowledge	Risk evaluation/ understanding	Acceptable Range
From	Univariate • other PPs fixed	Univariate • CQA by CQA	Partial	Local & partial	Robust at set-point
To	Multivariate • other PPs varying	Multivariate • all together	Complete	Global	Robust within possible PPs variability

Monte-Carlo Simulations
Take Home Message

- Provide functional answers through approximation of complex problems with difficult (no) analytical solution
- Probabilistic instead of a "black or white" vision
- Easy way (low costs) to gain further process understanding from existing data
- Multiple applications
  - Better understanding of operational process limits
  - Error propagation: unit operations linkage
  - Sample size calculation, etc.

"Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and help avoid problems at commercial scale."