Two years on: Assessing practical significance of process parameters in small molecule technical development

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Background and Notation

The Impact Ratio

Examples

Relevance, Summary and Conclusions

Scope

- Process characterization of small molecule synthesis steps

Objective

- Quantitate process parameters' practical impacts on Critical Quality Attributes (CQA)
- Classify process parameters (PP) as critical or not critical

Background

- Current guidelines of the ICH[1] and FDA[2] stress statistical significance to evaluate their impact.
- FDA's "QbD for ANDAs" mentions the terms "significant" or "significance" 78 times.

1) FDA (2011) QbD for ANDAs: An Example for Modified Release Dosage Forms.
2) ICH (2009) Pharmaceutical Development Q8 (R2)

P-values do not assess practical significance

- Definition: the p-value is the probability of observing an effect size as large or larger when repeating the experiment under the null hypothesis that the effect size is 0.
  - P-value is a function of the effect size and standard error, not the of specifications!
- Most DoEs have very few degrees of freedom, hence variation of experimental system is typically poorly estimated, making the p-value highly variable
- Variation of the experimental system might be very different than the variation of the system of interest, making the p-value irrelevant

Impact Ratio: quantifying practical significance

- The Impact Ratio compares
  - the effect of the PP on the CQA

  with
  - the allowed range: process mean value -> next CQA specification limit(s)
- Computed for each combination of PP x CQA
- Requires:
  - Specifications for CQA
    - USL = upper specification limit and / or
    - LSL = lower specification limit
  - Acceptable ranges for PP
  - Predictive model relating PP to CQA
    - Typically a regression model from a DoE

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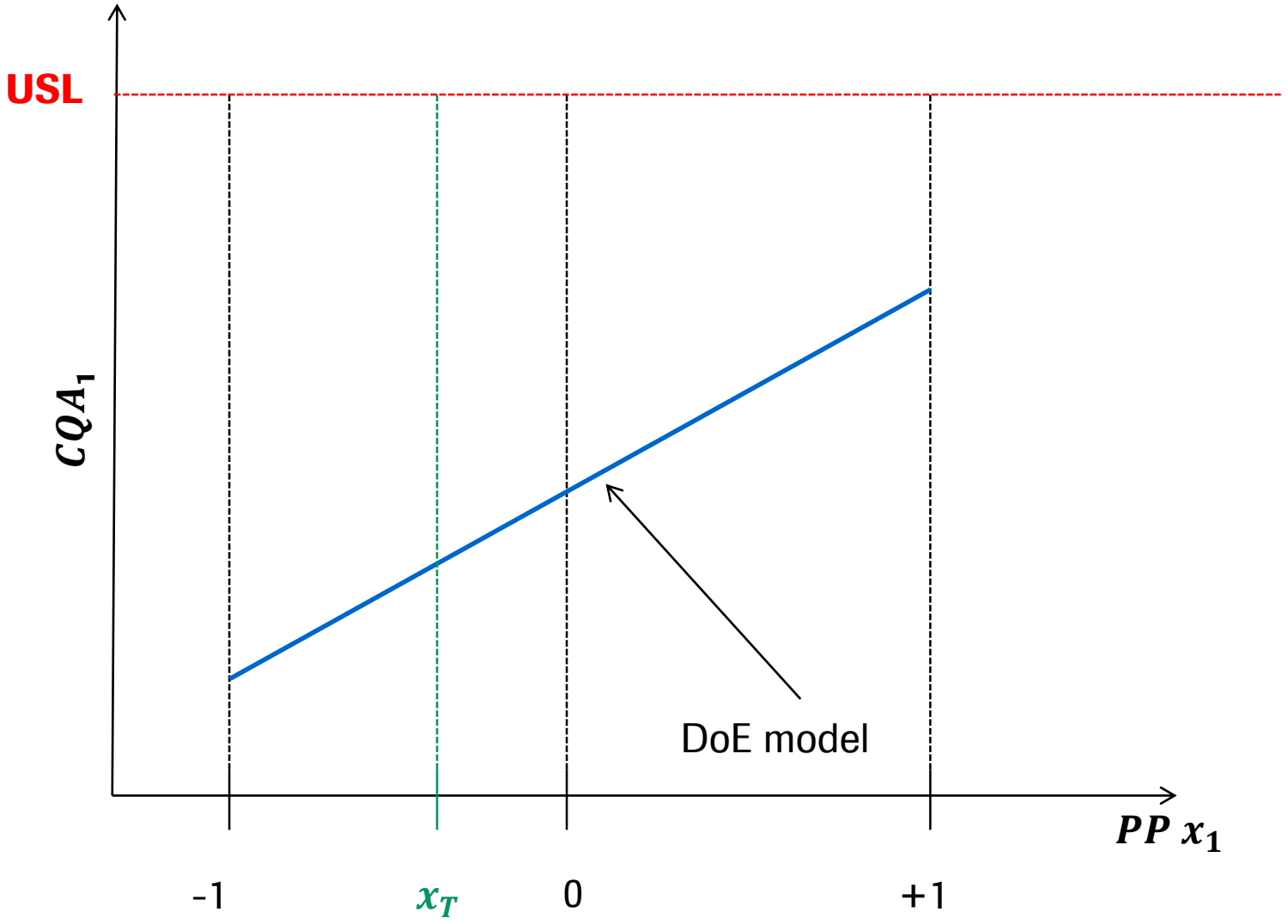
One-sided Impact Ratio:
Comparing the effect of a PP with the allowed range



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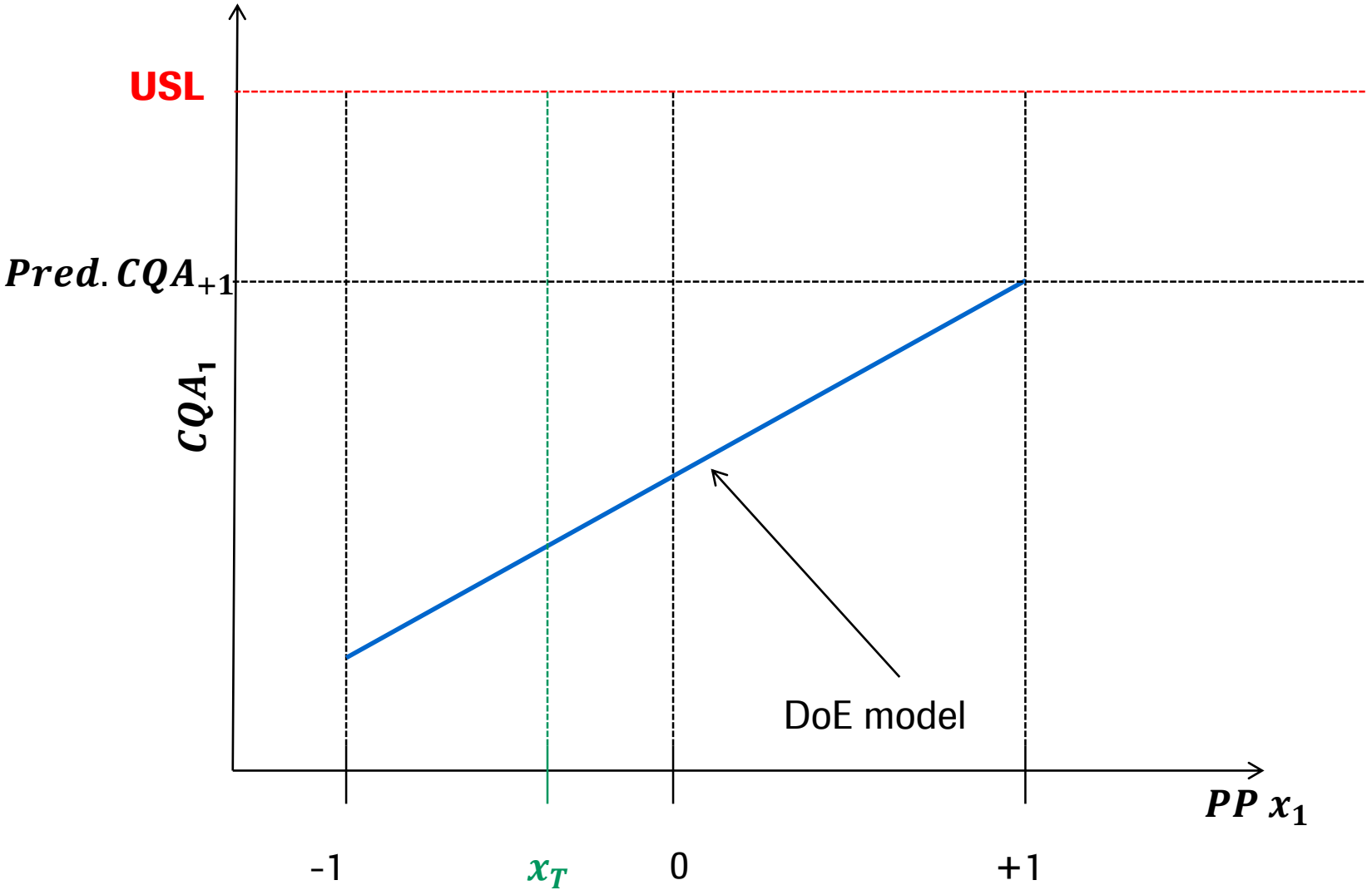

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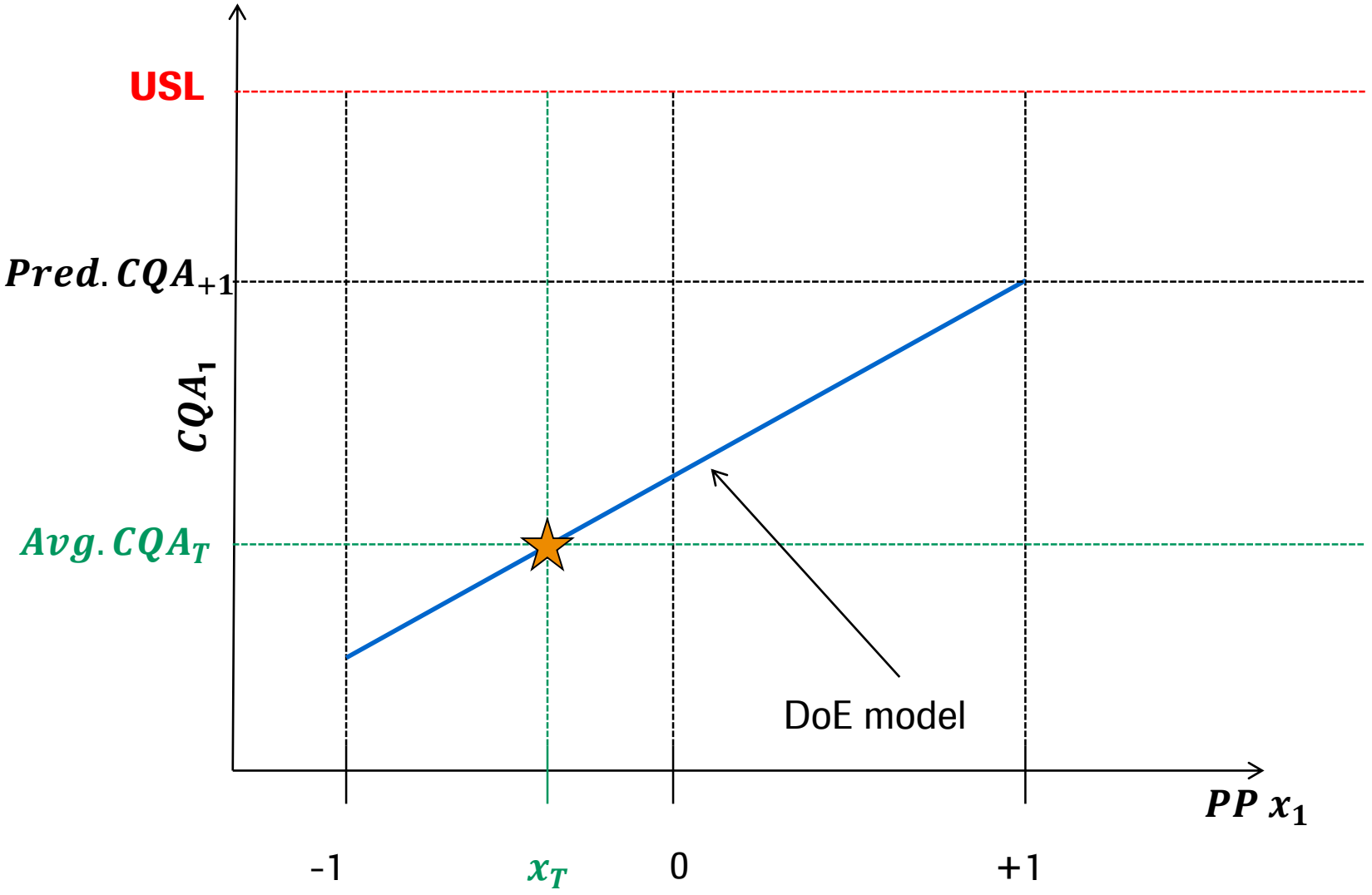

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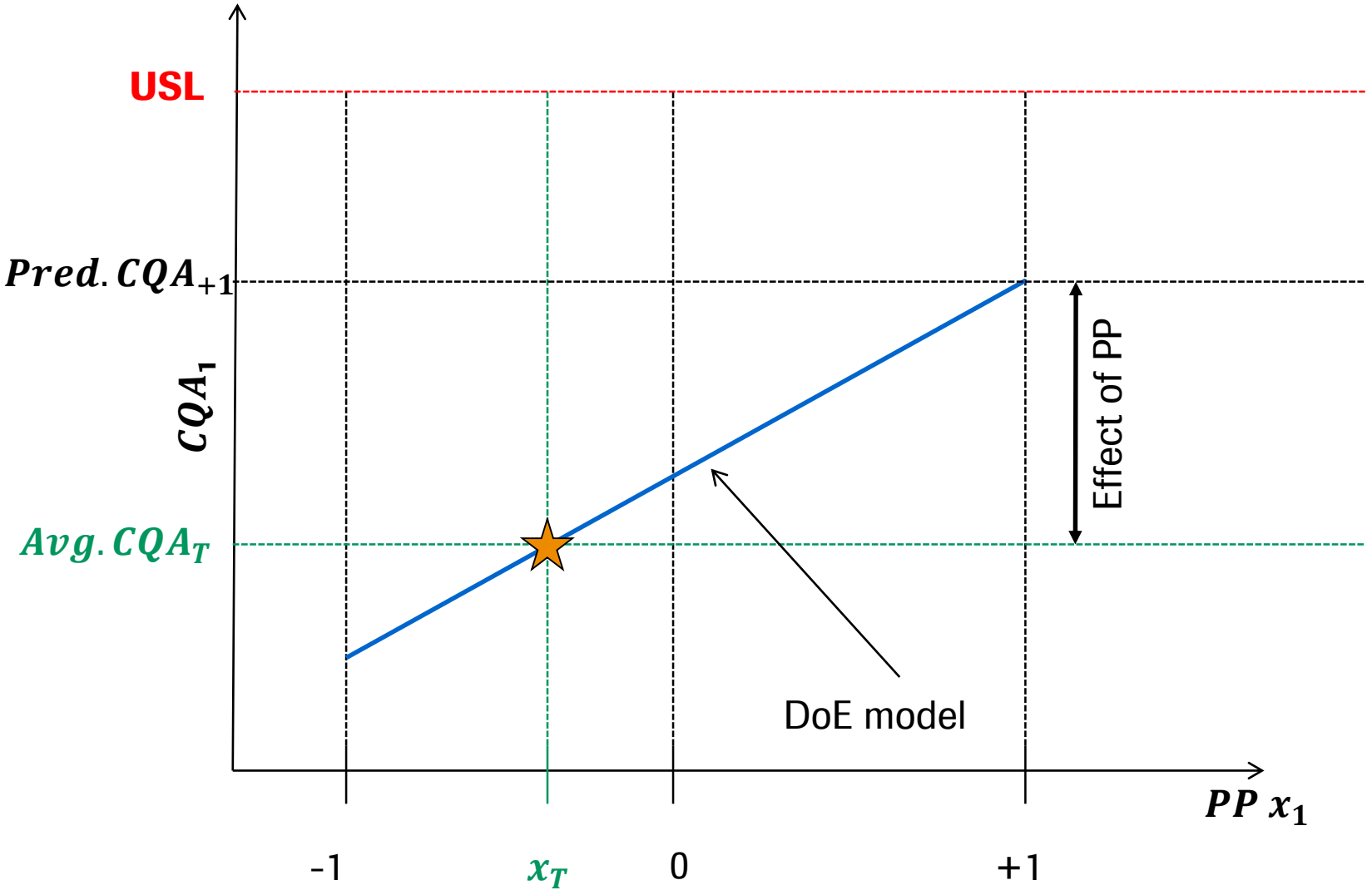

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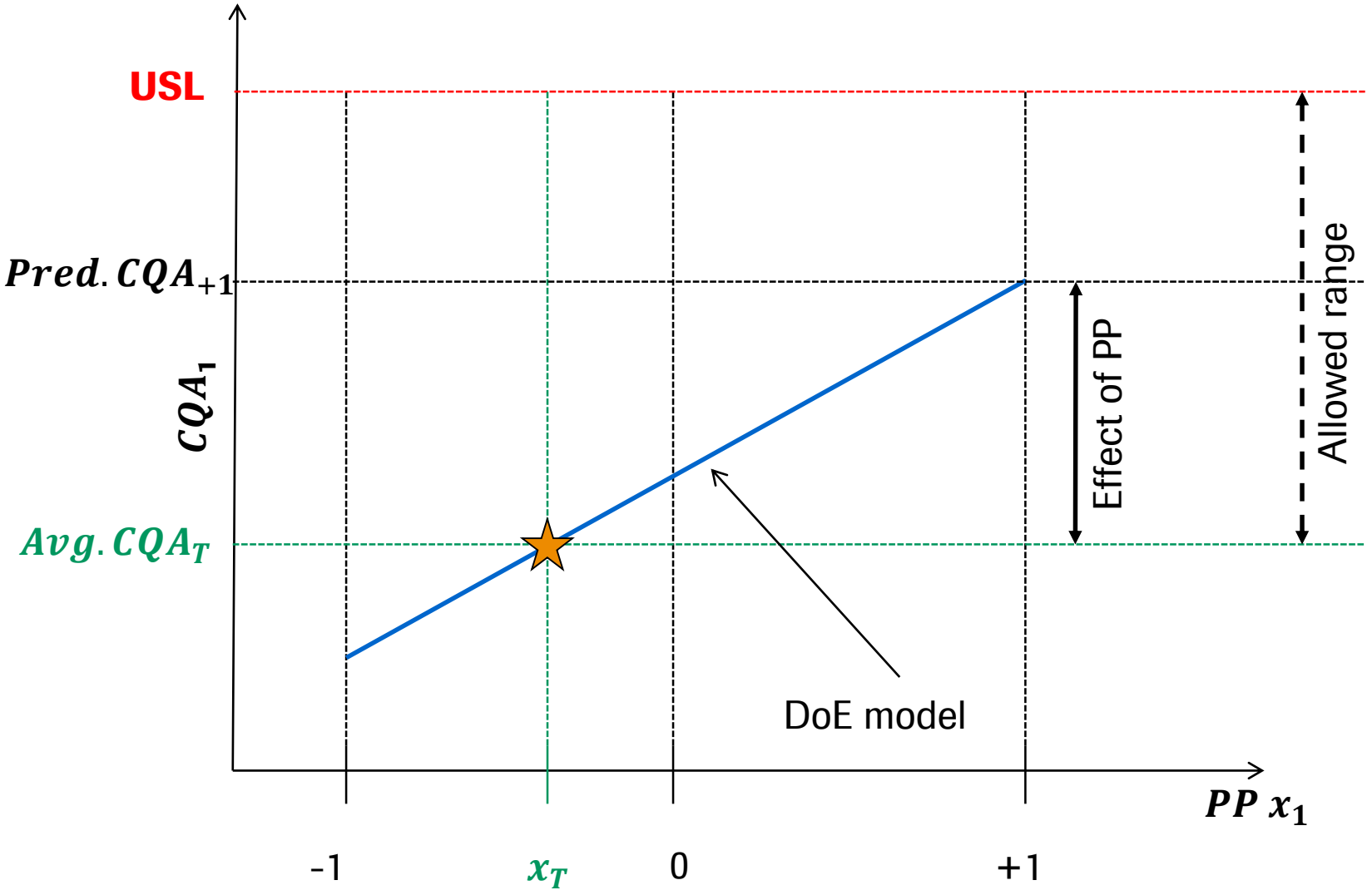
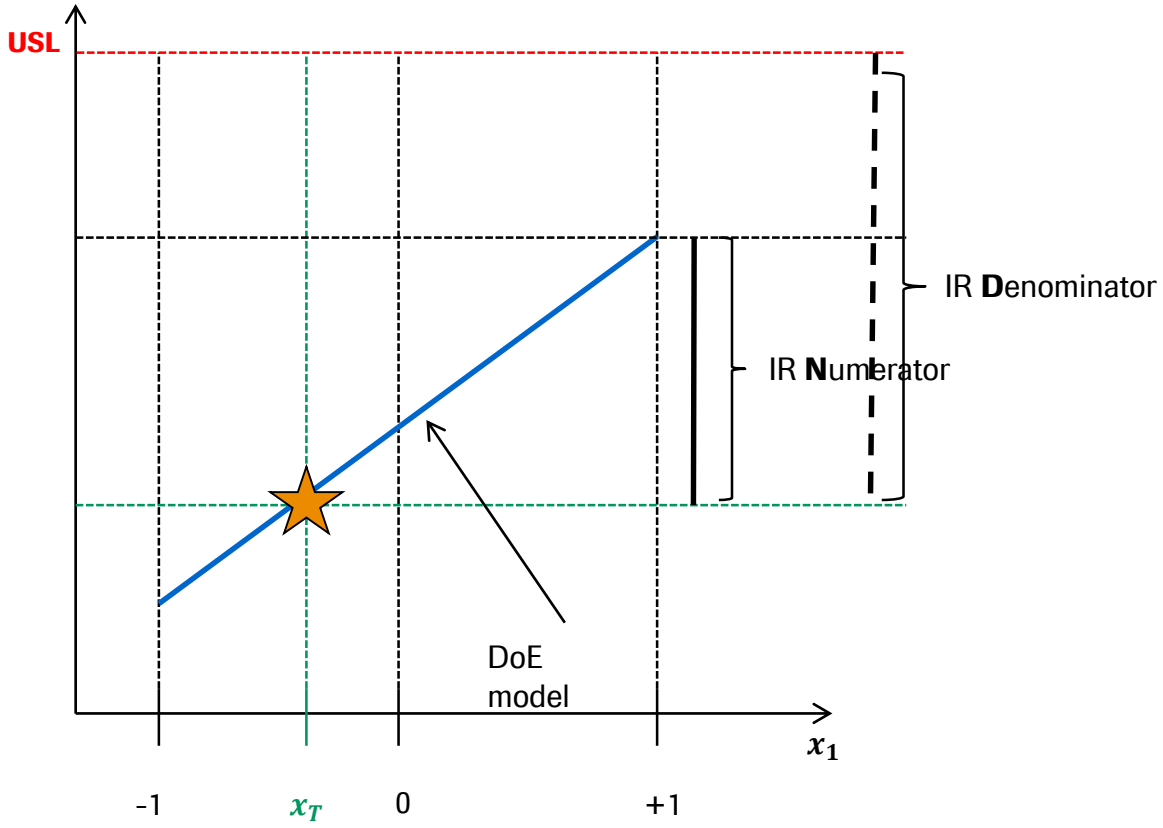


Impact Ratio – Definition for Small Molecules Chemistry at Roche

Definition of impact ratio (IR) of a process parameter x_1 on CQA_1

IR is the ratio of

- **Numerator:** Change in CQA when x_1 changes from its target (i.e., set point) to the extreme of its acceptable range, while all the other PP are set to target
- **Denominator:** Difference between USL, and process mean when all PPs are set at target level



Case I – Observed Process Mean at Target Setting and One-sided Specification (USL)

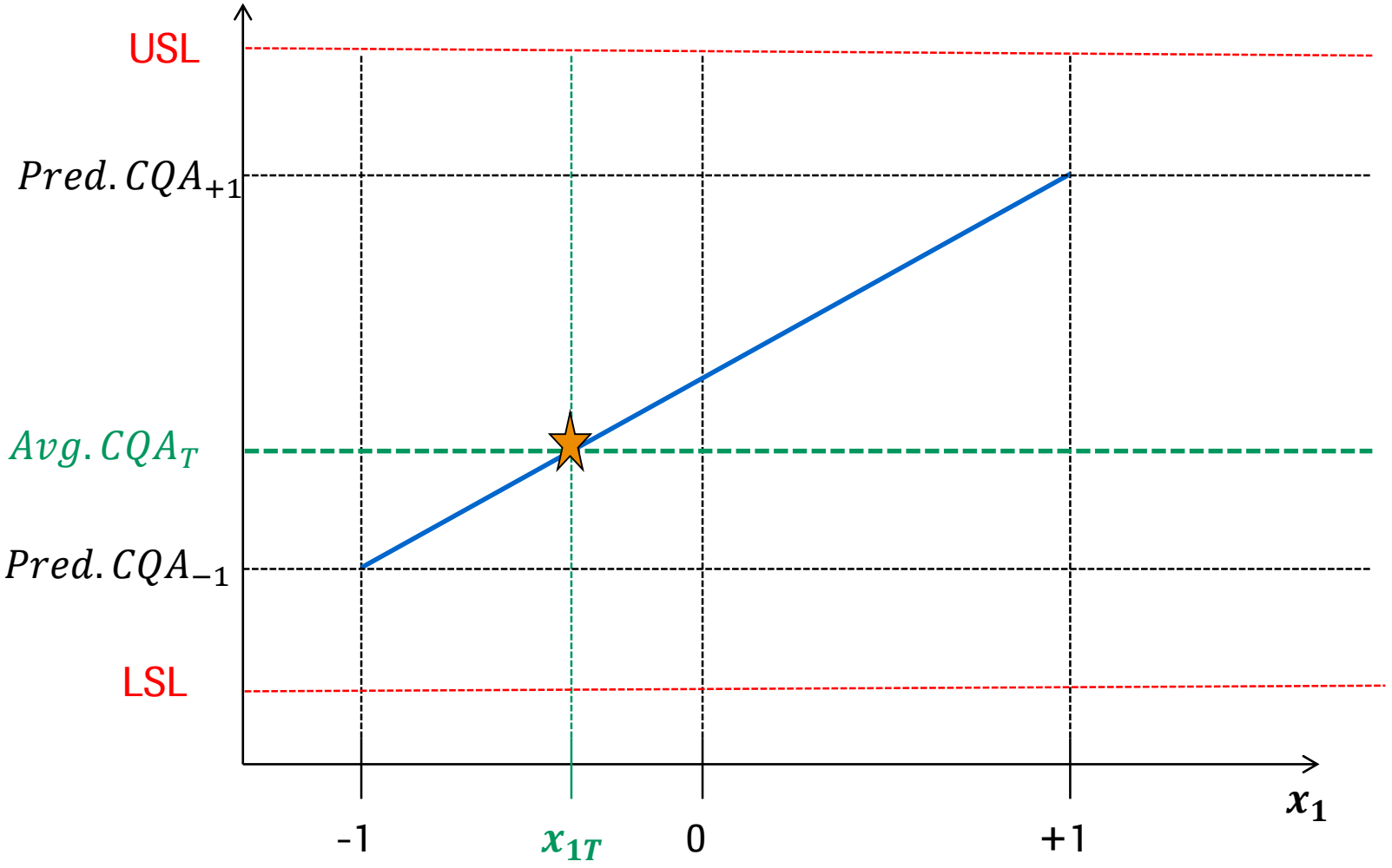
Computing IR for x_1

Effect of PP x_1 = IR Numerator = $Pred.CQA_{+1} - Avg.CQA_T$

Allowed Range = IR Denominator = $USL - Avg.CQA_T$

$$\text{IR} = \frac{Pred.CQA_{+1} - Avg.CQA_T}{USL - Avg.CQA_T}$$

Case II: Impact Ratio with both USL and LSL



Case II: Impact Ratio with both USL and LSL

Computing IR for x_1

- We compute two predictions for CQA using DoE linear model
  - Prediction of CQA when x_1 is set at high (i.e., $x_1 = +1$) and all the other parameters are set at target

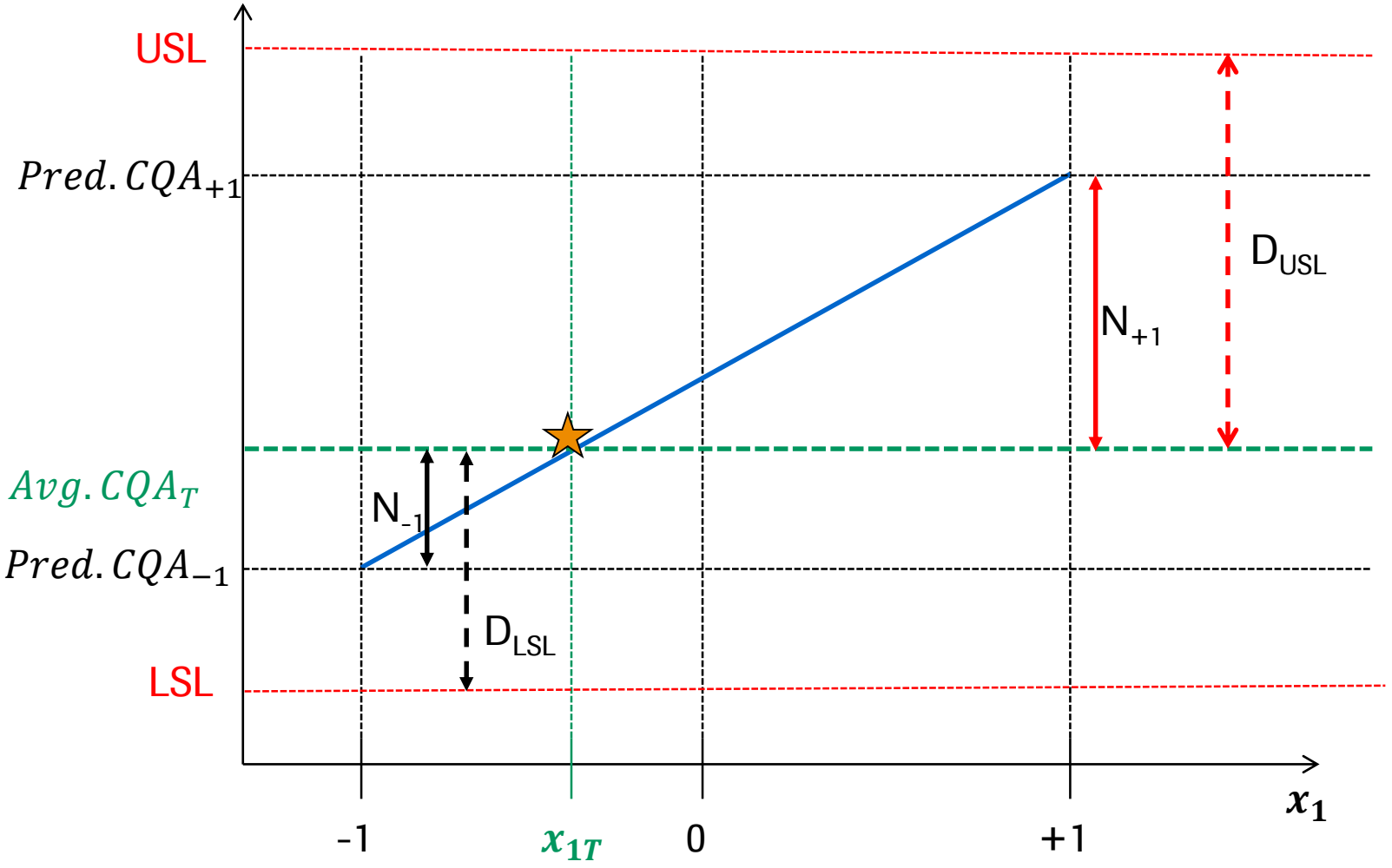
$$Pred.CQA_{+1} = f(x_1 = +1, x_{2T}, \dots, x_{pT})$$

  - Prediction of CQA when x_1 is set at low (i.e., $x_1 = -1$) and other parameters are set at target

$$Pred.CQA_{-1} = f(x_1 = -1, x_{2T}, \dots, x_{pT})$$

- We compute average CQA, $\boldsymbol{Avg.CQA_T}$, either from DoE runs or from previous runs at target

Case II: Impact Ratio with both USL and LSL



Choose the most conservative IR from all combinations of N_{+1}, N_{-1}, D_{USL} and D_{LSL}

$$\mathrm{IR} = \max\left(\frac{N_{+1}}{D_{USL}}, \frac{N_{-1}}{D_{USL}}, \frac{N_{+1}}{D_{LSL}}, \frac{N_{-1}}{D_{LSL}}, 0\right)$$

0 in case all IRs are negative (case shown later in slide 25)

Choose the most conservative IR from all combinations of N_{+1}, N_{-1}, D_{USL} and D_{LSL}

$$\mathrm{IR} = \max\Big(\underbrace{\frac{Pred.CQA_{+1} - Avg.CQA_T}{USL - Avg.CQA_T}}_{\text{IR1}}, \underbrace{\frac{Pred.CQA_{-1} - Avg.CQA_T}{USL - Avg.CQA_T}}_{\text{IR2}}, \frac{Pred.CQA_{+1} - Avg.CQA_T}{LSL - Avg.CQA_T}, \frac{Pred.CQA_{-1} - Avg.CQA_T}{LSL - Avg.CQA_T}, 0\Big)$$

IR3 IR4

Note:

- Considers the direction (= sign) of effects with regard to the direction to the next critical specification limit.
- “0” in case all IRs are negative (case shown later in slide 25).
- This method takes into account any possible curvature.

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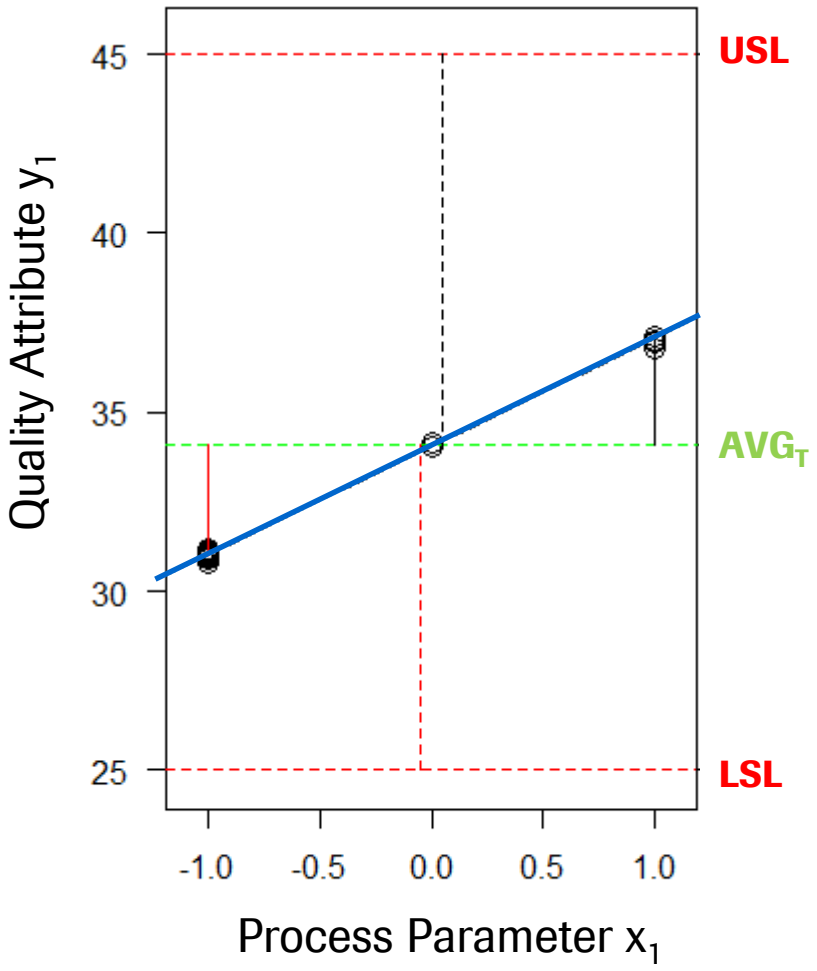
Example #1: with simulated data

IR = 0.335

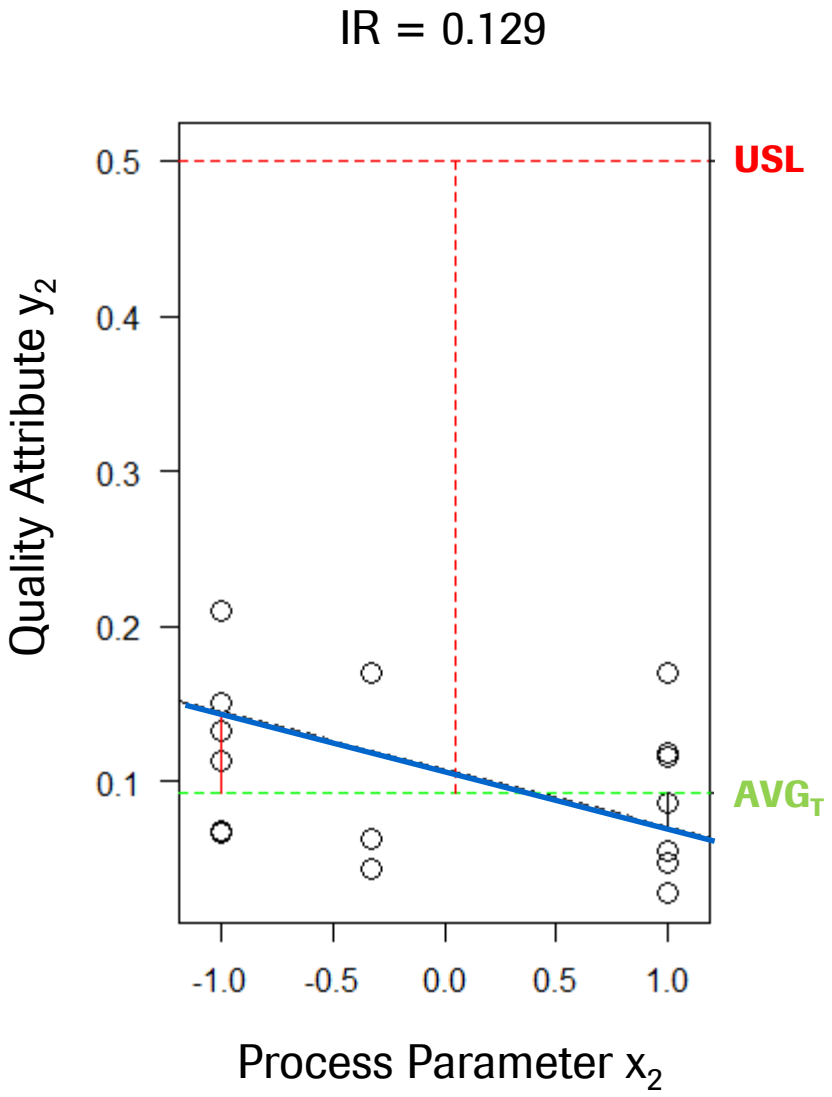


- USL = 45.0 %
- LSL = 25.0 %
- Avg.CQA$_T$ = 34.1 %
- Pred.CQA$_{+1}$ = 37.1 %
- Pred.CQA$_{-1}$ = 31.0 %

- IR$_1$ = 0.273
- IR$_2$ = -0.278
- IR$_3$ = -0.329
- IR$_4$ = 0.335

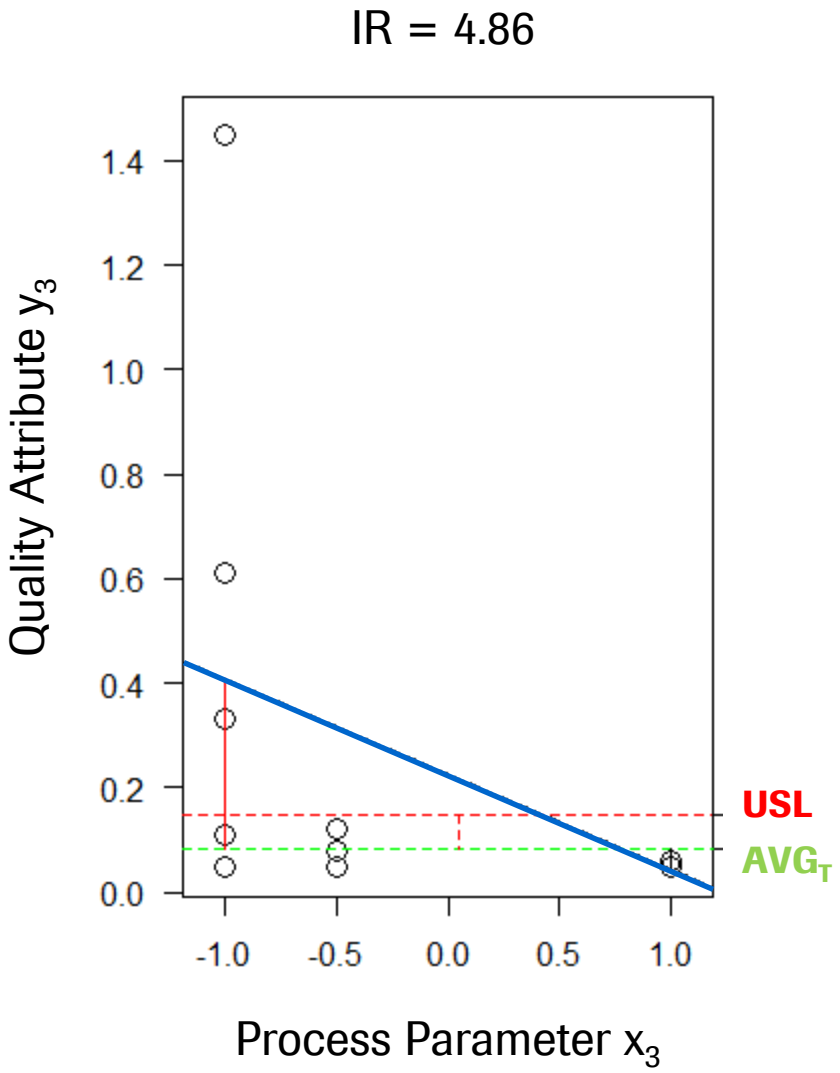
$$IR = \max\left(\underbrace{\frac{Pred.CQA_{+1} - Avg.CQA_T}{USL - Avg.CQA_T}}_{IR1}, \underbrace{\frac{Pred.CQA_{-1} - Avg.CQA_T}{USL - Avg.CQA_T}}_{IR2}, \underbrace{\frac{Pred.CQA_{+1} - Avg.CQA_T}{LSL - Avg.CQA_T}}_{IR3}, \underbrace{\frac{Pred.CQA_{-1} - Avg.CQA_T}{LSL - Avg.CQA_T}}_{IR4}, 0\right)$$

Example #2: Negative Slope



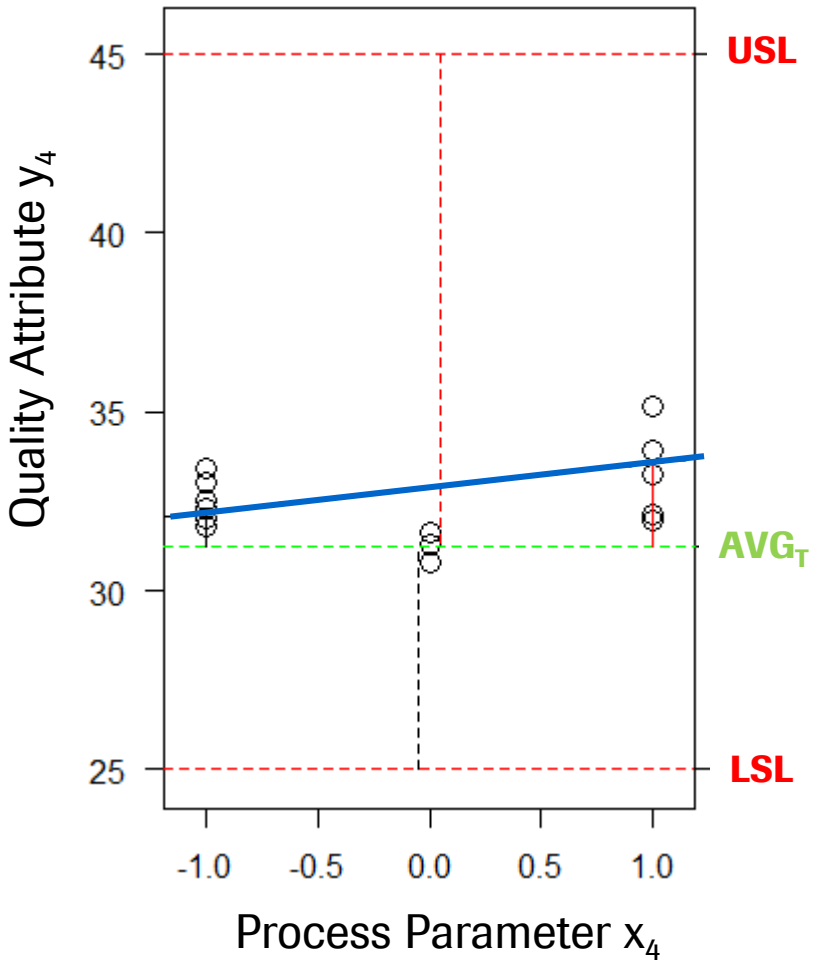
- Example with only one specification limit, USL.
- IR = 0.129, the impact of PP x_2 on CQA y_2 levels with regard to the specification limit is low.
- Negative slope: Risk is higher at lower amounts of PP x_2.

Example #3: Data out of Spec yields IR > 1



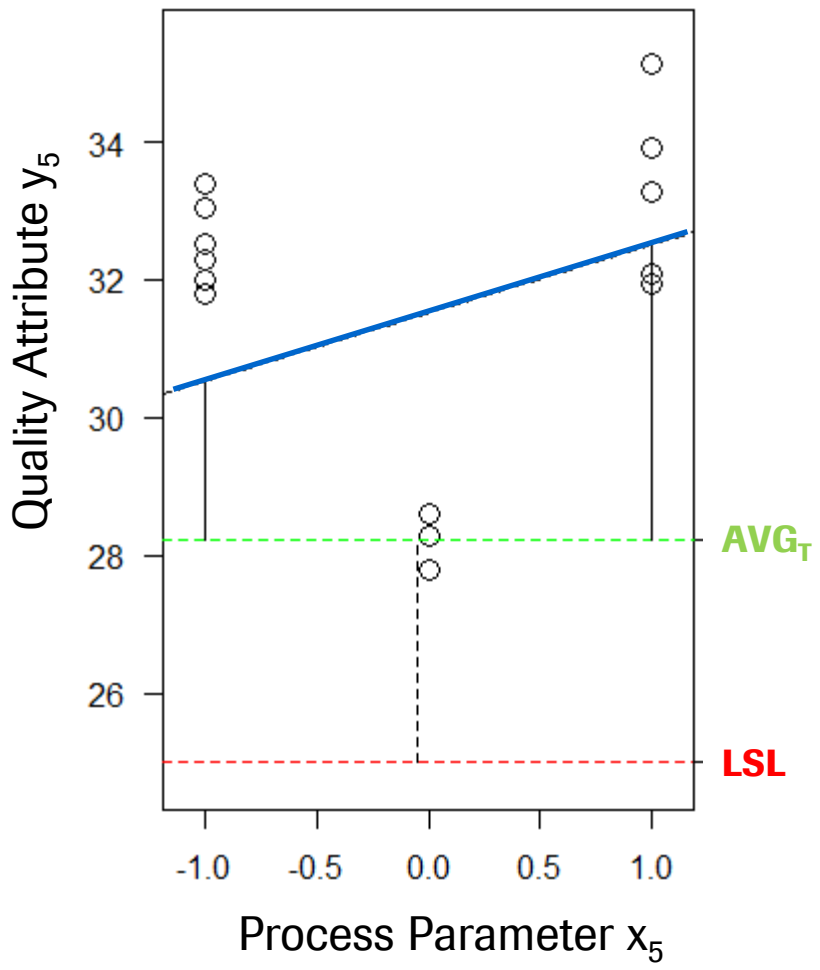
- With IR = 4.86, the impact of PP x_3 on levels of QA y_3 with regard to the specification limit is extremely high.
- The algorithm is robust to large effect and computes results with IR > 1.0.
- Problematic responses (data out of spec) will be identified.

Example #4: Curvature in response



- The magnitude of CQA y_4 at target of PP x_4 is lower than at extremes -1 and +1.
- Both red (right) and black (left) solid lines are compared to the red dashed line to compute the Impact Ratio.
- The algorithm is robust to parabolic curvature in the data.
- IR = 0.17

Example #5: Curvature in response and IR = 0



- Example with curvature, and CQA at both extremes of CQA range trend away from CQA at target setting.
- Moving parameter away from Target, moves CQA away from specification, hence parameter has no impact.
- IR = 0

$$\mathrm{IR} = \max\left(\frac{N_{+1}}{D_{USL}}, \frac{N_{-1}}{D_{USL}}, \frac{N_{+1}}{D_{LSL}}, \frac{N_{-1}}{D_{LSL}}, \mathbf{0}\right)$$

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Role of the Impact Ratio at Roche Technical Development of Small Molecules

- Two years after its implementation, the Impact Ratio is an important pillar in process characterization of API synthesis steps at Roche Technical Developments of Small Molecules.
- The Impact Ratio is estimated for
  - all CQA,
  - all PP,
  - in all critical synthesis steps
  - of all small molecules in late stage development,
  - which will be manufactured internally.
- The Impact Ratio ***supports*** the SME in deciding whether a PP is
  - critical (CPP), IR ≥ 0.3,
  - or not critical (PP), IR < 0.3.

by Howard Miller, 1943

Summary

- The effect of Process Parameters on CQA is investigated in Designed Experiments.
- A Process Parameter with significant effect on a CQA does not always have a relevant impact.
- Additionally, PPs effect on a given CQA may be small in comparison to the allowed range defined by the CQA specification limits. Furthermore, the intended process mean value of a CQA may be numerically far away from these limits.
- Therefore, an additional quantitative metric could substantially help the assessment of practical relevance of process parameters and their interactions, the **impact ratio (IR).**
- IR quantifies the maximum risk of reaching the CQA specification limits and its calculation is based on data from a DoE.

Summary

- The proposed simple algorithm for the computation of Impact Ratios
  - Is flexible to different designs
  - Allows process set (i.e., target) points being different from the center points in the DoE
  - Is robust to quadratic curvature in the data
- Considers the direction (= sign) of effects with regard to the direction to the next critical specification limit.

Acknowledgments

- Wolfgang Goehring
- Stefan Hildbrand
- Pankaj Rege
- Andreas Schuster
- Helmut Stahr

Doing now what patients need next