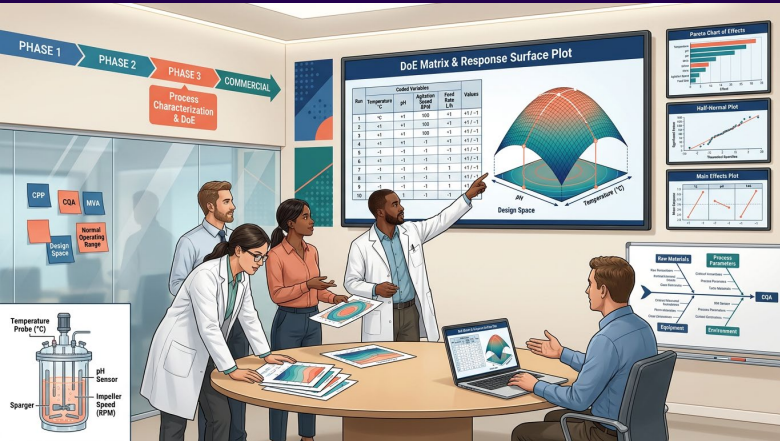


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Process Characterization and associated DoEs considerations in R&D CMC

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team from Sanofi R&D*

CCD , PPD & Digital teams from Sanofi R&D



DoEs for Process Characterization _ Agenda

- Introduction
- DoEs building
- DoEs analysis
 - Model selection
 - PAR calculation, for one factor
 - PAR calculation, situation with a block factor
 - Impact Ratio, 3 formulae
 - Impact Ratio, situation with a block factor
- Conclusion and perspective

DoEs for Process Characterization _ Introduction

Objectives of the Process Characterization

Characterizing change

Characterize the commercial manufacturing process and understand how changes in the process parameters over manufacturing relevant ranges impacts product quality and process performance

PARs

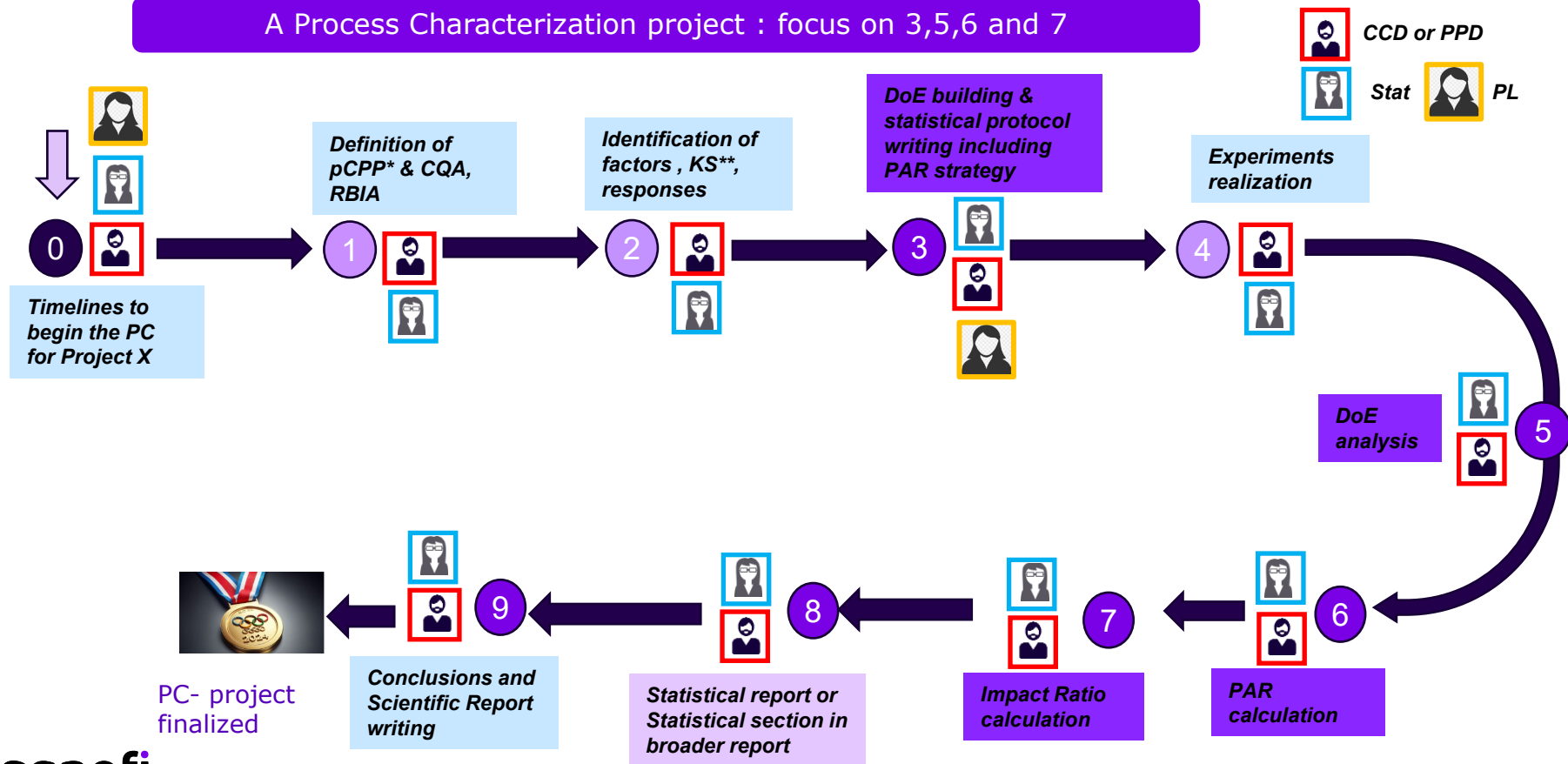
Establish Proven Acceptable Ranges (PARs) for important process parameters, where a PAR is defined as the “characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (ICH Q8 (R2)).”

Impact Ratio

Evaluate the severity of the impact of each characterized parameter on both product quality and process performance. The severity scores can then be input into a Failure Mode and Effects Analysis (FMEA) to identify Critical Process Parameters (CPPs) and Key Process Parameters (KPPs) which may have significant impacts on product quality and process performance, respectively (ICH Q9 (R1))

DoEs for Process Characterization _ Introduction

A Process Characterization project : focus on 3,5,6 and 7



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DoEs building

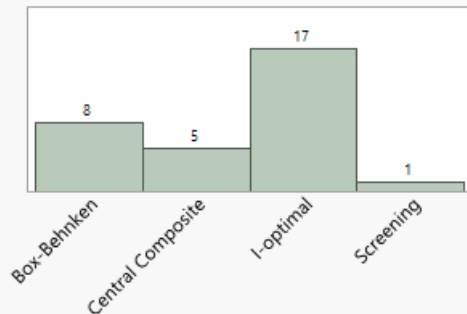
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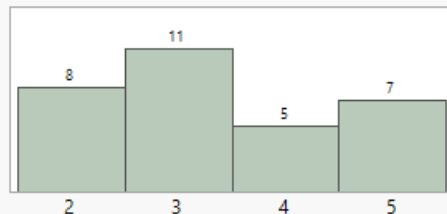
DoEs for Process Characterization _ DoEs building

Examples of 31 DoEs for USP and DSP

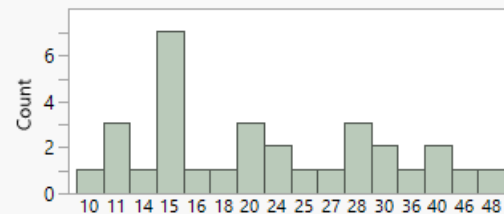
Type of DoE



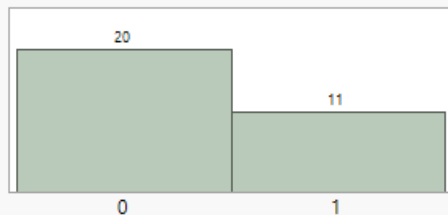
Number of DoE's Factors



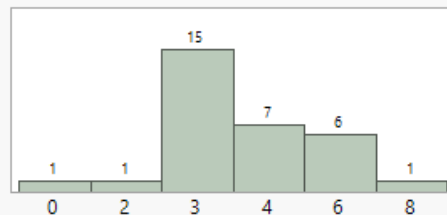
Number of runs



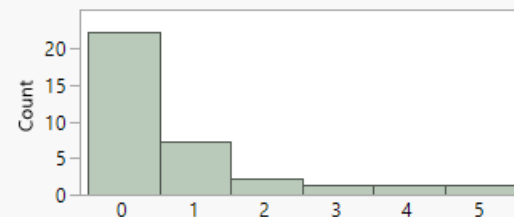
Number of Block factor



Number of Center Points/Set points



Nb factors OFAT





DoEs Analysis



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DoEs for Process Characterization _ DoEs analysis

Model selection

With DoE's factors coding

Column Name: Factor 2

☐ Lock

Data Type: Numeric

Modeling Type: Continuous

Format: Fixed Dec Width 15 Dec 1

☐ Use thousands separator ()

Column Properties

Coding

Coding declares that when you fit it in a model, the range Low to High is transformed into the range -1 to 1. This property makes tests and parameters estimates more meaningful.

Low Value: 2,9

High Value: 5,1

Remove

Fig 1 : example of factor 's coding with JMP software

Model's terms selection

From a Response Surface Model generally

Mainly backward regression with p-value cut-off = 10% , or AICc

With the effect heredity principle

Stepwise Regression Control

Stopping Rule: P-value Threshold

Prob to Enter: 0,1

Prob to Leave: 0,1

Direction: Backward

Rules: Combine

Go Stop Step

Training Rows: 15

Fig 2 : Example of backward regression with JMP software

Model's quality criteria

R^2_{adj} , Pred R^2 , Residuals assumption, potential outliers...

Residual	SSE	RMSE	RSquare
Press	4,8084378321	0,56618241	0,8074
Ordinary	0,6101719447	0,29524129	0,9756

Fig 3 : Example of Pred R^2 (PRESS) with JMP software

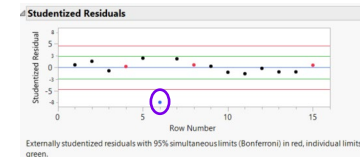


Fig 4 : Example of Residuals analysis with JMP software

Final model

Endorsement and use : CQA with a good-enough model, eg with Pred $R^2 \geq 0.6$

Term	Estimate	Std Error	t Ratio	Prob> t	Uncoded Estimate
Intercept	98,609	0,111754	882,37	<.0001*	-269,2592
Factor 1(0,166,0,533)	-0,14717	0,118513	-1,24	0,2543	60,218965
Factor 2(2,9,5,1)	-0,493175	0,114513	-4,31	0,0035*	12,721878
Factor 3(34,5,38,5)	-1,415225	0,105852	-13,37	<.0001*	18,950792
Factor 1*Factor 2	-0,361478	0,176668	-2,05	0,0800	-1,790826
Factor 1*Factor 3	-0,541528	0,176336	-3,07	0,0180*	-1,475553
Factor 2*Factor 3	-0,756096	0,163858	-4,61	0,0024*	-0,34368
Factor 3*Factor 3	-0,973588	0,154319	-6,31	0,0004*	-0,243397

Fig 5 : Example of Parameter Estimate Table (with JMP software)

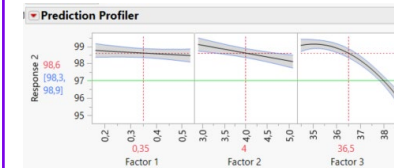


Fig 6 : Example of Prediction Profiler , with factors at their set point (with JMP software)

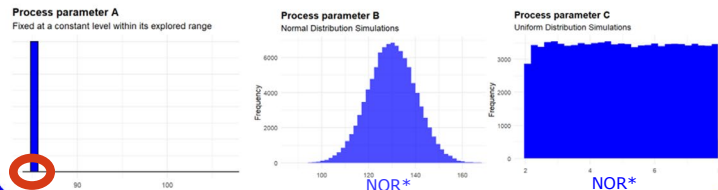
-
- PAR calculation, for one factor
-

DoEs for Process Characterization _ DoEs analysis

PAR calculation, for one factor : « Univariate PAR »

Probability of failure estimation at one level of process parameter A

Step 1



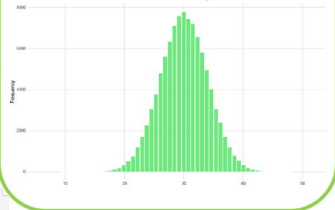
Step 4

N : Total number of Monte Carlo simulations
D : Number of Monte Carlo simulations uncompliant with the acceptance criterion

Risk of failure (%) of the point
 $100 \times \frac{D}{N}$

Step 2

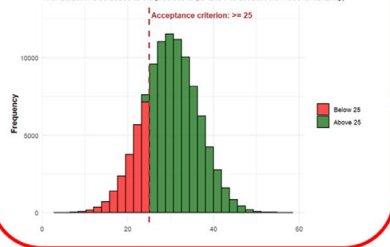
Predicted distribution of the Quality Attribute
Without random noise added to the predictions



Student random noise added

Step 3

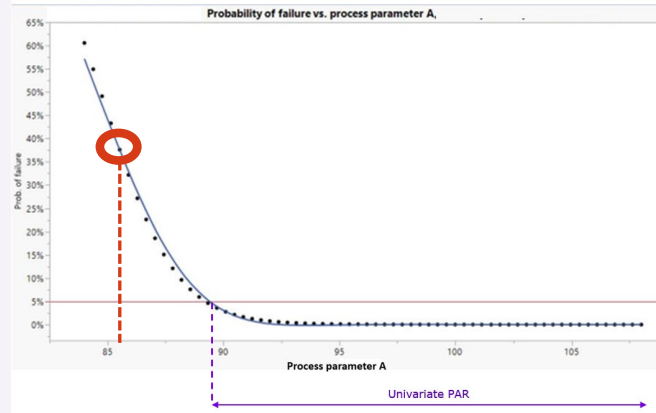
Predicted distribution of the Quality Attribute
With Student noise added to the predictions (to take into account the model uncertainty)



Combined for all the CQAs

Probability of failure calculation

Redo those 4 steps for several values covering the explored range of process parameter A



*Normal and uniform distribution utilized depending on anticipate control performance with ranges set at estimated at-scale NOR (Normal Operating Range)

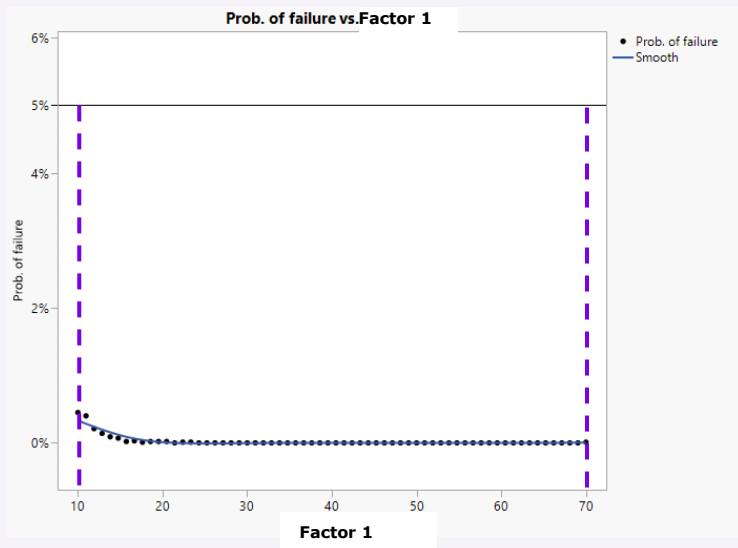
Estimation of the probability of failure provided by Modde software

PAR limit set so that defect rate $\leq 5\%$ for all CQAs

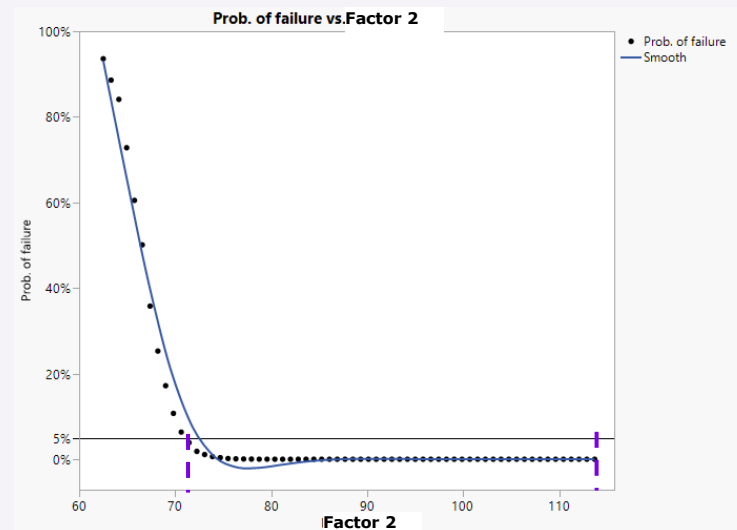
DoEs for Process Characterization _ DoEs analysis

PAR calculation, for one factor : « Univariate PAR »

Univariate PAR for 2 factors and for all the CQAs with a « good-enough » model



Univariate PAR = Knowledge Space (KS) = [10;70]



Univariate PAR = [71,4;113,7]

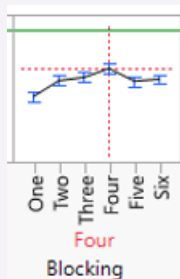
DoEs for Process Characterization _ DoEs analysis

PAR calculation, situation with a block factor

Example of a DoE with the Block, one of the highest effect

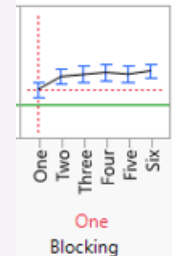
Response A

Scaled Estimates			
Nominal factors expanded to all levels			
Term	Scaled Estimate		Prob> t
Factor	-0,195785		<.0001*
Blocking HT group_[One]	-0,123266		<.0001*
Factor	-0,076627		<.0001*
Blocking HT group_[Five]	-0,004753		0,7414
Blocking HT group_[Two]	-0,000117		0,9935
Blocking HT group_[Six]	0,0107421		0,4518
Factors	0,0137943		0,1069
	0,0164431		0,0791
Blocking HT group_[Three]	0,0242967		0,0982
Blocking HT group_[Four]	0,0930973		<.0001*
Factor	0,1177565		<.0001*
Intercept	0,8336954		<.0001*



Response B

Scaled Estimates			
Nominal factors expanded to all levels			
Term	Scaled Estimate		Prob> t
Factor	-0,20777		<.0001*
Blocking HT group_[One]	-0,129728		<.0001*
Factors	-0,078823		0,0002*
	-0,067602		0,0007*
	-0,064156		0,0017*
	-0,048387		0,0979
Blocking HT group_[Two]	-0,003596		0,8966
Factor	0,0165981		0,3033
Blocking HT group_[Three]	0,0186349		0,5031
Blocking HT group_[Five]	0,0212468		0,4462
Factors	0,0252241		0,0993
	0,0354962		0,0614
Blocking HT group_[Four]	0,0390046		0,2294
Factors	0,0468143		0,0134*
	0,0543287		0,0718
Blocking HT group_[Six]	0,0544374		0,0567
Factors	0,0560492		0,0753
	0,068313		0,0002*
	0,0783636		0,0002*
	0,0876417		<.0001*
Intercept	3,2029233		<.0001*



DoEs for Process Characterization _ DoEs analysis

PAR calculation, situation with a block factor

Example of a DoE with the Block, one of the highest effect

Analysed as random

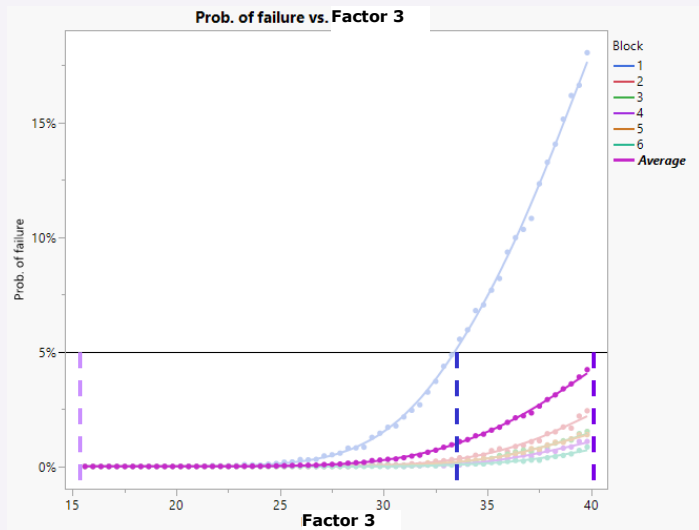
Response A

Parameter Estimates						
Term	Estimate	Std Error	DFDen	t Ratio	Prob> t	Uncoded Estimate
Factors	-0,195809				<,0001*	
	0,1180118				<,0001*	
	0,8337054				<,0001*	
	-0,077028				<,0001*	
	0,0158065				0,0909	
	0,0136428				0,1105	
REML Variance Component Estimates						
Random Effect	Var Ratio	Var Component	Std Error	95% Lower	95% Upper	Wald p-Value
Blocking HT group_						71,405
Residual						28,595
Total						100,000

DoEs for Process Characterization _ DoEs analysis

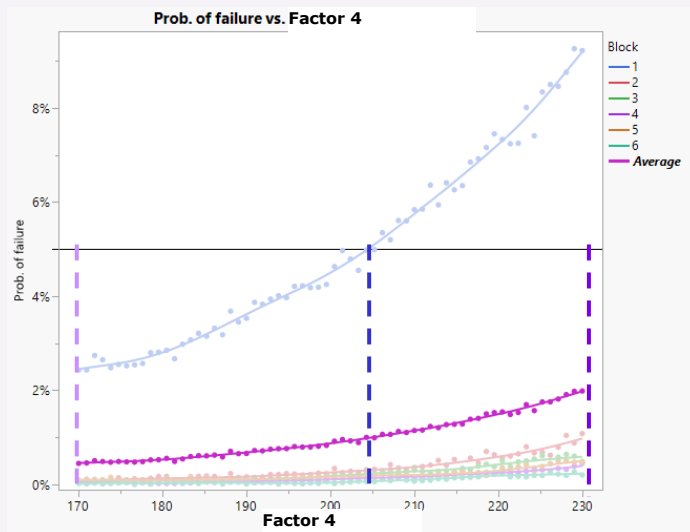
PAR calculation, situation with a block factor

Example of a DoE with the Block, one of the highest effect



Univariate PAR Block 1 = [15.6;33.3]

Univariate PAR Average= [15.6;39.8]=KS*



Univariate PAR Block 1 = [170;204]

Univariate PAR Average= [170;230]=KS*

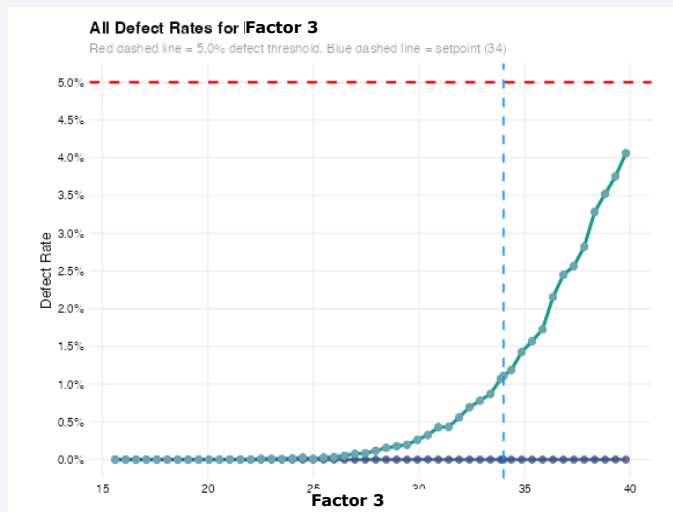


Average relevant if block not practically significant, or experimental nuisance, or not present at manufacturing scale ...

DoEs for Process Characterization _ DoEs analysis

PAR calculation, situation with a block factor

Example of a DoE with the Block, one of the highest effect
Analysed as random



Univariate PAR Random block = [15.6;39.8]=KS*



Random relevant to reflect the experimental variability or if block categories not representative of all the possibilities at e.g. manufacturing scale; results close to the averaging across block levels

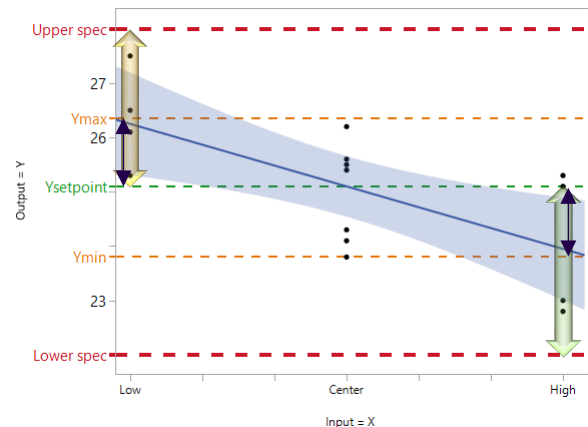
Impact Ratio

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DoEs for Process Characterization _ DoEs analysis

Impact Ratio, 3 formulae

Formula 1 without confidence interval



Worst case = $\widehat{Y_{min}}$ or $\widehat{Y_{max}}$

Acceptance limit = Lower or Upper Specification

$\widehat{Y_{Setpoint}} \Rightarrow$ prediction at setpoint

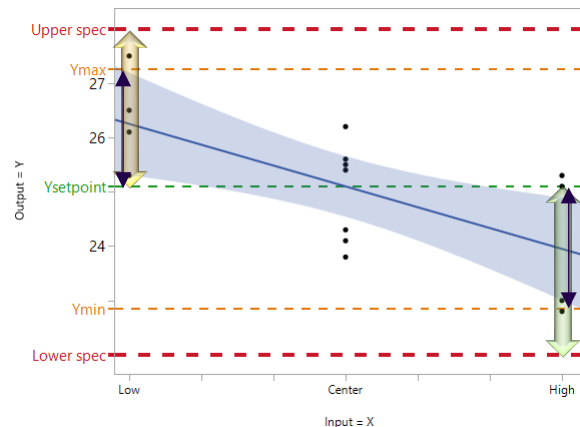
$$IR_{formula\ 1} = \left| \frac{\text{Worst case} - \widehat{Y_{Setpoint}}}{\text{Acceptance limit} - \widehat{Y_{Setpoint}}} \right| = \frac{\text{Effect size}}{\text{Distance to spec}}$$

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Calculated in the
Knowledge Space
(KS) or in the PAR

Formula 3 : Formula 1 with Fieller confidence interval (95% upper bound will be displayed)

Formula 2 with confidence interval



Worst case_{lower/upper} = Lower or Upper Bound of $\widehat{Y_{min}}$ or $\widehat{Y_{max}}$

Acceptance limit = Lower or Upper Specification

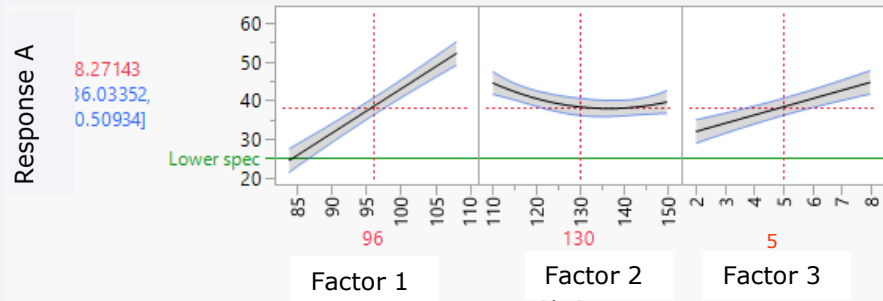
$\widehat{Y_{Setpoint}} \Rightarrow$ prediction at setpoint

$$IR_{formula\ 2} = \left| \frac{\text{Worst case}_{lower/upper} - \widehat{Y_{Setpoint}}}{\text{Acceptance limit} - \widehat{Y_{Setpoint}}} \right|$$

DoEs for Process Characterization _ DoEs analysis

Impact Ratio, 3 formulae : in KS or in PAR

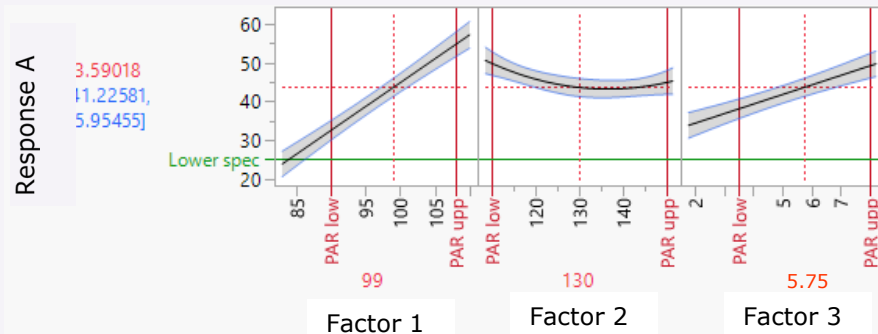
In the Knowledge space



Impact ratio	Factor 1	Factor 2	Factor 3
Formula 1	106.24%	3.14%	48.67%
Formula 2	129.69%	19.37%	72.12%
Formula 3	134.25%	9.78%	68.52%

In KS : Calculation is always possible using the setpoint

In the Univariate PAR



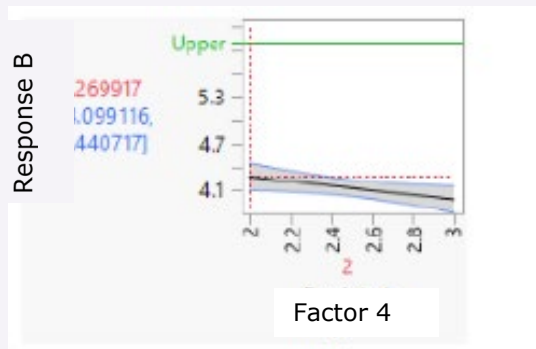
Impact ratio	Factor 1	Factor 2	Factor 3
Formula 1	60.82%	2.23%	30.13%
Formula 2	74.70%	14.49%	44.01%
Formula 3	75.57%	6.77%	41.68%

In PAR : When the setpoint falls outside the PAR, calculation uses the PAR midpoint instead

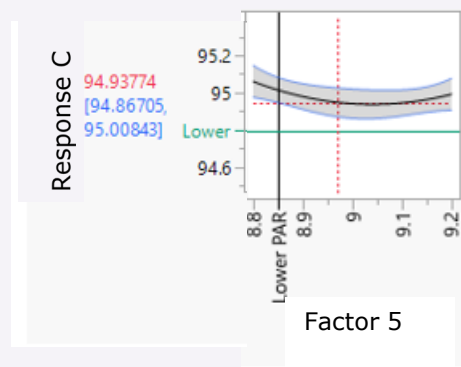
➡ lower values than in KS

DoEs for Process Characterization _ DoEs analysis

Impact Ratio, 3 formulae : Case of set point close to the worst case



Impact ratio	Factor 4
Formula 1	0%
Formula 2	10%
Formula 3	0%



Impact ratio	Factor 5
Formula 1	7%
Formula 2	58%
Formula 3	49.1%

IR is equal to or close to 0 with Formula 1 , and 3 in first example, as the worst case is close to the set point



In in this particular situation , Formula 2 with confidence interval better expresses the risk of being close to the limits

DoEs for Process Characterization _ DoEs analysis

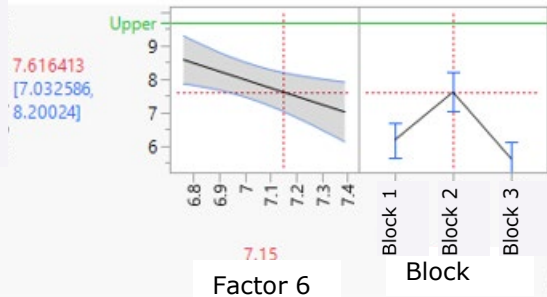
Impact Ratio (Formula 1), situation with a significant block factor

Calculation with the block the closest to the limit

Calculation with the averaging over block levels*

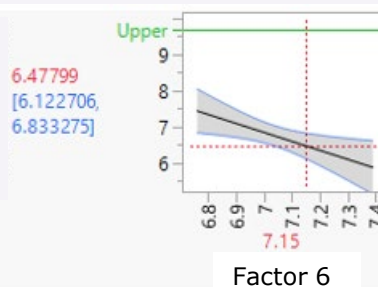
Calculation with the block as random

Response D



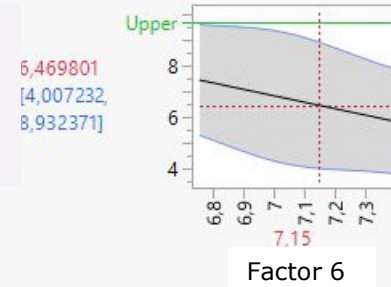
IR =46%

Response D



IR =30%

Response D



IR =30%

Lowest Impact Ratio (IR) with the averaging over block levels or with the block as random

Relevant if block not practically significant, or experimental nuisance, or not present at manufacturing scale ...

*Such as predicted mean values across the blocks or the 'block-effect' design role

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Conclusion & Perspectives

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Conclusion and perspectives

- For the DoEs building : mainly RSM DoEs, like I-optimal, for 3 or 2 factors, with 3 or 4 CP
- For the DoEs analysis : Model selection
- For the Impact Ratio :

- Carefully investigate the impact and nature of the block factor before averaging over block levels
- Analyze the block as random when appropriate by its nature
- Use confidence interval (CI) formula for the IR.

Since IR is the ratio of 2 statistics, it is an IR on a ratio → Fieller formula.

For specific cases when the worst case is close to the set point, Formula 2 with predicted value at worst case

- Simulate different cut-off to better justify them or find new ones per study or per CQA , currently :
- Propose a « multivariate » Impact Ratio

- For the Univariate PAR :

- Carefully investigate the block factor impact/nature before averaging over block levels or considering it random
- Propose additionally the « Multivariate PAR » or Multivariate Acceptable Ranges « (similar concept than MODR in ICH Q14), to better take into account the interactions between factors, to summarize a Design Space and in case of deviations of 2 or more factors from their set point at manufacturing scale

Impact Ratio	Category
$IR > 0.25$	High Impact
$0.1 \leq IR \leq 0.25$	Medium impact
$IR < 0.1$	Low impact

References and Acknowledgements

- International Council for Harmonization (ICH), *ICHQ8(R2) – Pharmaceutical Development*, Current Step 4 Version, August 2009.
- *ICH Q14-Analytical Procedure Development* , Final Version, Step 4, 1 November 2023.
- « Questions and answers : Improving the understanding of NORs , PARs DSp and normal variability of process parameters », EMA/CHMP/CVMP/QWP/354895/2017
- « An improved Impact Ratio for Identifying Critical Process Parameters in Pharmaceutical Manufacturing Processes » J.Lamerz, O. Mihaela Danila, A.Schuster et al., PDA J Pharm Sci and Tech 2022, 76 497-508.
- « Process characterization and Design Space definition » C.Hakemeyer, N.McKnight, R.St.John et al., Biologicals 2016, 44 .
- Fieller, E. C. (1954). Some problems in interval estimation. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, 16(2), 175-185.
- USP < 1034> Analysis of Biological Assays
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Thank You! Questions ?

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