First Approach Applying QbD in a Scale-Up of a Lyophilization Cycle for an Antiviral Product

Authors:
Laura Noguera
Enric Jo, PhD

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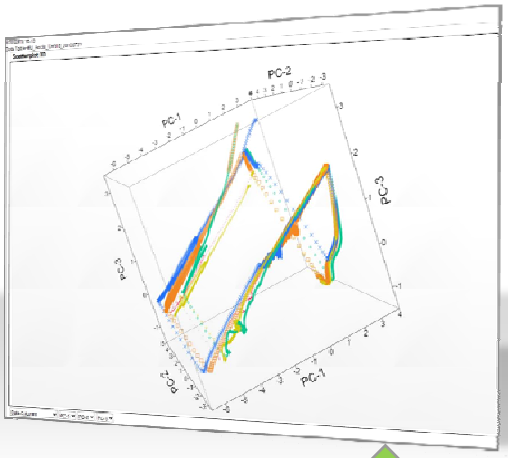
Quality by Design in Lyophilization



Can we avoid that by means of that?

Quality by Design in Lyophilization

The sequence of QbD:

Quality Target Product Profile (**QTPP**)

Critical Process Parameters (**CPP**) (**Inputs**)

Risk Assesment linking **CPP** & **CQA** (**RA**)

Design Space (DS)

Step 1 → Step 2 → Step 3 → Step 4 → Step 5 → Step 6 → Step 7

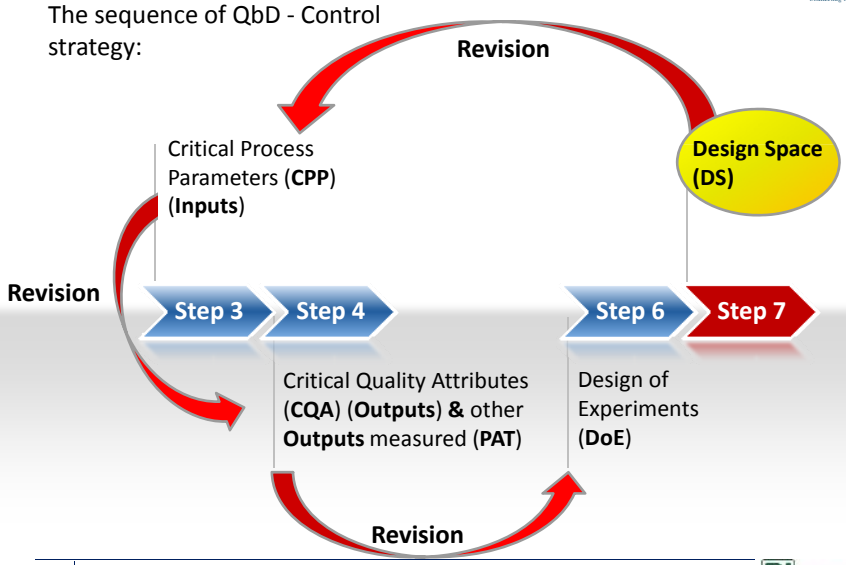
Critical Material Attributes (**CMA**)

Critical Quality Attributes (**CQA**) (**Outputs**)

Design of Experiments (**DoE**)

Quality by Design in Lyophilization

The sequence of QbD - Control strategy:



Quality Target Product Profile (QTPP)

- The **TPP** is a summary of drug labeling concepts. The **QTTP** is its natural extension for product quality.
- Each element of the **QTPP** is related with one of the **CQA** for the product.
- The **CQA** selected for the product (an antiviral) are related to the freeze drying process:

QTPP Element	Target (CQA)
Appearance	**Right**
Residual Moisture Content (RMC)	**< 6 %**
Reconstitution Time	**< 2 min**

- **Critical Quality Attributes:** 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 Material Attributes (CMA)

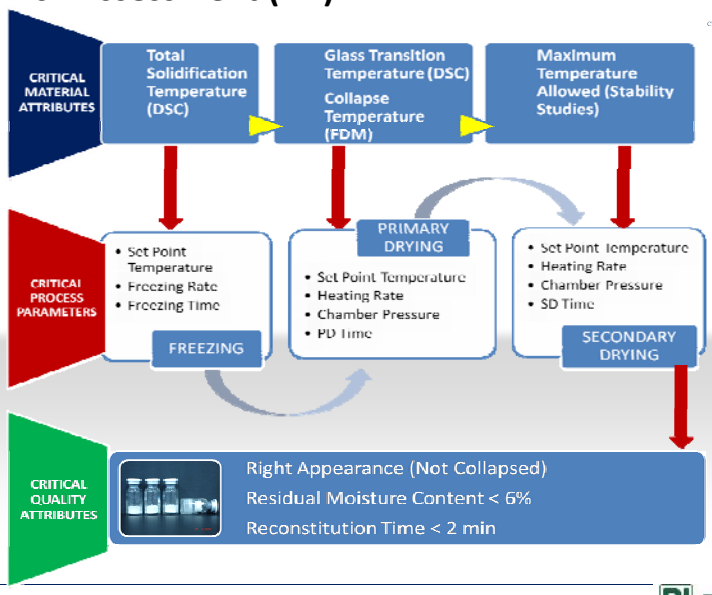
A key parameter or attribute may eventually be designated as "critical" depending on severity and probability of failure and its ability to be detected. Nosal R and T. Schultz, PQLI Definition of Criticality. *J. Pharm. Innov*. 3:pp 69-78, 2008

Key Attribute	Analytical Source	Rank
(1) Temperature of Total Solidification (T_{ts})	**DSC/FDM**	**< -26 °C**
(2) Glass Transition Temperature (T_g')	**DSC**	**[-72:-32] °C**
(3) Collapse Temperature (T_{co})	**FDM**	**[-58:-56] °C**
(4) Melting Temperature (T_m)	DSC/FDM	[-20:-13] °C
(5) Height of the Solution (inside the vial)	Measure	10 mm
(6) Solid Material Content	Defined (TPP)	10.5 %
(7) Max. Exposure Temp. Allowed (T_{max})	**Stability Studies**	**<35°C**
(8) Volume (to ensure the API dose)	Defined (TPP)	2.8 0.1 ml

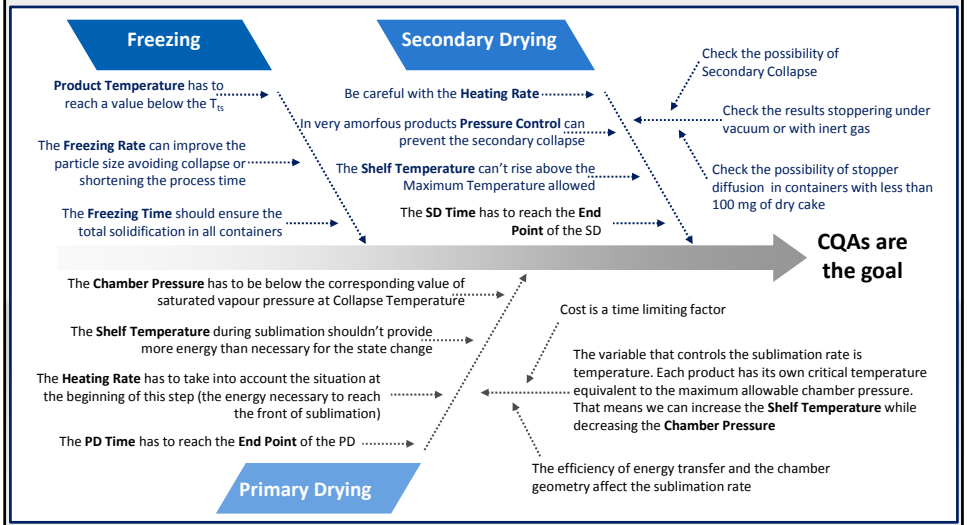
Critical Process Parameters (CPP)

Critical Process Parameter	Related Variable	Process Step
Set Point Shelf Temperature	T	FREEZING
Freezing Rate	Fr	
Freezing Time	Ft	
Set Point Shelf Temperature	T	PRIMARY DRYING
Heating Rate	HRa	
Chamber Pressure	P	
Primary Drying Time	PDt	
Set Point Shelf Temperature	T	SECONDARY DRYING
Heating Rate	HRa	
Chamber Pressure	P	
Secondary Drying Time	SDt	

The Risk Assessment (RA)



The Risk Assessment (RA)



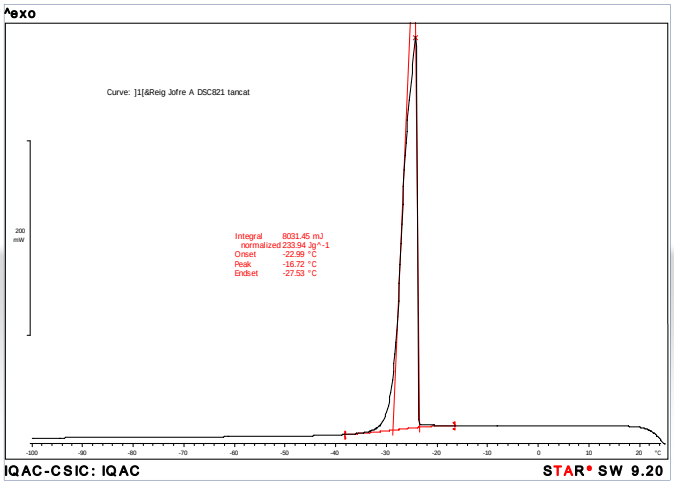
The Case Study (QTPP)

- **Appearance:** Right. Structural collapse leads to a variety of changes in cake properties of both esthetical and stability concerns. That means the changes in cake morphology and inner structure were clearly influenced by the different drying conditions and may impact degradation reactions and storage stability of the product.

- **Residual Moisture Content (RMC):** The specification is under 6 % in most of the Aciclovir formulations. Some dossiers describe the specification as under 4 %. The experience indicates that obtaining a value from 2 up to 3 %, at time zero, doesn't produce stability problems at the expiry date, currently 3 years.
- **Reconstitution Time:** < 2 min. It is also possible to reach values less than 1 min.

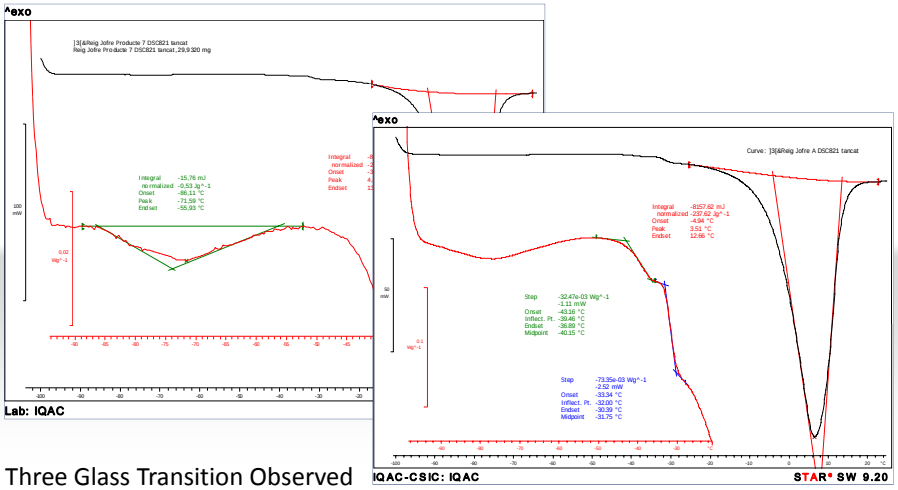
The Case Study (CMA)

(1) Temperature of total solidificaction **(T_{ts})** < -26 °C



The Case Study (CMA)

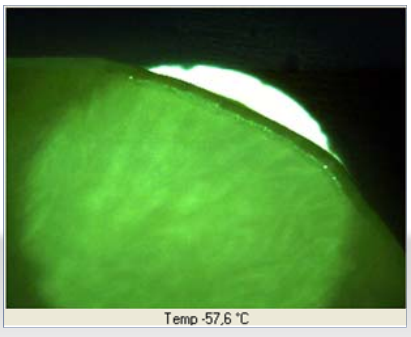
(2) Glass Transition Temperature **(T_g')** : [-72:-32] °C



Three Glass Transition Observed

The Case Study (CMA)

(3) CollapseTemperature **(T_{co})** : [-58:-56] °C



(7) Maximum Temperature (T_{max}) Allowed by the product: The stability studies, regarding the impurities generated, marked the value of 35 ºC as maximum temperature the product can withstand.

The Case Study (RA Conclusions)

1. The attempts to avoid the collapse by means of annealing turned out not useful.
   - The range of T_g' & T_{co} is too low for the equipment capabilities. Little or nothing can be done during the freezing step.
2. A certain time interval will be needed until the energy supplied by the shelves reaches the sublimation front of the frozen product.

The Case Study (RA Conclusions)

3. During the Primary Drying (PD) the sublimation front temperature is controlled by the chamber pressure.
   - Considering this value as the Critical Temperature (CT), several strategies can be carried out to establish the initial DoE.
   - Anyway, the sublimation rate is controlled by the shelf temperature. The initial DoE will analyze the variations of two factors at a time: P & T; taking five different CTs for the product, from the more aggressive criteria (Cycle 1) to the more conservative (Cycle 5).
   - The time (t) only justifies the reach of the end point.
   - In order to guarantee the process outcomes, the chamber pressure will be set at 50 % of the one corresponding to the CT.
4. The Secondary Drying doesn't show any collapse problems.

The Case Study (Initial DoE)

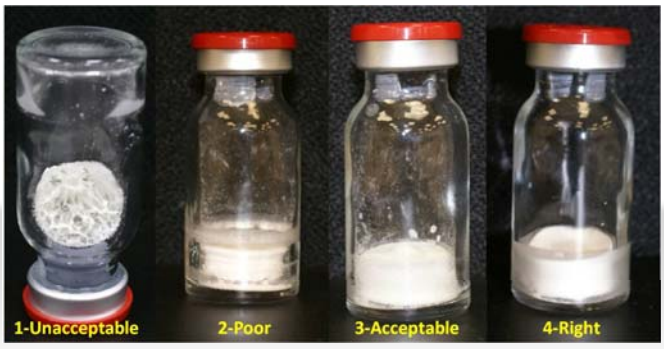
Five different CT's for the product, from the more aggressive criteria (Cycle 1) to the more conservative (Cycle 5):

Process Parameter	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Critical Temperature (CT) [°C]	-25	-30	-35	-40	-45
Corresponding Pressure -Pirani- [mbar]	9.7×10^{-1}	5.8×10^{-1}	3.4×10^{-1}	2.0×10^{-1}	1.1×10^{-1}
Set Points in the equipment					
Shelf Temperature [°C]	-5	-10	-15	-20	-25
PD Time [hours]	18	22	26	30	34
Chamber Pressure (Pirani) [mbar]	4.8×10^{-1}	2.9×10^{-1}	1.7×10^{-1}	1.1×10^{-1}	4.5×10^{-2}
Total Process Time [hours]	34	38	42	46	50

The chamber pressure will be set at 50 % of the one corresponding to the CT.

CQAs

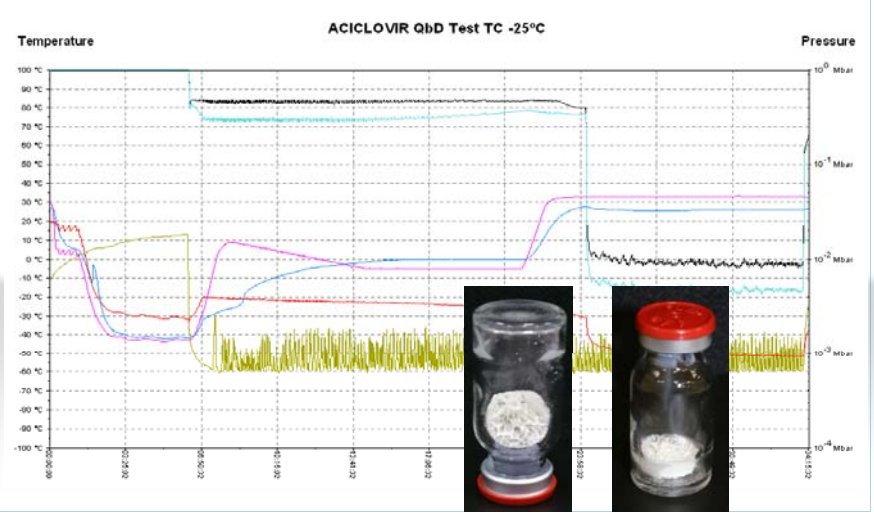
1. **Appearance:** A ranking of four categories has been established as the following Five different CT's for the product, from the more aggressive criteria (Cycle 1) to the more conservative (Cycle 5):



2. **RMC:** Under 6 %. Optimal results between 2-3 %.
3. **Reconstitution time:** less than 2 minutes. Optimal results less than 1 minute.

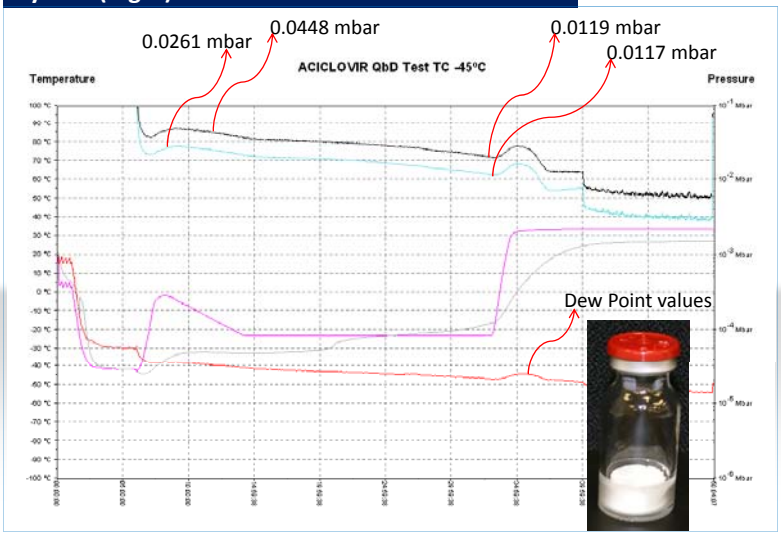
Results

Cycle 1 (Unacceptable) – CT: -25°C



Results

Cycle 5 (Right) – CT: -45°C



Results (Quality Attributes Obtained)

Quality Attributes Obtained					
Quality Attribute	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**
Appearance (Aspect)	Unaccept.	Poor	Accept.	Right	Right
RMC (Hr) [%]	7.16	5.13	3.08	1.92	1.82
Reconstitution Time [sec]	No	partial	45	30	30

The Design Space (DS)

- Is our DoE the best for the purpose?

First DoE Approach

Design Space

- It will check the contribution of the CPP selected

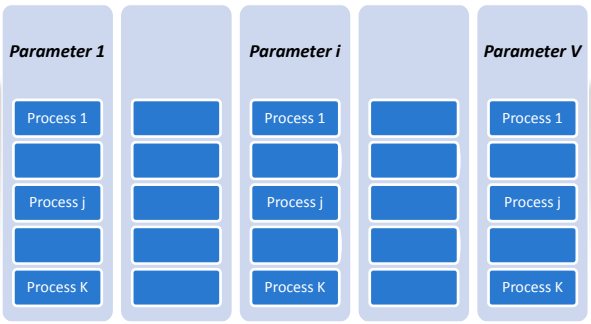
Second DoE

- Allows us adjust the limits for the CPP
- A new DS will be created from the new DoE

The Design Space (DS)

- How are we going to build the DS?

- Confection of one unfolding matrix:
  - **Variables (columns):** Available process parameters (18).
  - **Objets (rows):** Grouping each process in vertical (different lenght for each process).



The Design Space (DS)

DATA TREATMENT (How manage the scale and the noise)

- We have obtained a matrix of 18 columns and 33,128 rows.

- **AUTOSCALING:** It is necessary to give the same weight for all the data when comparing the different variables:

$$f(x) = \frac{x_{i,A} - \overline{x_A}}{\sigma_A}$$

Where $x_{i,A}$ is each one of the values for the variable A, $\overline{x_A}$ is the average of the values and σ_A is the standard deviation for the values of the variable A. Thereby the average value will be 0, and the standard deviation will be 1. That means given weight to σ .

The Design Space (DS)

DATA TREATMENT (How manage the scale and the noise)

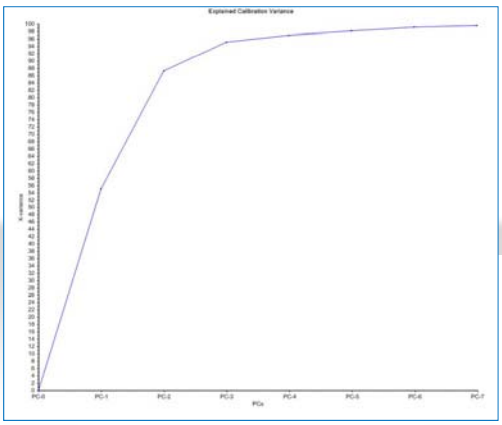
- **NOISE:** the instrumental and electrical noise, produced by the equipment limitations, should still be reduced:
- Four different techniques, in order to reach this reduction, were assayed: Moving Average, Median Filter, Savitsky-Golay and **Gaussian Filter**:

$$g(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\frac{x^2}{2\sigma^2}}$$

Fitting by means of the Gaussian Filter returned the best results. The data window tested was one of either of 9, 15 or 21 data points, with 21 being selected.

The Design Space (DS)

DATA TREATMENT (Principal Component Analisys -PC-)



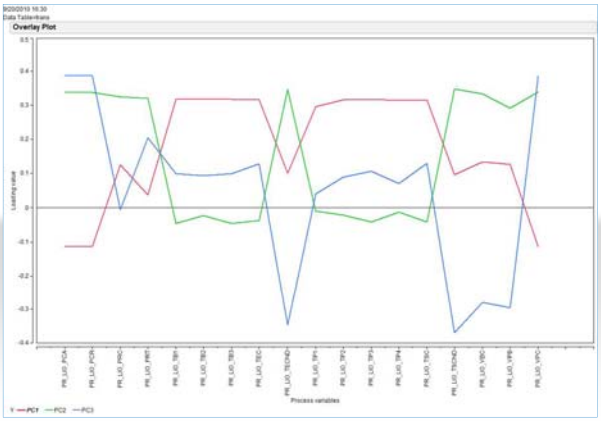
Graphic of Explained variance

The fitting determines an analysis of 7 principal components (PC), each one grouping the 18 variables, giving different weight for each variable, in different fitting functions.

The first PC explains 53 % of the fitting; the second one explains 33 % and the third one explains 9 %. **With the three first PCs, we can explain 95 % of the fitting.**

The Design Space (DS)

DATA TREATMENT (Principal Component Analisys -PC-)

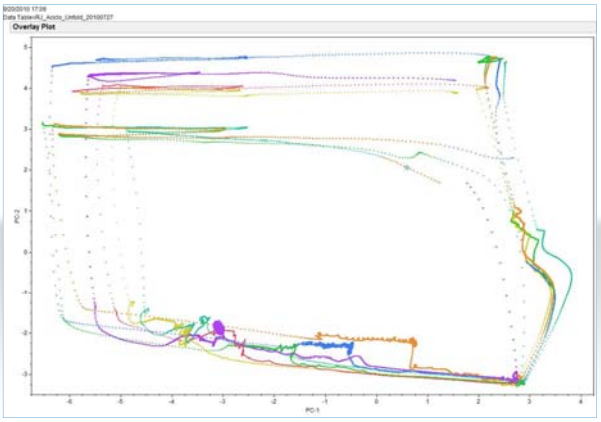


Loadings Graphic

Contribution of the variables and their correlation for the principal components: PC1, PC2 & PC3 (Two dimensions).

The Design Space (DS)

DATA TREATMENT (Design Space in two dimensions -PC1 & PC2-)

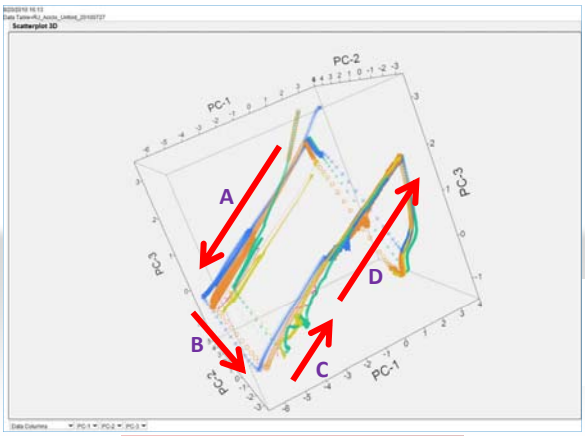


2D Graphic of Scores

Representation in two dimensions for the frame of the 33,128 data, using the assayed cycles, working with PC1 & PC2 (86% explained).

The Design Space (DS)

DATA TREATMENT (Design Space in three dimensions -PC1, PC2 & PC3-)



3D Graphic of Scores

Representation in three dimensions for the frame of the 33,128 data, using the assayed cycles, working with PC1, PC2 & PC3 (95% explained).

The different stretches are marking the different process steps.

Conclusions

First

The first question

- The process can be explained by means of the used statistical tool.

Second

Next steps

- A further step should be done using cycles whose corresponding parameters are between the third and fifth one tested. The second approach would be carried out with, at least, three cycles. Fewer variables should be selected, from the 18 variables, because just 12 really help us to define the DS. More variables can be added from the use of other PAT techniques, such as NIR.

Third

The Target

- Now we are going to build a new DoE, whose results will be tackled with the matrix corresponding to the CQA in order to obtain an operator that will establish the correlation between CPP and CQA to reach the golden batch (process signature) for the product.

Thank you!
Any questions?

Contact

Reig Jofre Group
Laura Noguera & Enric Jo

Av Gran Capitan, 10
08970 Sant Joan Despi, Barcelona
Spain

Phone: +34934806708
Email: laura.noguera@reigjofre.com
enric.jo@reigjofre.com

www.reigjofre.com

Questions & Answers

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