Avec le soutien de la DGO6

Design Space ou Espace de Conception

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Facts

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Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud
And Scott Hensley

BusinessWeek

MAY 3, 2004

SPECIAL REPORT -- QUALITY MANUFACTURING

Making Pills The Smart Way

Drugmakers are revamping factories to save money and avoid production mishaps

Desired state

- Product quality and performance achieved and **assured by design** of effective and efficient manufacturing processes

- Product specifications based on mechanistic **understanding** of how formulation and process factors impact product performance

- Ability for **continuous improvement** and **assurance of quality**

Regulatory Framework

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

Quality **by Design** (QbD) vs. Quality **by Testing** (QbT)

Increased **knowledge**

Science based

Assurance of quality

Design Space (DS)

Regulatory Framework

- ICH Q8: Design Space (DS):

- "*the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality*"

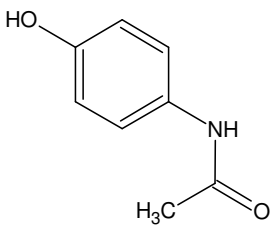
- "*working within the DS is not considered as a change*"

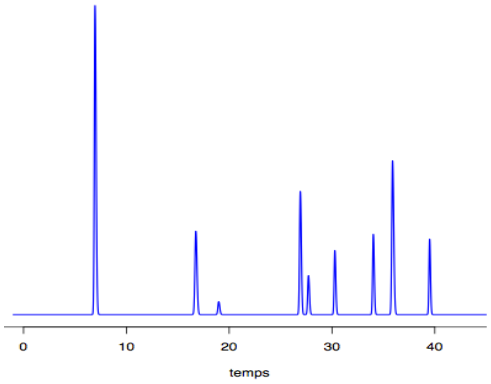
- "*Understand and gain knowledge about a process to find a parametric region of reliable robustness for future performance of this process*"

Analytical Chemistry Lab focus

- How to build DS for Analytical methods ?

- Objective:
  - Define a robust region of input factors that guarantees obtaining future appropriate separation of complex mixture components





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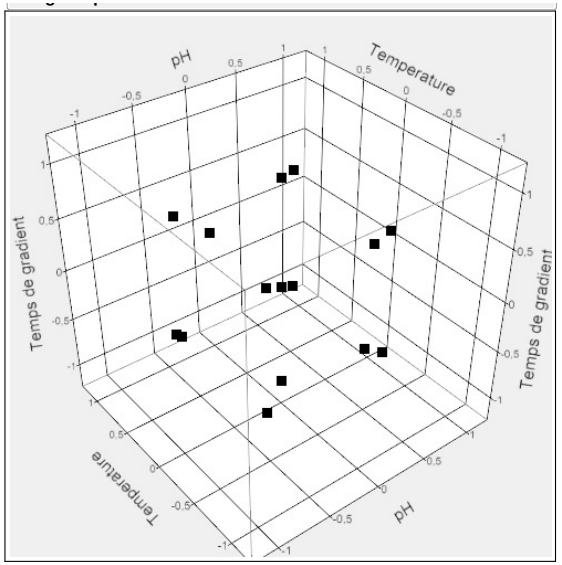
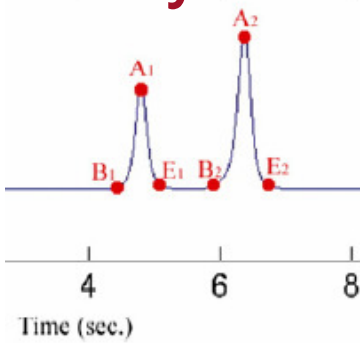
Analytical Chemistry Lab focus

- Multivariate:
  - Key input factors: pH, temperature, Gradient time, etc
  - Key responses: retention times



➔ Designs of Experiments (DOEs):

- Critical Quality Attribute: Separation (**S**)



$$S = B_2 - E_1$$

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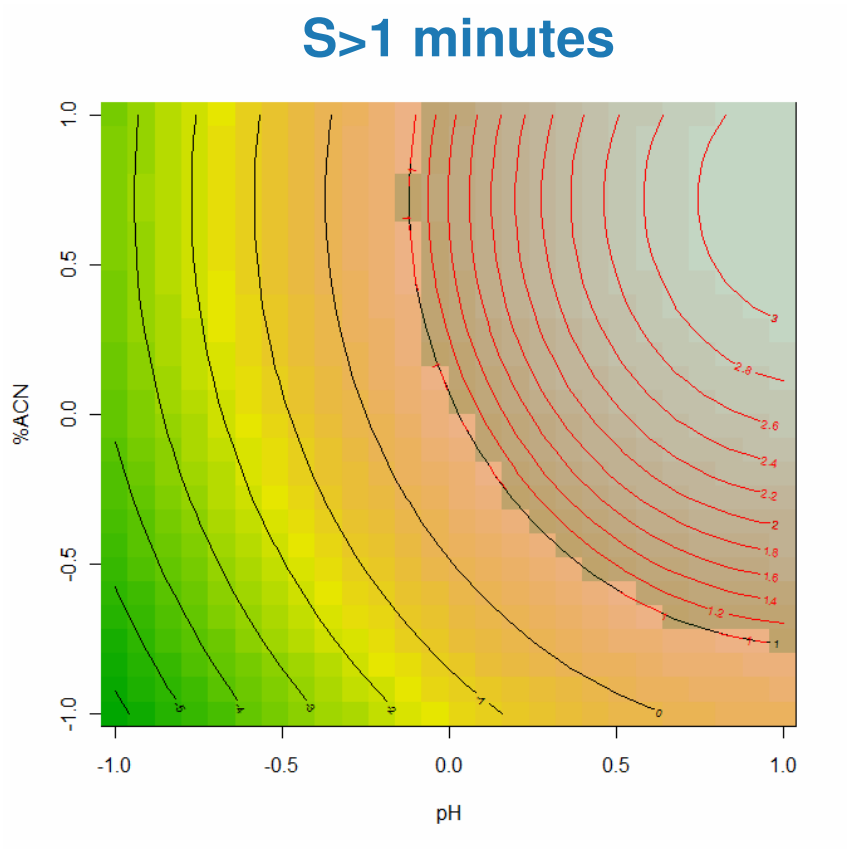
Design of experiments

- Mean Response Surface ?



→ Generally, mean responses are used for optimization

✗ do not provide any clue about process reliability

✗ fail to give any information on how the process will perform in the future

✗ will certainly give disappointing and unexplained results for the future use of the method

With parameters pH>0 and %ACN>-0.8, will my separation really be at least 1 minutes?

Guarantee ??

Design Space

Optimized Robust assay : Take into account the uncertainty about future run for defining a Design Space. Think risk, instead of mean. Here, probability to have a Separation > 1 minutes.

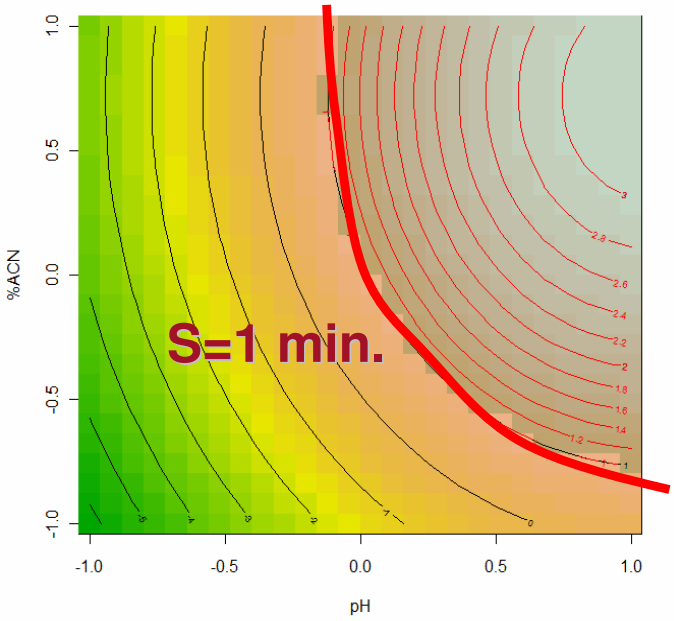
Mean based

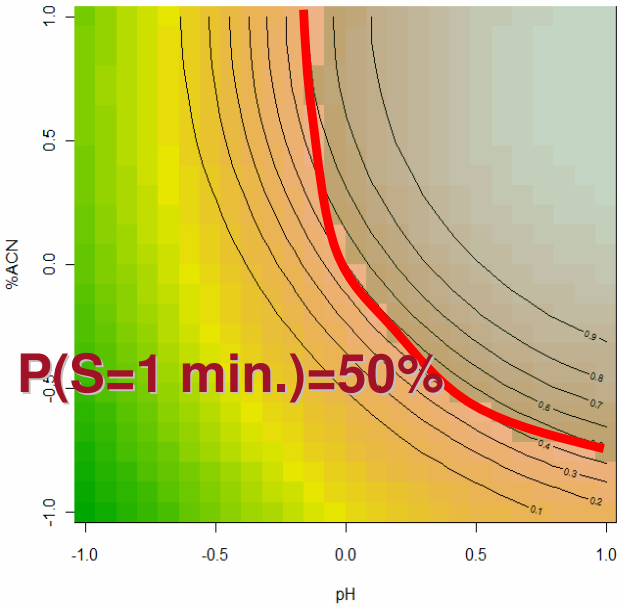
S>1 minutes

mean responses = there is about 50% of chance that my response is, say, 1 minutes.

DS Risk based

P(S>1 min.)





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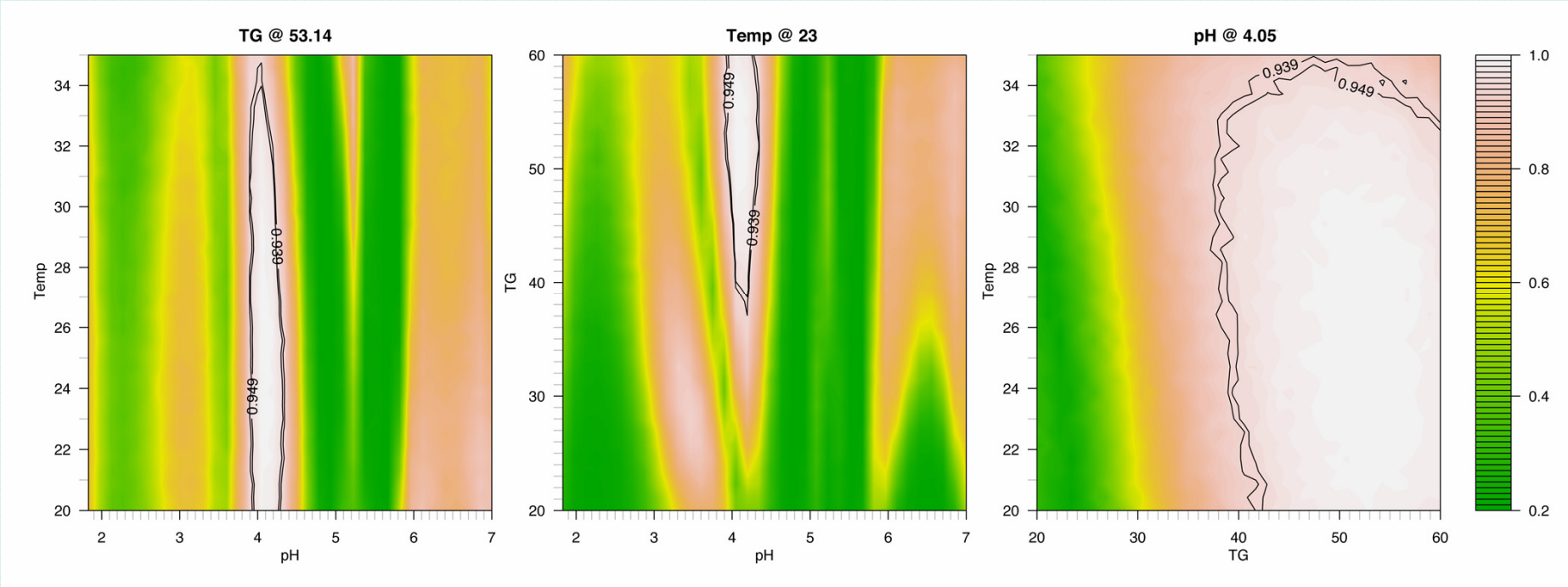
Example

Separation of 9 AINS by HPLC

Design Space



P(S>0) = 94.6%

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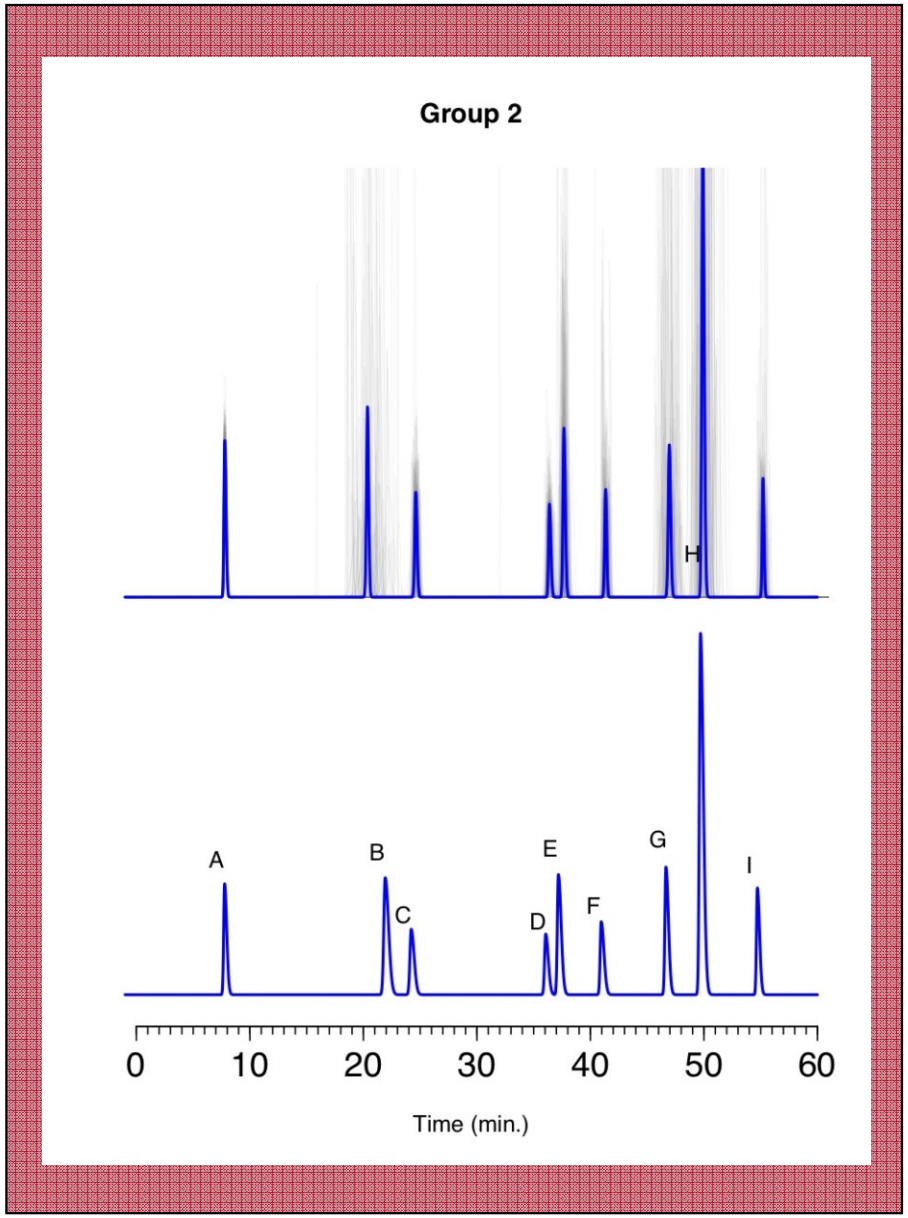
Example

Legend *: A. Paracetamol - B. Benzoate - C. Nipagine - D. Nipasol – E. Nimesulide – F. BHA - G. Ibuprofen; H. Mefenamic acid - I. BHT*



Predicted

Experimental

Birth of the project

- Limitations of the classical statistical methodologies
  - to provide risk-based solutions
  - even for simple statistical models
- Opportunity to develop new ways of thinking
  - integrate predictive uncertainty in the results

→ Creation of the PPP

  - between University of Liège, Arlenda and RW

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Organization

- University (Lab. analytical chemistry)
  - Wide expertise in analytical method development
- Industry (Arlenda)
  - Wide expertise in biostatistics, design of experiments and Bayesian statistics

Bayesian methodologies

~~Classical methodologies~~

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Organization

- How to build the bulldozer ?
- University
  - 1 chemist
  - 1 statistician
  - 1 pharmacist
- Arlenda
  - Several PhD in statistics
  - 1 I.T. manager

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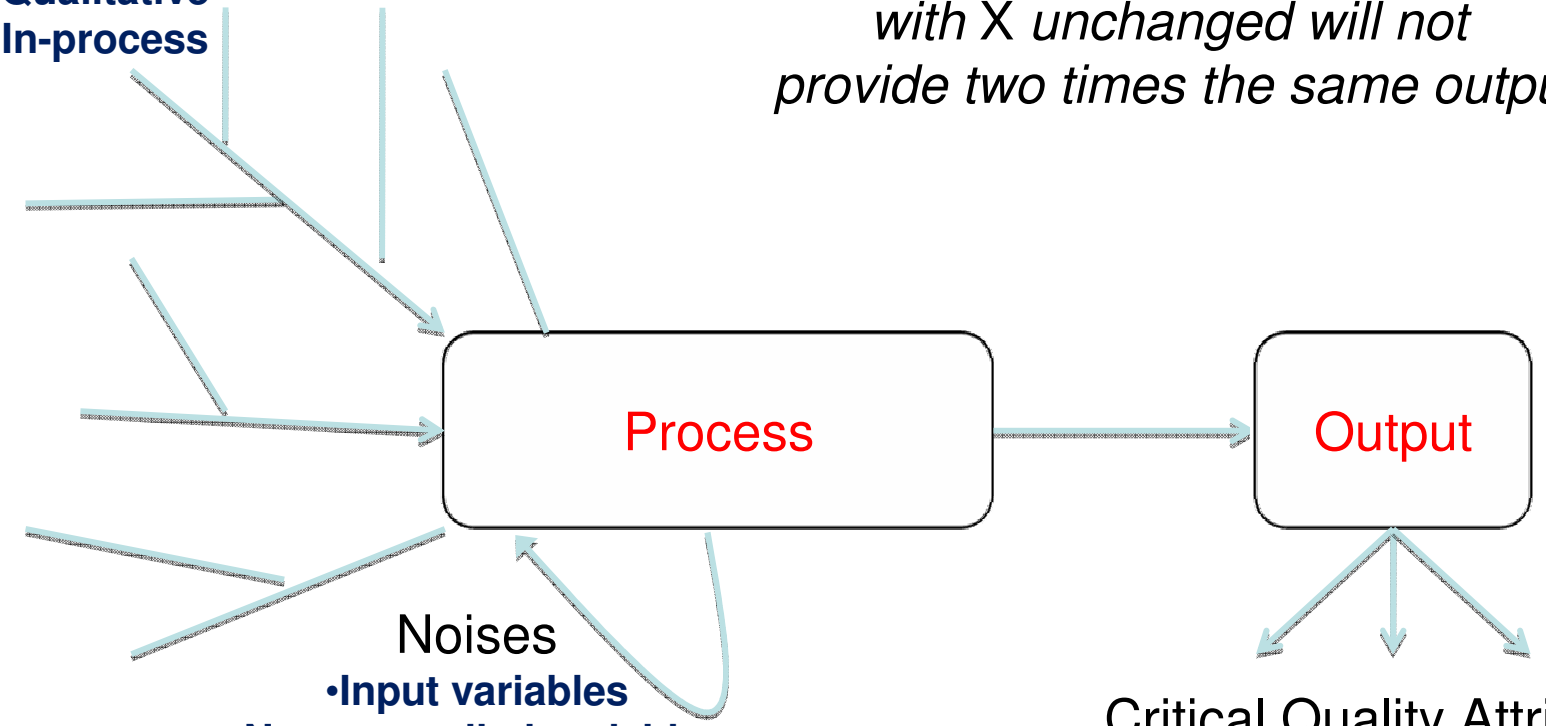
Example for process

- A very general Process

Critical Process Parameters (X) :

- **Quantitative**
- **Qualitative**
- **In-process**

Running two times the process with X unchanged will not provide two times the same output



Spray-drying process

- Spray-drying is intended to create a powder with small and controlled particle's size for pulmonary delivery of a drug substance
- Several Critical Process Parameters (CPP) have an influence on several Critical Quality Attributes (CQA)
  - CPP: inlet temperature, spray flow-rate, feed rate (other process parameters are kept constant)
  - CQA: yield, moisture, inhalable fraction, flowability
- Specifications on CQA defined as minimal satisfactory quality
  - yield > 80%
  - moisture < 1%
  - Inhalable fraction > 60%
  - …

Spray-drying process

- The process must provide, in its future use, **quality outputs**
  - e.g. during routine
- According to specifications derived from safety, efficacy, economical reasons
  - Whatever future conditions of use, that are not always perfectly controlled
  - Then, outputs should be **not sensitive** to minor changes
- This is **Quality by Design**
  - The way the process is developed leads to the product quality
  - This quality and the associated risks are assessed
  - Achieved using Design Space methodologies

Spray-drying process

- Design Space, Risk and ICH Q8
  - ICH Q8 proposes to use the Design Space (DS) risk-based methodology to fulfil these objectives

Target : "*Understand and gain knowledge about a process to find a parametric region of **reliable robustness** for **future performance** of this process*"

→Assurance of quality

→Assessment of the risk not to achieve quality

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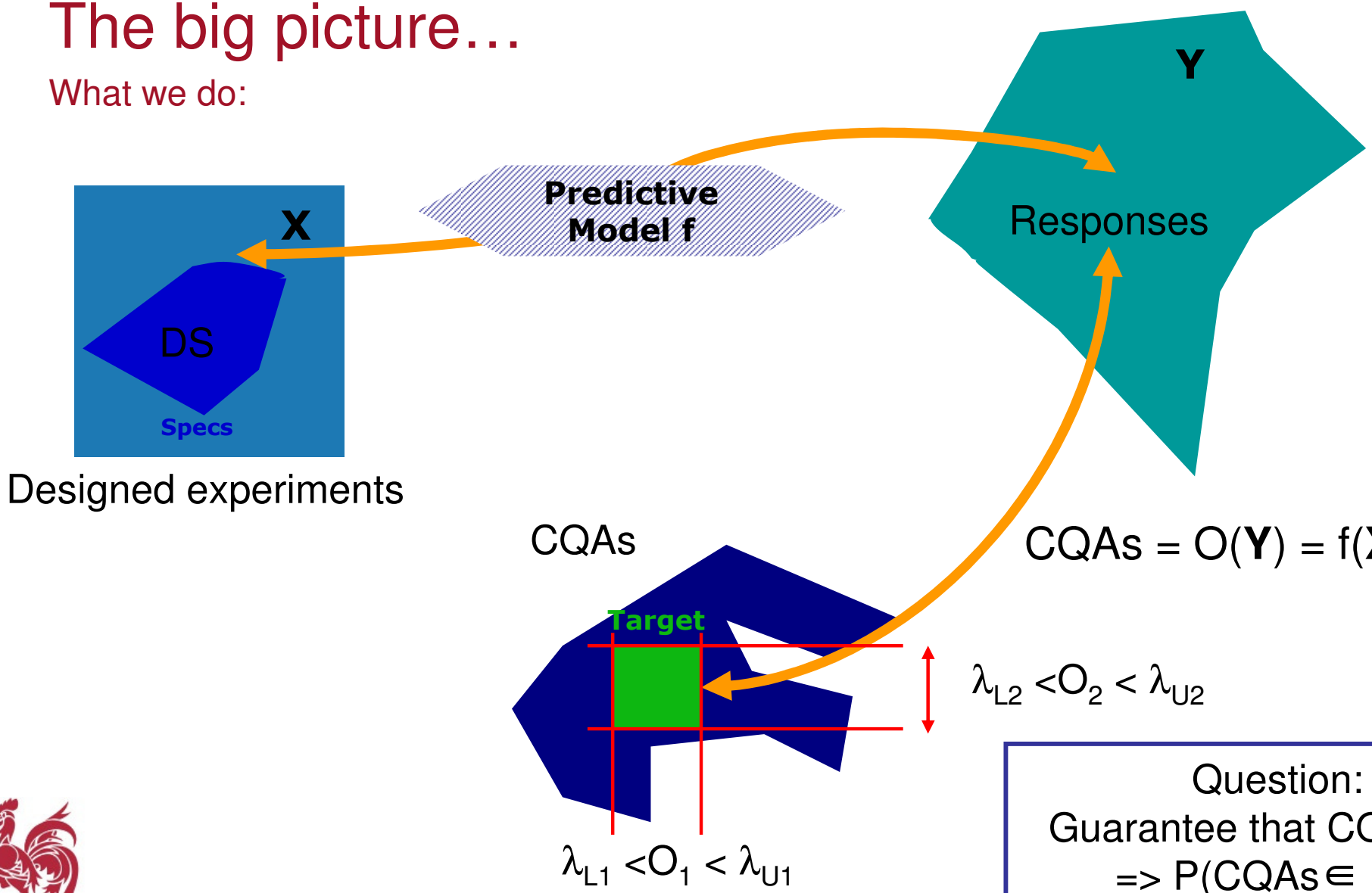
Spray-drying process

The big picture…

What we do:



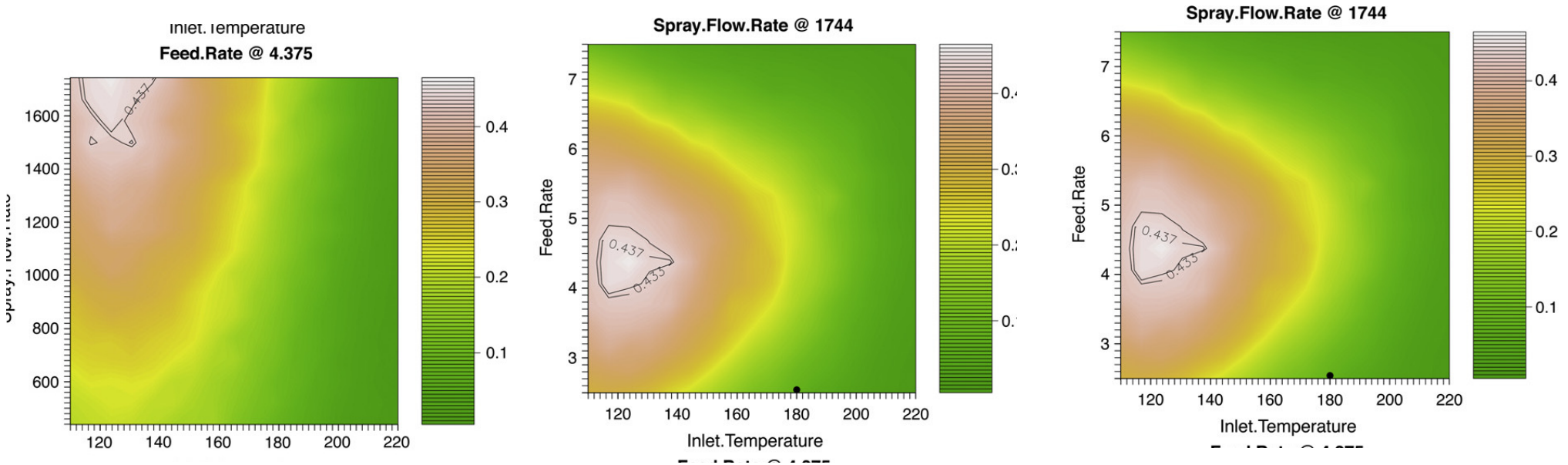
Question:
Guarantee that CQAs ∈ λ
=> P(CQAs ∈ λ) ?

Computation

- This implies to know the behavior of the CQAs in the future
  - How they change when CPPs change
  - How they are statistically *distributed*
  - How they are dependent
- Fortunately, solutions exist in the Bayesian statistical framework for every problem !

Spray-drying process

- Risk-based design space: predicted P(CQAs∈ λ)



- In the Design Space, there is 45% of chance to observe each CQA within specification, jointly
- There is also 100-45% = 55% of risk not to observe the CQAs within specification (jointly) !

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Spray-drying process

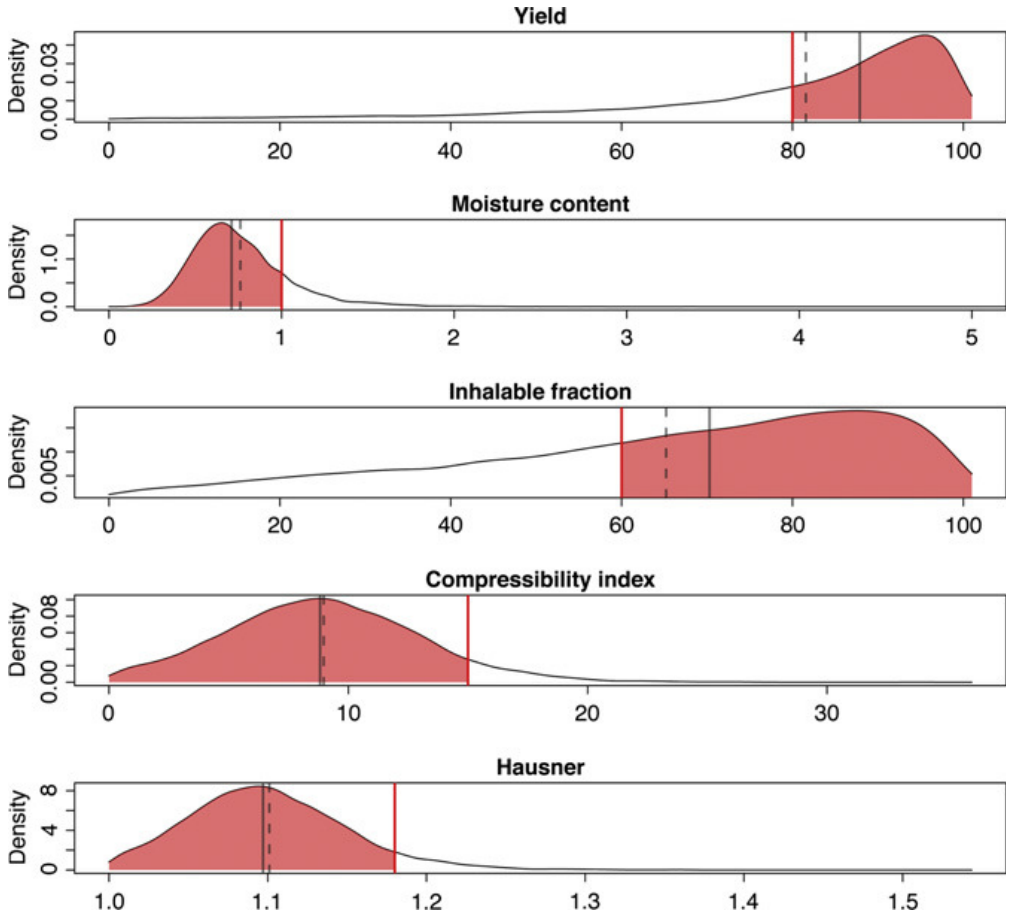
- Validation
  - Experiments have been repeated 3 times independently at optimal condition, i.e.
    - Inlet Temperature: 123.75° C
    - Spray Flow Rate: 1744 L/h
    - Feed Rate: 4.69 ml/min

Batches	Yield (%)	Moisture content (%)	Inhalable fraction (%)	Compressibility index	Hausner ratio
1	88	<0.2	63	11.6	1.13
2	89	<0.2	62	12	1.14
3	88	<0.2	59	11.5	1.13
Mean	**88.7**	**<0.2**	**61.18**	**11.76**	**1.13**
Standard deviation	0.61	NA	1.82	0.22	0.01

- Jointly, 2 out of the 3 runs within specification

Spray-drying process

- Post-analysis (« How they are statistically *distributed* »)
  - Marginal predictive densities of the CQAs



Compared with validation SD, these uncertainties seems huge !

In fact, the model does not fit well the data

Predictive uncertainty = data uncertainty + model uncertainty

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Spray-drying process

- Conclusion
  - Effective Design Space is the ultimate tool to optimize a process or a method while concurrently assessed its robustness
    - To provide guarantee that future runs will be on specifications
  - Even in presence of poor model fit…
    - Here, due to a poorly designed set of experiments
  - … it allows providing risk-based results
    - But guarantee is kept low (45%)

Gain

- What are the benefits for industry ?
  - Classical benefits due to DOE
    - The time to run experiments before obtaining results is controlled
    - This time is generally reduced in comparison to “handmade” optimization. Costs are reduced as well
  - Benefits due to risk-based Design Space
    - Guarantee and risk to be on specification are controlled
    - Process/method knowledge leads to quality product and robustness
    - Robustness generally eases transfer between manufacturing sites, for instance
    - Better quality products also allows reducing costs
      - Less batches out-of-specification
      - Improvement of process reliability

Role of the partners

- Before PPP, University and Arlenda had a recognized expertise in Statistics for (Bio)Analytical methods
- Now, growing expertise in Quality by Design and Design Space computations
- Arlenda is extending its activity
  - Opening new offices in the US
  - Hiring a major QbD and non-clinical statistics expert from the US

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- For a research implying academic developments and publications
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- For a research for commercial purposes
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- Merci pour votre attention !