Design Space ou Espace de Conception

29 novembre 2011

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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

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

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.
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)

\[ S = B_2 - E_1 \]
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??
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.)

P(S=1 min.)=50%
Example

Separation of 9 AINS by HPLC

Design Space

P(S>0) = 94.6%
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
Organization

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

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

Noises:
- Input variables
- Non-controlled variables
- Material noise

Critical Quality Attributes (Y) => specifications
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
Spray-drying process

The big picture…

What we do:

Specs

Predictive Model f

DS

X

Responses

CQAs

CQAs = O(Y) = f(X)

λ < O < λ

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 \( P(CQAs \in \lambda) \)

- 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)!
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

<table>
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<tr>
<th>Batches</th>
<th>Yield (%)</th>
<th>Moisture content (%)</th>
<th>Inhalable fraction (%)</th>
<th>Compressibility index</th>
<th>Hausner ratio</th>
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</tbody>
</table>

• 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
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%)
• 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
• For a research implying academic developments and publications
  – Contact:
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• For a research for commercial purposes
  – Contact:
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• Merci pour votre attention !