QUALITY BY DESIGN IN PHARMACEUTICAL DEVELOPMENT – THE CONTRIBUTION OF DESIGN OF EXPERIMENTS

HOW CAN DESIGN OF EXPERIMENTS BE USED IN EFFICIENT DEVELOPMENT, AS SPECIFIED IN THE ICH Q8 AND PAT GUIDELINES

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Introduction

Pharmaceutical development more and more changes from an empirical, data-driven approach of development to a more systematic, knowledge-driven one. Nowadays, it is generally acknowledged that "quality cannot be tested into products; i.e. quality should be **built in by design**" [1,2]. But how can this be achieved?
One tool that proves essential in order to reach this goal is Statistical Design of Experiments (DoE). It allows gaining the required understanding of how formulation and process factors impact product performance. The obtained knowledge can furthermore be employed in the scope of PAT (Process Analytical Technology) for in-process quality control.
Subsequently, we present the current demands and treat different examples of how Statistical Design of Experiments can contribute to achieve these objectives. As modern software tools are indispensable in this context, the applications are illustrated using the DoE expert system STAVEX.

Regulatory framework

- **ICH Q8 [1]**
  - Objective: "identify any critical process parameters that should be monitored or controlled".
  - Method: "Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product."
  - Documentation: "summary tables and graphs are encouraged where they add clarity and facilitate review".
  - Advantage: Companies with good design and control strategies, good risk management strategies and good quality systems should benefit from a reduced regulatory burden: "greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches".

The FDA has responded to these topics by starting the:

- **PAT initiative [2]**
  - Insight: "Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system."
  - Documentation: "summary tables and graphs are encouraged where they add clarity and facilitate review".
  - Flexibility of regulatory approaches: "Risk-based regulatory approaches recognize:
    - the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
    - the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product."

Statistical Design of Experiments

- **Assessing important factors**
  Statistical Design of Experiments allows identifying important formulation attributes and process parameters which have an impact on the quality of the drug product.
- **Ensuring efficient experimentation**
  Using a systematic approach, the number of experiments needed to distinguish the important factors from the multitude of possibly important ones can be significantly reduced.

The above two items are of general interest in product development and are already acknowledged as good development practice. In process validation, the current practice is to specify parameter regions (e.g. pH 3-4 and temperature 40 to 60 °C) and to show that, if the parameters are inside these regions, the process yields an acceptable quality. A user-friendly DoE software tool enables to assess these regions without effort.
What is new in the ICH Q8 approach is that the process knowledge is used to define a so-called "design space", where the quality criterion (e.g. particle size) is expressed as a complex function of the parameters, describing their relationship in more detail. As long as the process runs within the borders of the design space, it is not considered to have changed.

In the regulatory process, the design space is proposed by the applicant and is subject to regulatory assessment and approval. If the process is well understood and the design space is not altered, then in certain cases a new validation can be omitted, e.g. for proposing a new process analyser.
The design space concept can be fully exploited by using DoE on purpose in the three following related contexts.

- **Defining the design space**
  Using Statistical Design of Experiments, the complex function assessing the total impact of the various process parameters can be estimated. Fig. 1 shows how the quality attribute (the titer of a metabolite in a biotechnological process) is linked to the three factors *cottonseed*, *protein content* and *sucrose*. It easily can be seen that the information contained in specifying a design space exceeds the information given in a traditional setting, where only parameter ranges are given. The latter procedure would mean to have to control the quality attribute in the entire region spanned by the three factors, i.e. the entire cube. A software as STAVEX allows to easily identify the link between the quality attribute and the parameters and to generate clear and meaningful graphics which also can be used for validation purposes.
- **Assessing correctly the variability of the response [region and design plot]**
  Obviously, process analytical techniques (PAT) can hardly be used without reliable predictions of the quality parameters based on the various process factors. It is therefore essential to be able to evaluate the uncertainty of the predictions. Using Statistical Design of Experiments, this can be done for each experimental design as well as for each location within the design space. Similarly to Fig. 1, the accuracy of the quality measure prediction depending on the parameter region can be visualized. For instance, one could then see that the quality prediction is precise at the centre of the design space, but less reliable upon approaching its corners.
- **Designing robust processes**
  Finally, a further important goal in quality-by-design consists in ensuring that variations in hardly controllable process parameters – e.g. in the homogeneity of the raw material (powder sampling procedures are known to be not very reliable) – do not provoke critical lacks of quality. Using the methods developed by Taguchi, Statistical Design of Experiments can be used here to find ranges for the controllable process parameters such that the uncontrolled ones only lead to small deviations in the response variable (quality attribute). By already using this information when transferring the process from the laboratory to production, unpleasant surprises can be avoided. The resulting process becomes easier to control.

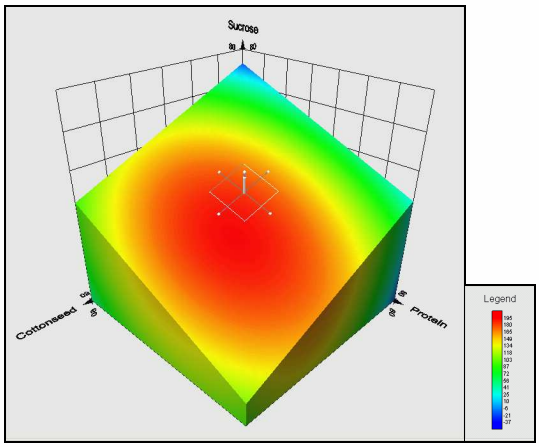

Fig. 1: Visualization of the titer variations within the design space.

Conclusion

The advantages of using quality-by-design are evident and encouraged by the regulatory authorities. One tool of choice in this context is Statistical Design of Experiments. Modern software tools such as the expert system STAVEX enables process engineers, production managers and quality specialists to gain the necessary process knowledge without effort. In this way, the indispensable high quality of the pharmaceutical products can be achieved at a lower cost.

References

[1] ICH Guideline Q8 – Pharmaceutical Development, http://www.ich.org (10 Nov 2005).

[2] U.S. Food and Drug Administration *Guidance for Industry. PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance,* http://www.fda.gov/Cder/OPS/PAT.htm (Sep 2004).

[3] J.C. Berridge An Update on ICH Guideline Q8 – Pharmaceutical Development, www.fda.gov/ohrms/dockets/AC/06/slides/2006-4241s1_2.ppt, ISPE Vienna Congress 2006.