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AXIOMATIC DESIGN IN PHARMACEUTICAL PROCESS DEVELOPMENT: "QUALITY BY DESIGN"

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ABSTRACT

This paper outlines an innovative approach to pharmaceutical process development using advanced Design for Six Sigma (DFSS) supported by a knowledge management system. DFSS has been the toolkit of choice for many pharmaceutical companies when implementing the requirements of ICH Q8 Quality by Design. Here we will show how the Independence and Information Axioms and a Design Knowledge Matrix can be used to optimize the use of Design Of Experiments (DOE) and minimize risk, merging some of most innovative tools of the Design For Six Sigma toolbox to ensure patient safety while maintaining maximum flexibility for continuous process optimization.

Keywords: Quality by Design, Design for Six Sigma, Design Of Experiments, non-square Design Matrix, Axiomatic Design

1 INTRODUCTION

This paper aims to show how the use of an advanced Design Matrix and the application of Axiomatic Design [Suh, 1990] can increase effectiveness and speed of knowledge creation in pharmaceutical process development.

Traditionally regulatory bodies required pharma manufacturers to keep their processes fixed once a drug had been approved. In recent years this mindset started to change fundamentally, inspired by insights delivered by a growing Lean Six Sigma community. Risk management and statistical process control are now accepted as elements of Good Manufacturing Practice (GMP) [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009]. "Quality by Design" (Figure 1) is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009].

Quality by Design employs a six step process of requirements management, knowledge management, and risk management, leading to a strategy for process control and continuous improvement. The framework of ICH Q8 (Table 1) outlines what needs to be done, not how. Many industry users have adopted elements of DFSS and Lean Six Sigma to implement ICH Q8 requirements.

Table 1. Quality by Design process steps.

Process Step	ICH Q8 Requirements
Target Product Profile	Definition of Product Intended Use and of Quality targets
Knowledge Mapping	Summary of prior scientific knowledge (drug substance, similar formulations and processes). Initial Risk Assessment
Development	Overview of Quality by Design key actions and decisions taken to develop New Scientific Knowledge, e.g., DoE, PAT, Risk Assessment and Risk Control
Design Space	Summary of Scientific Understanding of Product and Process. Justification and description of Multi-dimensional Space that Assures Quality (interrelation-ships and boundaries of Clinical Relevance).
Control Strategy	Definition of Control Strategy based on design space leading to Control of Quality and Quality Risk Management (Process Robustness)
Continuous Improvement	Proposal of Regulatory Flexibility based on Product and Process Scientific Knowledge and Quality Risk Mgmt. (Materials, Site, Scale, etc).

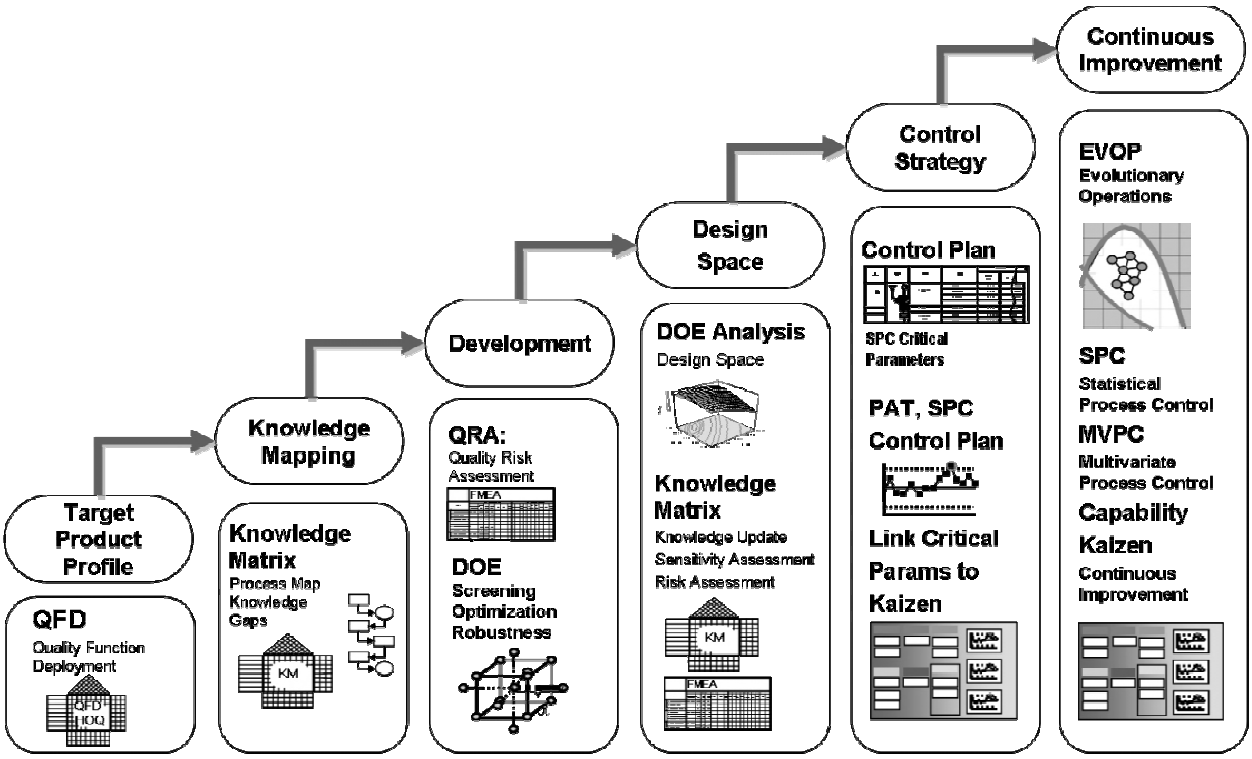

Figure 1. Quality by Design process development roadmap.

DOE PLANNING

One fundamental element of ICH Q 8 Quality by Design is the requirement to establish a "Design Space" of important process parameters. The Design Space is typically derived from a Response Surface Model (RSM) experiment. Efficient experimental design becomes the key to success in Quality by Design. Typically a screening experiment and a response surface experiment are required at a minimum per chemical step, resulting in at least 30, sometimes 60 or more experimental runs [Arcidiacono *et al.*, 2006].

Successful DOE requires thorough planning and documentation. Most experimenters use Fishbone Diagrams or Cause Effect Matrices to identify factors and responses. Results and conclusions are typically summarized in a free-form report. This approach however has a number of drawbacks. Responses (FRs) are not prioritized or linked to Customer Needs, results are difficult to assess for non-experts, transfer of knowledge is limited and the format does not facilitate discussion. The Cause Effect Matrix is used for planning only but never updated.

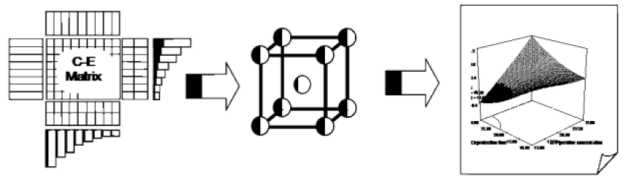

Figure 2. Conventional DOE planning.

2 DESIGN MATRIX

In a more thorough approach a Design Matrix between Critical Quality Attributes (CQAs) and Design Parameters (DP) is first created from a process map. Inputs and outputs of each process step are used to identify CQAs and DPs.

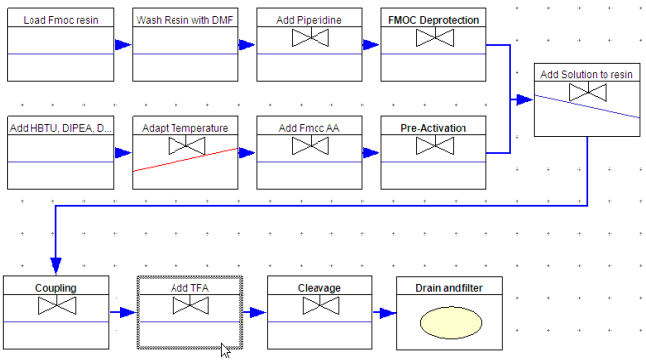

Figure 3. Example process flow.

Desired characteristics of processed products like chemicals, pharmaceuticals, or materials are determined by the combination of ingredients (chemical composition) and process factors (such as processing temperatures, pressures, timing etc.) [Arcidiacono *et al.*, 2009]. Design Parameters (DPs) are the factors required to obtain the desired characteristics. Typically DPs (chemical composition and process variables) cannot be varied independently. Interactions between DPs require an experimental approach and model building to understand and control desired characteristics. Models are

frequently non-linear. The design process and design matrix serve the purpose of assisting the planning and documenting experimental results.

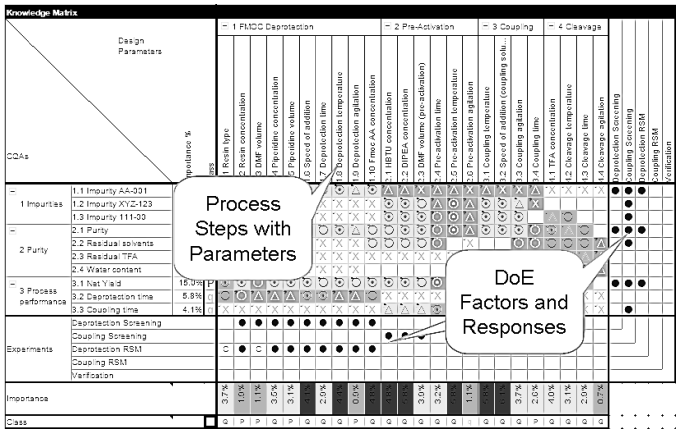

Figure 4. Draft design matrix.

The matrix is initially filled based on existing knowledge. QFD symbols are used to indicate the strength of the relationship. Colour coding is used to indicate the level of knowledge: Assumption only (red), currently under study (amber) or established fact backed up by data (green).

Candidate Factors and Responses for DOE are identified from this information: any strong correlations marked red are potential risks to process stability and primary candidates for Design Of Experiments [Smith and Schurr, 2003].

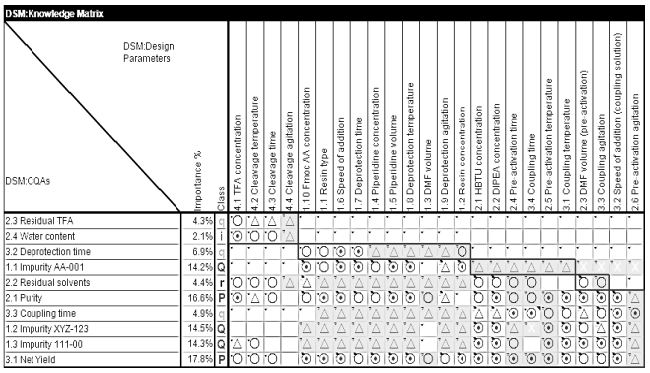

Figure 5. Design matrix after pseudo-triangularization.

At this stage the Axiomatic Design's Independence Axiom is applied to maximize the efficiency of the planned experiments. The objective at this stage is to separate less strongly connected process steps (some major process steps are strongly coupled).

Using the Qualica Planning Suite 2009 for Quality by Design software tool, the Design Matrix was transformed into a lower triangular form to identify coupled, redundant, and decoupled items. Note that the Design Matrix is not square. Qualica Planning Suite applies a proprietary algorithm to transform an arbitrary Cause Effect Matrix to a pseudo-triangular form. Shaded rectangles of height 1 represent redundant DPs in a decoupled design. Shaded rectangles of height >1 represent coupled subsections of the design.

A typical pharmaceutical process may include > 100 potentially significant factors. With reasonable effort even the most efficient Experimental Designs may be able to produce Response Surfaces for no more than 6 to 10 factors. By applying the decoupling algorithm the process design team is able to efficiently break down a complex process into manageable, coupled chunks. These can be optimized by a sequence of DOEs. Any decoupled items can be optimized using the OFAT (One Factor A Time) approach.

A key advantage over the conventional approach is an optimized selection of DOE scope. The alternative would be planning individual experiments for each process step. This approach however would ignore potential coupling between critical steps, increasing the risk of not understanding critical interactions.

From a practical point of view, the typical square Design Matrix and zigzagging approach is not practical at this point of process design. It does apply to the earlier process of chemical route selection, where the chemical synthesis process is still open. At the point where Quality by Design is started the major process steps however will largely be fixed and parameters known. Most Chemists and Process Engineers will find it easier to list all available DPs in a matrix rather than develop the required ones through zigzagging. at this point.

3 KNOWLEDGE MANAGEMENT

After analyzing their DOE, most experimenters will summarize their findings in a DOE report. This report is valuable in itself, but the Design Matrix should also be updated after each DOE to reflect learnings. Relationships should be added or removed based on DOE findings. Assumptions should be turned into facts if proven by DOE.

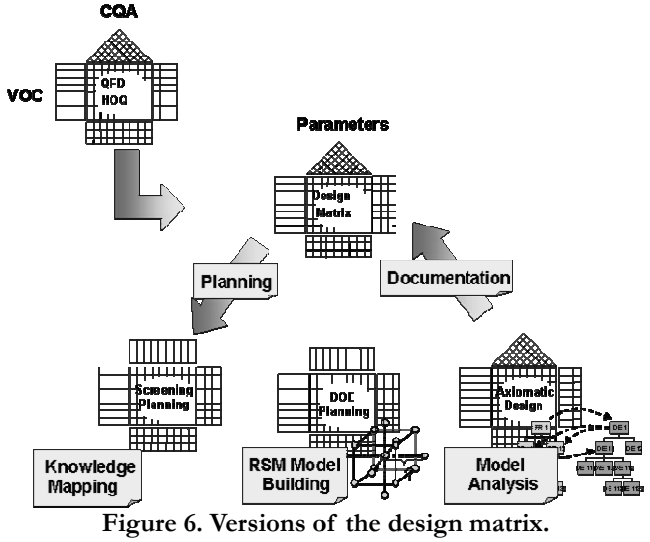

Figure 6. Versions of the design matrix.

In this way the Design Matrix serves as a central knowledge management document for the design team. It was used extensively throughout the course of our process design projects. In the early phase, it was used to document previously existing knowledge. Then it served as a planning matrix for the various DOEs conducted, and finally it was updated with learnings from the DOEs to reflect and document the knowledge established by the project team.

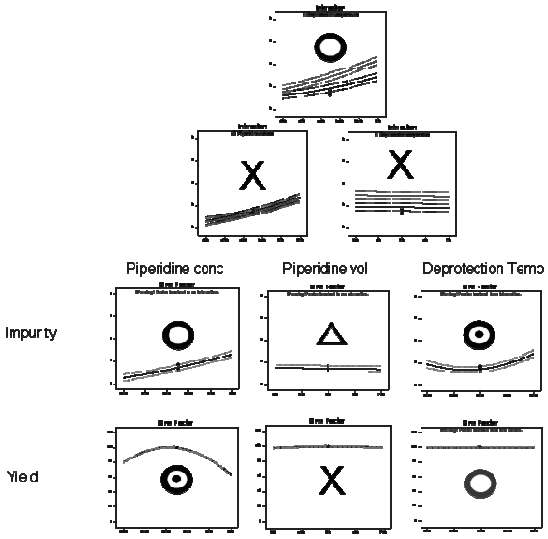

Figure 7. Mapping DOE results to matrix values.

Low p-values and large effect sizes indicate significant relations. Keep in mind p-values always depend on signal-to-noise, i.e. your choice of parameter ranges in the experiment. Parameters may be significant despite low p-values. A decision on whether a significant relation exists has to be guided by experience to some extent. The Knowledge Matrix is a simplified summary representation of knowledge established in experiments. Its purpose is to facilitate project management by highlighting gaps and risks. It also helps to document findings for future reference.

4 APPLYING THE INFORMATION AXIOM

The second Design Axiom - the Information Axiom – states that of any two decoupled designs, the design with lower information content is the preferred one. Information content is defined by the probability of failure. In Design for Six Sigma, failure rates are typically controlled by means of Quality Scorecards. Quality Scorecards track failure probabilities in the form of DPMO or Process Sigma. When transfer functions are obtained from DOE - as is the case with the Design Space in Quality by Design - POE (Propagation Of Error) analysis can be added to scorecards for an accurate analysis of behaviour. POE will produce a model of failure probability which indicates the DPs contributing most, while at the same time allowing the designer to select a more Robust Design. In doing so, the scorecard backed up by Propagation Of Error can be used as a measure for the information content of different process settings:

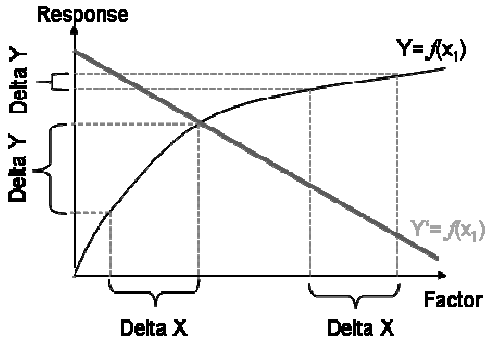

Figure 8. Propagation of Error

For a given transfer function (1) the Propagation Of Error is determined by taking variance into its partial derivative (2):

$$\hat{Y} = \beta_0 + \beta_1 x_1 + \beta_{11} x_1^2 \quad (1)$$

$$\sigma_y^2 = \left(\frac{\partial Y}{\partial x}\right)^2 \sigma_x^2 + \sigma_{resid}^2 \quad (2)$$

The total variation of the CQA due to the variability of the factors and residual variation can then be expressed by (3):

$$\sigma_y = \sqrt{(\beta_1 + 2\beta_{11} x_1)^2 \sigma_x^2 + \sigma_{resid}^2} \quad (3)$$

Transfer functions for all CQAs, together with POE, can be summarized in a Quality Scorecard. DPs with high sensitivity can be identified and highlighted on the Design Matrix as candidates for Tolerance Design.

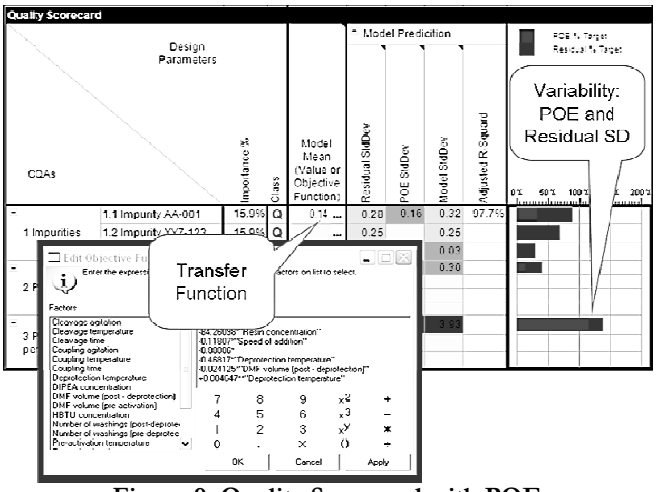

Figure 9. Quality Scorecard with POE

5 DEVELOPING A CONTROL STRATEGY

After documenting the learnings from DOE, Axiomatic Design's Independence Axiom was used again to analyze the coupling in the design and to establish a control strategy for each functional requirement. At this point redundant DPs could be eliminated and fixed. Generally only one DP is needed to control a CQA.

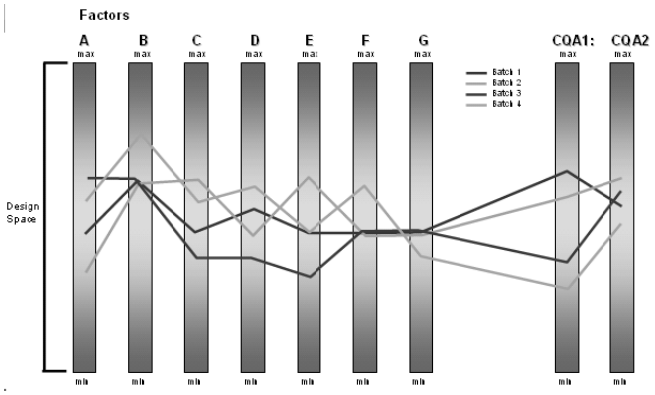

Figure 10. Results from individual production batches

In chemical, pharma or materials industries, just like any manufacturing industry, it is of extreme importance to provide clear indications to production on how to operate and control the process. The Design Matrix provides a first template for process management. It identifies which parameters to use if any functional requirement needs to be changed or brought back on track. In the next step, this knowledge is mapped and an APQP conformant control plan and Process FMEA are developed.

6 CONCLUSIONS

Using DFSS and Axiomatic Design best practices in pharmaceutical process development provides a structured, methodical and scientifically sound approach to implementing quality risk management practices required by regulatory authorities. The use of the Design Axioms in particular will help to develop a project plan for process development optimized to obtain a maximum of information with minimum effort. The approach has been implemented in practice in several pharmaceutical organizations. Similar approaches have been applied in chemical and steel industry.

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