From Understanding to Control : A Successful Application of Multivariate Modelling in Commercial Manufacturing

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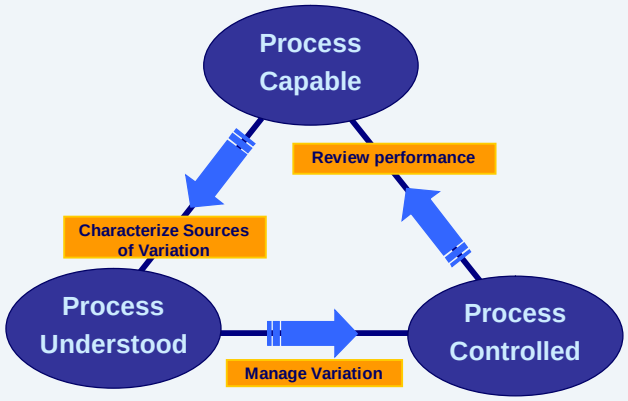
Executive Summary

This poster demonstrates an approach for developing post-market design space for an established orally inhaled drug product. The Six Sigma framework of Define-Measure-Analyze-Improve-Control (DMAIC) was followed to provide the backbone for successful implementation. Multivariate modelling techniques and Quality By Design tools were applied to improve process understanding and predictability. A combination of scientific and technical expertise, the appropriate technology, and a commitment to change were critical in improving process robustness in a full scale manufacturing environment.



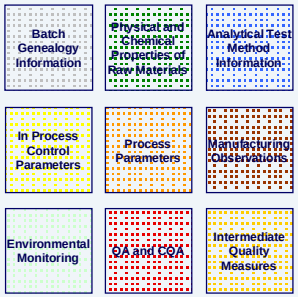
Define

- In an effort to continuously improve the quality of the drug product as part of its product lifecycle management, a project team was set up. to pilot the concepts of Quality by Design (QbD) and Process Analytical Technology (PAT) as recommended by FDA[1] and ICH[2,3]
- The following elements are identified as critical to success:
  - Determining the Critical Quality Attributes (CQA)
  - Linking Quality Critical Raw Material Attributes and Process Parameters to CQA
  - Developing a post-market design space
  - Evaluating control strategies including a feasibility study on the development of functional raw material specifications
  - Verifying the post-market design space and future operating control strategies

Measure

Measure phase focused on the following:

- Baselined current and historical performance including process capability assessment
- Used value stream map as reference, constructing process flow diagrams and unit operation Input-Process-Output Diagram to enhance process knowledge
- Identified all data sources, variables and gaps to understand current limitations of data and measurements
- Collected and collated all data into required format
- Reviewed Measurement System Analysis (MSA) output
- Familiarized the project team with the data by performing trending and basic statistical assessment
- Some key blocks of data included in the assessment are shown below



Multivariate Data Analysis (MVA)

- Mathematical reduction of many variables into a few variables and plots for interpretation
- Development of models describing CQA's as a function of inputs….based on the relationships & interactions between many variables

Analyze

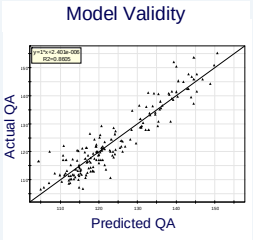
Analyze phase is an integral part of the journey. During this phase, the team:

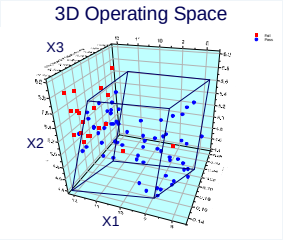
- Brainstormed / designed the appropriate statistical data analysis and modelling strategy. The multivariate projection techniques of Principal Component Analysis (PCA) and Partial Least Squares (PLS) were applied[3]
- Applied a range of data pre-processing techniques including:
  - Variable selection
  - Outlier removal
  - Filtration
  - Scaling and weighting
- Identified model performance criteria such as R^2 (explained variation) and Q^2 (predictability)
- Evaluated different models by using decision tree analysis
- Stated any model assumptions and limitations of the approaches
- Assessed and validated the selected model using cross-validation and model diagnostics
- Tested the model execution prior to introduction to the production environment

By applying the above, the sources of variation should be characterized and both CQA and other associated parameters defined. The post-market design space was developed in the multivariate hyper-planes.

The optimal operating range was selected. The control strategy was challenged using process knowledge.

The multivariate design space can be translated back to a few key univariate parameters to form the main control strategy.

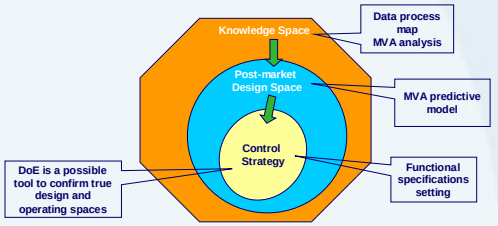




Control

Control phase plays a key part in sustaining the change:

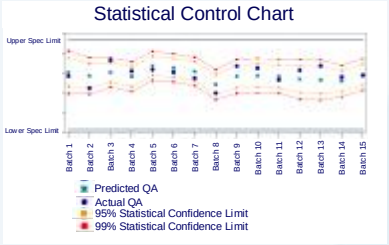
- Performance metrics and the control strategy can be implemented to monitor and safe guard the raw materials and the processing conditions
- An automated data capture and model execution system is recommended as part of the risk mitigation plan
- The operating space should be reviewed periodically to ensure its validity and to understand any shift in the process
- A Design of Experiment (DoE) can be one approach to review and verify the true design space. The multivariate models should be improved and stabilized



Improve

Key elements to consider in the Improve phase:

- The improved scientific understanding from the QbD exercise may change the existing ways of working through the inclusion of a risk-based multivariate mathematical model
- Perform Failure Mode Effect Analysis (FMEA) to capture all potential risks and appropriate actions
- Assess risk by calculating the appropriate statistical confidence intervals for the control strategy
- Design new business processes and performance metrics for routine monitoring
- Identify model automation requirements and execution plan



Reference

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