Success story

Biopharmaceutical Company Uses a Quality by Design Approach to Successfully Demonstrate Formulation Robustness of a Monoclonal Antibody

This quality-by-design example case shows how a multivariate study can be used to successfully predict formulation robustness of a biopharmaceutical product with a specified shelf life. Using Umetrics Suite, scientists at Hoffmann-Roche were able to create a design of experiment (DOE) study to predict antibody formula robustness using regression models that were both statistically significant and produced parameters for predicting the acceptable limits of robustness for the formula over time. As a result, the company created a reliable quality-by-design process that meets the International Conference on Harmonization Q8 (ICHQ8) standards for assessing the robustness of a formulation and could predict the critical quality attributes for a 36-month shelf life using less than 24 months of data.

MODDE makes Design of Experiments easier

Using MODDE, Hoffmann-La Roche Ltd. (Basel, Switzerland) was able to apply a Quality by Design process (QbD) in the Design of Experiments (DOE) to develop stability studies that would assess and ensure formulation robustness for a biological product—a monoclonal antibody.

Among the challenges for scientists in creating robustness studies are:

1. The study must result in a regression model that is statistically significant
2. The study must provide output parameters (quality attributes) that are within predefined limits

"Using MODDE, Roche scientists were able to apply multiple linear regression methods to show statistical significance while analyzing formulation robustness," said Erik Johansson, Lead Data Scientist for Sartorius Data Analytics. *"With MODDE, defining the acceptable limits for assessing robustness became easier, as well. The scientists only need to understand the science, not be experts in statistical analysis in order to develop reliable robustness studies."*
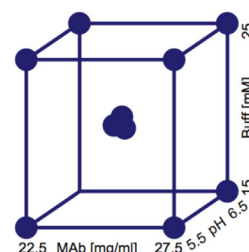
Designing a multivariate robustness study

The Roche multivariate stability study used three formulation factors at two levels:

- Antibody (MAb) concentration
- Solution pH
- Buffer concentration

These factors were investigated in a full factorial design resulting in 8 experiments and 3 center points.

The cube represents a visualization of the area within which parameters for the quality attributes must fall in order to be considered robust.

Results of the analysis

The study used four case situations to evaluate how well the experiment design stood up to testing. The first was a measure of low-molecular weight species (LMWS). It provided little knowledge about how formulation factors affect product performance. However, it represented the ideal outcome of a formulation robustness study because it reflected that the critical quality attribute response is not significantly affected by the input (formulation) parameter variations, thus confirming a robust formulation within the predefined limits.

"Quality by Design (QbD) is 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 Harmonization
(ICH guidelines Q8 and Q8(R2)

The second case ("acidic variants") also confirmed formulation robustness within predefined acceptance criteria. In addition, the statistically significant model shows how formulation factors affect product performance and allows extrapolation according to ICH guidelines if end-of-shelf-life data are not available at time of analysis.

The third case ("oxidized variants") provided information on how formulation factors affect product performance but showed that the formulation is not robust within the tested formulation composition range. As the regression model is statistically significant, it allowed the identification of formulation parameters or formulation parameter ranges that are accountable for the values outside the specified limits.

Furthermore, the model can be used to predict an acceptable formulation parameter range where all the values for the assessed quality attributes will be inside the specified limits, thus supporting formulation robustness by adjustment of, for example, formulation parameter ranges.
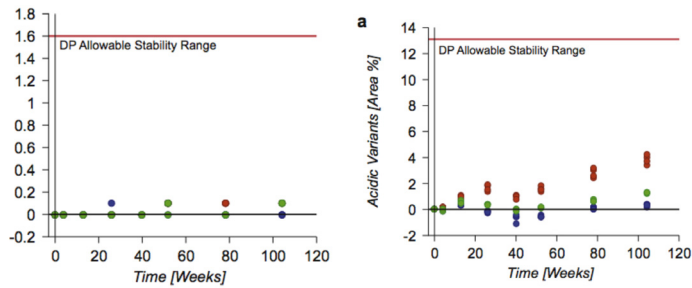
Finally, the fourth case provided little formulation knowledge as all measured values were close to zero (0) and well below the allowable Stability Range so formulation robustness can be claimed.

Conclusion

Formulation robustness studies are important both in setting the parameters of a formulation, as well as in providing justification for the specifications of critical quality attributes.

The Roche study showed that a formulation can be claimed as robust if all data sets and drug product critical quality attributes remain within their respective end-of-shelf-life critical quality attributes – acceptance criterion throughout the entire claimed formulation composition range.

Furthermore, using solutions such as MODDE allows scientists, no matter what their level of statistical expertise, to develop regression model studies that result in statistically significant data and can reliably identify the attributes that may have an affect on drug product shelf life.
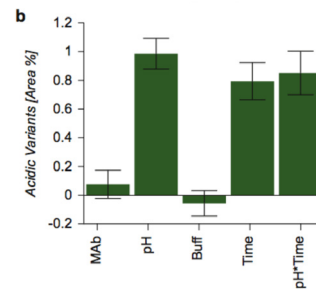
The customer:

Pharmaceutical manufacturer of biological antibodies, F Hoffmann-La Roche Ltd. (Basel, Switzerland.)

The challenge:

Develop a reliable design of experiment study to identify the parameters of a biological antibody formulation that affect product robustness and can be used to accurately predict shelf-life.

The solution:

Using MODDE, a multivariate formulation robustness study for a monoclonal antibody was developed to demonstrate the acceptable ranges of quality for the target composition, define the allowable edges of the composition range, and predict the stability requirements needed to reach a 36-month shelf life.

The result:

The DOE successfully extrapolated 24 months of robustness data to define the formulation composition parameters needed for a 36-month shelf life claim.

MODDE® from Sartorius Data Analytics

MODDE® is a Design of Experiments solution that helps you get it right from the start. MODDE is part of the Umetrics™ Suite of Data Analytics Solutions, a family of proven data analytics tools that work seamlessly together.

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