Customer Story

Mylan

Challenge

Ensure the optimal formulation and quality manufacture of drug products in a highly regulated environment.

Pharmaceutical formulations get an innovative update

Mylan Pharmaceutical applies state-of-the-art statistical methods to improve formulation science and experimental design

In the United States, one in every 14 prescriptions is filled with a pharmaceutical product made by Mylan. In France, Mylan holds the largest share of the generics market. And in India, Mylan's investment in a global R&D hub in Hyderabad has made it the nation's fastest-growing multinational, with major breakthroughs in oncology, hepatitis and critical care. With a workforce of 35,000, Mylan employs experts in a broad range of disciplines who collaborate to deliver medicines to customers in 165 countries – generating $12 billion in annual revenue.

Achieving a worldwide footprint takes more than just lifesaving therapies. It also requires a robust approach to statistics that helps the company move products from development to market quickly – without sacrificing quality. The result of Mylan's statistical innovation is a deep well of product and process knowledge that can be applied to optimize both the science and manufacture of new therapies. "The knowledge pharmaceutical manufacturers gain through experimentation and characterization enable a statistically sound basis for proposing specifications for product performance," says John Twist, Senior Research Fellow for Mylan.

Pharmaceutical manufacturing by the numbers

The FDA has outlined a Quality by Design (QbD) approach to pharmaceutical development that begins with predefined objectives, emphasizes product and process control and is based on sound science and risk management. "QbD gives manufacturers potential advantages," Twist says, "such as a lower number of failed batches and regulatory flexibility around post-approval changes within the approved 'design space.'" A key aspect of QbD is the identification of quality-critical attributes for formulation components, process variables and product characteristics, Twist explains. "Those characteristics could include tablet hardness, in-vitro dissolution and physical-chemical stability over time."

Within this context, Mylan must address two key issues. First, scientists need to manage variability. "There's a tendency to underestimate the inherent variance in measurements and replicated experimental runs," Twist explains. Mylan uses measurement system analysis (MSA) to systematically quantify variance components in order to assess operator training and the suitability of instruments. "MSA can guide an appropriate course of action such as choosing between using more refined instruments or a larger sample size," Twist says. Second, Mylan has to control costs. "Experimental runs can be expensive," Twist says. His team therefore relies on design of experiments (DOE) to efficiently replicate runs to estimate pure error.

For statisticians and non-statisticians alike

To help optimize its manufacturing capability – and implement the statistical best practices its scientists rely on – Mylan uses JMP® statistical software from SAS. Twist points to several key features in JMP that enable design and analysis of formulation experiments including:

Analyze – To look at distributions of data.

Measurement Systems Analysis – To evaluate measurement capability through Gage repeatability and reproducibility studies.

Graph Builder, Fit Y by X and Fit Model – To plot data and look for relationships among variables.

Custom Design – For constrained mixture-process designs to understand how formulation components and process-variable settings affect multiple response variables of intermediates and the final dosage form.

Profilers – For visually interpreting prediction formulas.

Twist cites *Strategies for Formulations Development: A Step-by-Step Guide Using JMP* by Ronald Snee and Roger Hoerl as a useful reference for scientists looking to use JMP for both mixture and mixture-process variable designs. The process outlined in the book, Snee says, allows "formulation scientists to get the right data in the right amount at the right time." The formulation development and manufacturing process can therefore be completed more quickly and at less cost.

jmp®
Statistical Discovery.™ From SAS.

JMP has robust tools for exploratory data analysis and provides a comprehensive set of modern statistical procedures.

John Twist, Senior Research Fellow

As President of Snee Associates, Snee now collaborates with Twist and his colleagues at Mylan to support a range of activities. "I encourage my formulation clients [like Mylan] to use JMP because it is the best available software for the design and analysis of formulation experiments," Snee says. "JMP provides methods that aren't available in any other software packages. It has the broadest array of tools available."

Snee and Twist agree that JMP has been a hit at Mylan in part because it appeals as much to industrial statisticians as to those without any formal statistical training. "JMP has robust tools for exploratory data analysis and provides a comprehensive set of modern statistical procedures," Twist says. "The JMP interface does an excellent job providing access to additional options in output windows using 'red triangle buttons,' plus a very convenient way to save re-usable scripts."

Such accessibility is important because pharmaceutical manufacturing brings together experts from a broad range of backgrounds. But "JMP makes possible the creation of custom experiments and the visualization and modeling of data by non-statisticians," Twist says. "Prediction profilers are an incredibly effective way to visually work with models and understand how controllable factors are influencing multiple response variables."

Breaking new experimental ground

Yet the most innovative use of JMP at Mylan is a new statistical mixture-process variable experimental design. The design was developed by Twist and colleagues at Mylan. Student interns from the Pennsylvania State University and the University of Charleston were also involved with the execution of batch manufacture of batches and physical testing of the compressed tablets. The method will allow scientists to study the blending behavior of direct compression excipients in powder mixtures and tablets. "A mixture-process variable experiment is ideally suited to efficiently characterize a multi-component formulation under various processing conditions," Twist explains.

The methodological challenge was complex. The experimental design had to cross a four-component mixture with specific tablet-press operating parameters. The mixture also involved two-step blending to account for differences in bulk density that could affect the blending dynamics of an internal lubricant. The blends were manufactured randomly but treated as whole plots of a split-plot structure for the tablet compression variables.

"Mixture-process variable designs are inherently complex to design, costly to execute and difficult to analyze by people who aren't statistically savvy," Twist says. The typical approach is one factor at a time, or factorial designs using a slack-variable component, or by adjusting the total weight of the formulation. "Our mixture-process variable approach doesn't conflate formulation component effects with a slack variable or variable weight of compositions," Twist says. "It also enables estimation of mixture-process interactions."

And JMP was a key player in the process. "JMP provided all the tools needed to accomplish the goals of our work," Twist reports. "JMP offers capabilities that aren't available or are less polished in other software. For example, the profilers and nonlinear model-fitting platform are first-in-class." In fact, Twist says several JMP capabilities were crucial to the success of the new experimental design, including the ability to:

- Create constrained mixture compositions, with upper and lower levels for each ingredient, assuming a second-order mixture model using d-optimality criteria.
- Fit models that include split-plot terms to the mixture-proces variable data.
- Fit nonlinear models for mixture-process variable data.

The team also used JMP to create data visualizations to communicate the new experimental design to internal stakeholders. In addition, the visualizations were used in a poster at the 2018 American Association of Pharmaceutical Scientists convention titled *The Application of Mixture-Process Variable Experimental Design in Evaluating Direct Compression Formulations* by Congcong Zhu, John Twist, Tyler Simmons, et al., and will continue to be used in training of Mylan's product development scientists.

For Twist, it's just another way JMP is helping Mylan bring new drug products to market – and, in the spirit of the company's mission, bring better health to a better world.

Solution

Innovative experimental design and robust statistical approaches to formulation science, all enabled by JMP®.

Results

A fruitful partnership between scientists and statistical consultants has helped Mylan to deepen product and process knowledge. Scientists at Mylan have developed an experimental methodology that will help the company bring new drug products to market faster and at lower cost.

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