Customer Story

Ono Pharmaceutical

Challenge

Adapt new process creation methods outlined in the ICH Guidelines that recommend the use of statistical methods for pharmaceutical product and ingredient quality management processes.

One quality imperative, many complicating factors

A statistical approach helps Ono Pharmaceutical build quality controls directly into manufacturing methods

Ono Pharmaceutical is now using statistical methods for the creation of new processes as recommended in the recent ICH Guidelines. Given the large number of factors related to quality control management in the pharmaceutical space, and in order to design the optimal manufacturing operation range, it is important to understand the interaction among factors. The aim is to create highly robust processes that help Ono achieve its quality goals with the use of statistical methods and JMP®.

Designing manufacturing processes that incorporate quality control

Founded in 1717, Ono has long worked to develop revolutionary new therapies that embody the company's core philosophy, "dedication to man's fight against disease and pain." For example, Ono's anti-PD1 monoclonal antibody, OPDIVO, recently received global attention as a wonder drug in the treatment of cancer.

Ono, like many of its counterparts in the industry, has accelerated its efforts to introduce quality control to the production of pharmaceutical ingredients. There was a time when all that mattered about a drug was its efficacy. But in the modern era, there is also a product quality mandate. The introduction of new guidelines known as the ICHQ Quartet and promulgation of the Quality by Design(QbD) concept have further accelerated the demand for detailed investigations into product quality.

In order to maintain and secure quality, a company must have a deep understanding of not only its manufacturing processes, but also the relationships among multiple manufacturing parameters. Within a matrix created by the interactions among these multiple parameters, a Design Space that enables the production of pharmaceutical ingredients with assured quality is set, and production occurs within the framework of that space. By taking a statistical approach to those manufacturing processes that have an effect on product quality, Ono is implementing a structure that will ensure robust processes.

"One method is improvement through experimentation based on previous experience," says Tatsushi Murase, Researcher in Chemical Process R&D at Ono. "But we really felt the appeal of a statistical approach whereby we could model the parameters and their relationship to quality. The old way of doing things also had its advantages, of course. But taking that into account, I felt strongly that statistics could be used as one of our analytical methodologies." Under ICH Guidelines, bulk drugs and ingredients are dealt with in ICH-Q11. Shortly after the publication of these new recommendations in 2012, Murase made preparations to roll out statistical methods using JMP.

JMP provides a set of easy-to-use tools for complex multifactor analyses

"With its simple operation method – 'put in data and results come out' – JMP is really easy to use," Murase says. "The effect of the contour line profiles (created based on the models) on quality within the manufacturing operation parameters is reflected visually. So creating highly robust processes with JMP is easy. In fact, learning the various functions of JMP helped me to develop a deeper knowledge of statistics."

jmp® Statistical Discovery.™ From SAS.

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Tatsushi Murase, Chemical Process R&D Researcher,
CMC and Production HQ, Ono Pharmaceutical

When raw materials pass through an intermediate body in the process of becoming new pharmaceutical ingredients, impurities generated during the reaction may remain. Design of experiments, or DOE, methods are useful in suppressing the occurrence of impurities. Murase says he and his team create models that include the interaction of parameters such as the amount of reagent or reaction temperature. A contour plot profile is then used to find the region at which impurities can be minimized below the target value, thereby helping to optimize the Design Space.

Murase anticipates that JMP will be useful as a means of communication between technical experts. "New pharmaceutical ingredients are developed by chemists, but the actual production is performed by engineers," he says. "They're both people with deep knowledge and broad experience, but their fields of expertise are different. The fact that the language of statistics can bridge that gap is extremely appealing. "Rather than trying to communicate their scientific and industrial knowledge in plain language, they can easily and immediately understand each other by looking at graphs created in JMP."

During the development of pharmaceutical ingredients, lab-based experiments are carried out in small reactor vessels. If the results of these experiments are good, commercial production moves to massive reaction tanks. With this increase in scale from a small lab reactor, stirring efficiency changes. As a result, ingredient particles may not form to the size originally expected during the crystallization process. In such a case, researchers must perform a multivariate analysis to identify the interaction between stirring efficiency and other factors. By selecting a production protocol that completely removes the effect of the stirring efficiency, it is then possible to maintain ideal particle size.

Internal seminars help researchers share statistical knowledge and applications

Statistical analysis is essential for researchers, says Chikara Honda, statistical training lead and consultant in the non-clinical field for Ono. "It is important for all researchers to examine things in a statistical manner. Researchers are happy when their experiment returns the results they were expecting, but they must dispassionately verify whether that experiment was carried out correctly. And this is where statistics is necessary. If the design of the methodology is poor, the results may be unusable. That alone makes DOE important for researchers."

As researchers at Ono introduce JMP to their colleagues, the number of users within the company is increasing steadily. Over the past few years, researchers have initiated a series of seminars on data analysis to share findings and teach each other about how they're using JMP.

"There are departments that perform biological experiments with individual differences where a more statistical means of observation is absolutely essential," asserts Honda. Analysis methods vary depending on whether or not those differences can be controlled. Luckily, as JMP has been updated and upgraded, the number of attractive methods keeps increasing, and it has become possible to perform analysis flexibly in accordance with the properties of the data. In addition to our own individual research field specializations, we're aiming to become a strong research group overall."

Solution

Researchers used JMP® to identify factors that affect product quality characteristics. Equipped with a better understanding of these factors and their interactions, Ono Pharmaceutical incorporated quality measures directly into the manufacturing process.

Results

Statistical methods continue to help researchers address experiments involving multiple factors. Optimal manufacturing operation parameters were set using models derived from these methods, and resulting processes are highly robust.

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