Pierre Fabre

Challenge
Sustained out-of-specifications outcomes at one of France's leading pharmaceutical and consumer health companies caused significant production inefficiencies and financial losses, while jeopardizing process validation requirements from national and global regulatory bodies.

Rooting out production challenges with statistical analysis

JMP® gives Pierre Fabre the tools to optimize its pharmaceutical and consumer health product lines

As the second-largest dermo-cosmetics laboratory in the world and the second-largest private French pharmaceutical group, Pierre Fabre boasts a broad array of consumer health, pharmaceutical and dermo-cosmetic products. However, with such a diverse portfolio of products comes a complex array of production lines governed by constantly evolving regulations.

Overseeing each of these production lines requires knowledge of both the manufacturing process and the relevant regulatory requirements. Thierry Taillandier, the quality project manager in charge of process validation at one of Pierre Fabre's manufacturing plants in France, is this liaison. This particular facility produces plant-based active ingredients for a variety of products, "from health to beauty," as Taillandier describes it. This botanical work falls within three primary areas: plant extraction, to collect ingredients for dermo-cosmetics such as shampoo or skin cream; fine chemistry, to manufacture pharmaceutical products; and semi-synthesis, a combination of plant extraction and fine chemistry whereby extracted plant compounds are combined and adjusted to increase their beneficial activity.

Regulatory requirements drive enhanced process validation for manufacturing pharmaceutical products

Validating these manufacturing processes is the final step in the commercial life cycle of Pierre Fabre's products – guidelines from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require process validation to ensure consistent, high-quality products and, ultimately, allow them into the marketplace. Starting in 2011, these guidelines changed significantly, driving the adoption of new statistical approaches across the pharmaceutical manufacturing industry to facilitate compliance. Pierre Fabre was no different. "These tools are not new, but for the pharmaceutical industry, it is new

thinking," says Taillandier. To support the development and submission of the new reporting requirements, Taillandier and his team sought new statistical software that served the facility's variety of needs.

Like many in manufacturing, Taillandier is trained in engineering, not statistics. His statistical expertise derives from practical, on-the-job experience in pharmaceutical research and development, and during his career he has used a variety of software. For this facility, Taillandier and his colleagues required software with broad functionality to support needs including research and development, design of experiments, root cause analysis, etc. "Our choice was driven by this [variety of needs], and we decided to go with JMP," he says. Another key factor was the ability to customize JMP software to the user's ability level. "It is important that you can personalize the software," he says. "I have some knowledge of statistics, but some people in the plant have no statistical knowledge, and we can adjust ... just click on a button to import a data table and run tests." For a team reluctant to adopt statistical approaches into the manufacturing environment, particularly at a facility with such a broad array of scientific functions, this simplicity was key.

Bringing 'out of specifications' in

Recently, one of the manufacturing lines at the facility was regularly out of specifications (OOS), meaning one of the analytical parameters for the active ingredient did not meet required quality standards. "The problem was very critical because ... we have no process for retreatment [of the batch]," Taillandier says, meaning any batch deemed OOS had to be destroyed. Over time, this issue recurred more frequently, costing the company several hundred thousand euros in 2016. Subsequently,

Statistical Discovery.™ From SAS.

a group of engineers at the plant created a production quality group, which used statistical detective work to identify the root causes of the problem. Since the implementation of the improvements recommended by the production quality group in 2017, no batches have been OOS, saving money and increasing efficiency.

A production team first sought Taillandier's expertise to identify the cause of increasing OOS outcomes for a certain project at the facility in January of this year. With the help of another working group, Taillandier made a list of relevant process and analytical parameters, and collected the corresponding historical data from the past five to seven years. Then he and his team investigated the relationship between the raw materials and active ingredients. "For this, we used the correlation platform in JMP, the correlation matrix. It was the best way to look at relevant information," Taillandier recalls. The team used different models, including linear regression and partition, to evaluate parameters in the production process. Because the raw materials could be in solid or liquid form, the working group knew the variability in this parameter could be a potential source of error. "The stability of the chemical reaction is based on equilibrium. We used the Profiler [tool in JMP] to identify the right quantity [of raw materials] to have at this chemical step." To validate their results, the working group used the JMP Prediction Profiler once again to conduct a linear regression and evaluate the effect of the raw materials on other parameters; with no warnings detected in this analysis, the group was confident to apply the changes derived from their assessments. Subsequent to implementation, production has significantly improved, with no batches OOS since.

Looking to the future of analytics at Pierre Fabre

Outside of addressing issues that arise in existing production lines, Taillandier has big ideas for further integration of analytics at the facility, where there are several areas for optimization. Three primary projects have garnered his attention:

1. **Increase yield for a product with a long manufacturing process:** Only a single batch is made each year, with manufacturing spread across 12 weeks. Complicating things further, some parameters are difficult to change, making it challenging to collect sufficient data on the effects parameter changes have on the production process. Because of the value of the product, any increase in yield would be highly beneficial; Taillandier expects that JMP will help the engineers refine these parameters faster and more effectively.

2. **Trend analysis in quality lab:** Scientists measure numerous parameters for each batch of each production line, such as pH, absorbance and water content. Although there is variation between batches in these parameters, they currently have no tools to identify potential trends in these data. JMP could be useful for this function.

3. **The array of electronic data capture systems used at the facility:** Currently, data is collected in several siloed systems, limiting the ability of site staff to conduct sophisticated analyses on data across these systems. A single data platform would allow Taillandier and his colleagues to unleash the potential of JMP and further optimize operations at their facility. "It's difficult now, but in the future, we need this system."

While JMP is currently used at just this single facility, Taillandier has shared his positive JMP experience and growing expertise in statistical analysis with colleagues throughout Pierre Fabre. "It's a good tool because we can predict the future," Taillandier says. With such rave reviews and dramatic results, JMP is a promising tool for Pierre Fabre's development goals.

Solution
Implementing targeted, user-friendly statistical tools in JMP allowed plant engineers to systematically identify the root causes for process inefficiencies and comply with regulatory requirements.

Results
Using JMP, this plant has drastically reduced manufacturing losses from 2016 to 2017, and engineers are exploring novel ways to integrate JMP in other areas of the company.

To contact your local JMP office, please visit: **jmp.com/offices**

§sas
THE POWER TO KNOW®