Rapid Process Understanding

Getting to the Root Causes of Revenue-Threatening Product Problems

Tunnell CONSULTING

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Following an FDA audit, an animal health company was surprised to be told that the processes for manufacturing its flagship product were insufficiently robust, resulting in problems meeting newly instituted USP stability requirements. The company decided to reformulate the product – which represented one third of annual revenues – and get the new formulation to market as quickly as possible. But the company's attempts to solve the problem resulted in processes that exhibited less control and worse stability. For help to achieve the process understanding and robustness required to satisfy the FDA and meet an ambitious time-to-market goal, the company turned to Tunnell.

***The Result:* The key drivers of variability in the process and the product have been identified, which will enable the company to:**

- *Achieve comprehensive process understanding*
- *Create and maintain a robust process that is able to tolerate variability while meeting the FDA's requirements for stability*
- *Stay on course to market with the new formulation*

"Tunnell was engaged to help characterize and optimize the manufacturing processes in order to eliminate the stability challenge with the new formulation."

Tunnell was engaged to help the company address the stability challenge of its flagship product as expediently as possible.

For more than a decade, the animal health company had been successfully manufacturing and marketing its highly valuable product. But because the product had been acquired from another company, process controls had not been well developed, resulting in poor process understanding. Meanwhile, the FDA had become more stringent in its regulation of animal health products and had begun enforcing a newly revised stability requirement. When the agency audited the company it found stability problems with the flagship product.

In the absence of a solution that would satisfy the FDA, the company faced the prospect of losing significant income from a product that accounted for one third of annual revenue. Stability issues can be particularly difficult to resolve because the problem may stem from multiple interacting factors, and one-variable-at-a-time studies may give misleading results. Furthermore, results from stability studies are usually not differentiating until after three months on accelerated stability – a significant time-lag.

The fact that the company's chief competitor in this therapeutic area was planning to exit the market gave the company added incentive to resolve the issue quickly. If the new formulation could be on the market during a window when there would be little or no competition, the company would be able to seize greatly increased market share and be in a good position to defend it going forward. With time of the essence, the company decided to reformulate the product and achieve a greater level of process understanding and robustness in order to:

- Ensure the capability to produce a stable product
- Improve the manufacturing processes to achieve a sufficient level of process robustness
- Submit Chemistry, Manufacturing, and Controls (CMC) to the FDA as soon as possible

Tunnell was engaged to help characterize and optimize the manufacturing processes in order to eliminate the stability challenge with the new formulation. The initial goal: identify the key drivers of variability and demonstrate proof of concept via a statistical model – within 14 weeks.

Tunnell applied its proven methodology for achieving greater process understanding and robustness: Process Capability & Control (PC&C).

To address the company's challenge in a structured, qualitative, and quantitative manner, Tunnell employed its proprietary PC&C approach. This adaptable solution has been successfully applied in many engagements where an understanding of the complex interactions among the critical-to-quality characteristics of raw materials, in-process parameters, and release specifications is essential for preventing or solving quality issues. In such engagements, a Tunnell team, consisting of a powerful combination of formulation scientists, process engineers, statisticians, and life science process excellence experts can:

- Extract key process understanding from historical data to minimize additional experiments
- Apply Design of Experiments (DOE) to avoid lengthy "one factor at a time" experimental plans that fail to capture interactions
- Identify critical parameters with appropriate control ranges
- Identify low-impact parameters that do not need to be closely monitored or controlled
- Scientifically establish specification limits

With a full understanding of the complex interactions of key variables that PC&C will generate, the animal health company will be able to map the possible combinations of the critical process parameters that will keep the product within specifications. They can then create a more robust process and more easily control it.

Tunnell's analysis uncovered three areas that could be addressed to resolve the stability problem. Those areas were related to formulation, process and packaging.

To identify and understand the drivers of process and instability variability, the Tunnell team undertook both qualitative and quantitative activities, including:

- Highly focused interviews with staff across 12 functions in order to assess current understanding of the process and product
- Process maps to create pictures of the process in its current and future states.
- Document reviews, process studies, and database creation
- Analysis and modeling of raw materials, processing conditions, release parameters, and stability data for both the existing and the new formulations
- Process observations of each work stream in order to appraise the existing manufacturing processes.

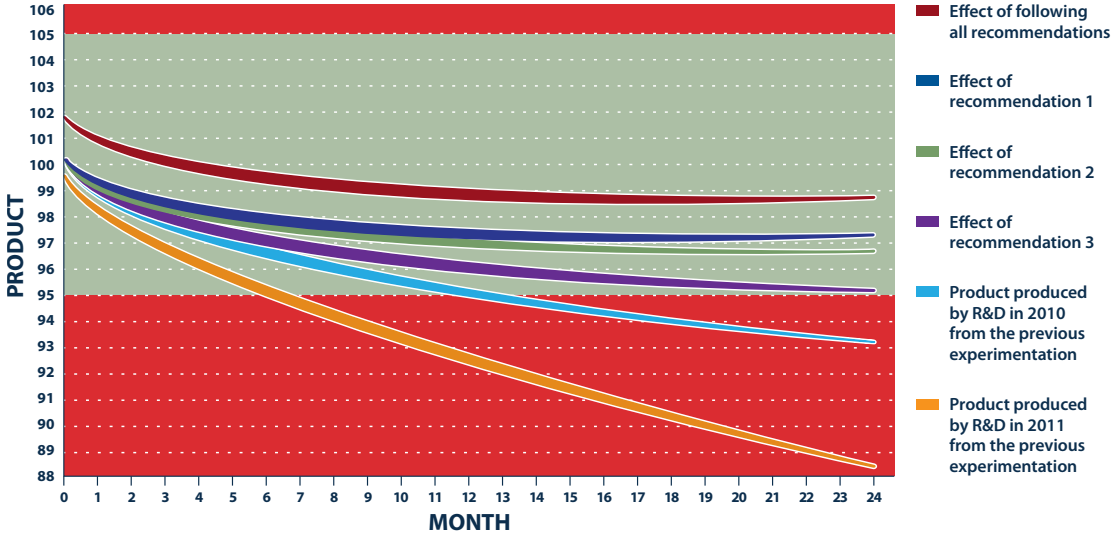
As a result of this work, the team developed a set of formulation-related, process-related, and packaging-related optimal operating parameters, the interaction of which would put the product at the center of a very robust process. Statistical analysis strongly demonstrated "proof of concept," as shown in Figure 1. In the figure, the top line depicts the cumulative effect of following all of Tunnell's recommendations, which would put the product squarely in the "green zone" – the range of acceptable specifications (potency of 95 - 105 percent) for stability. As the bottom line depicts, the product was in specification two years previously, when the potency specification was 90 -110 percent. But when the USP changed the potency specification to 95 -105 percent the product no longer complied with the specification, putting the product in the "red zone."

On the basis of this work, the team was then able to propose a design of experiments (DOE) that was executed to confirm the statistical findings. The work was completed ahead of schedule, and at the conclusion of the effort the company will be able to proceed with a new product formulation that will:

- Satisfy the FDA's requirements for stability
- Protect the company's flagship product from revenue loss
- Capitalize on the market exit of the company's chief competition

"We are confident," says the company's Director of Research and Development, "that the DOE will bear out Tunnell's identification of the root causes of the stability issue and enable us to get to market in a timely way."

Fig. 1. Additive Effect of Recommended Actions



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