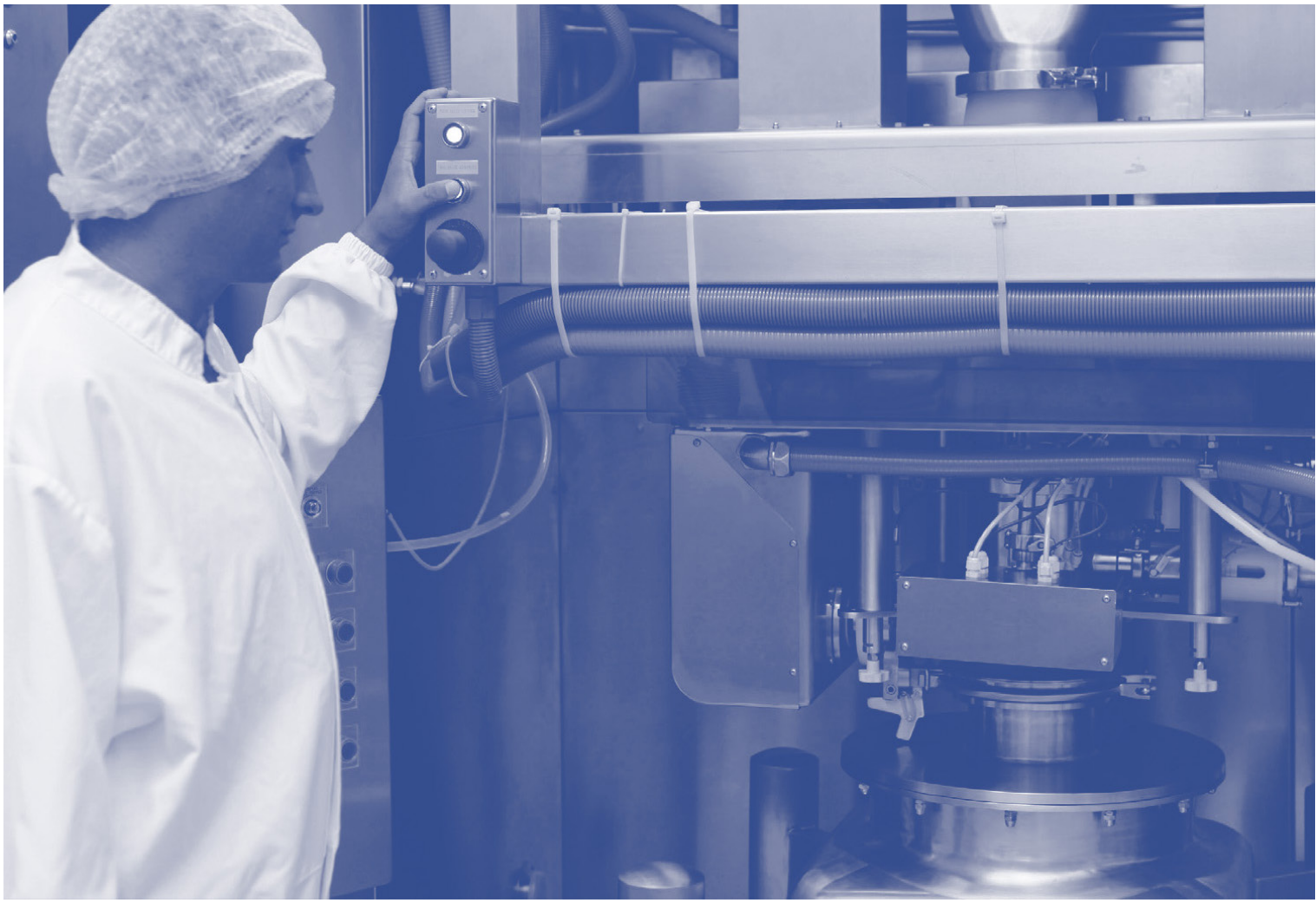
TUNNELL
life sciences consulting

PROCESS IMPROVEMENT



Process Capability and Control

Getting to the root causes of variation – and saving a product line

For three years a major generics pharmaceutical company struggled to correct variations in the dissolution rate of a high-demand, high-volume time-release product. They attempted to stabilize the dissolution rate by adjusting process parameters, replacing equipment, and working with API and excipient suppliers to get to the root of the recurring problem. Nevertheless, the variation and high product failure rate continued. After 161 investigations – and facing the possibility of the FDA shutting down the product line – the company turned to Tunnell.

The Result:

Employing its unique Process Capability & Control (PC&C) methodology, Tunnell uncovered the key drivers of variation, optimized process parameters, and re-validated the process. Working with Tunnell, the pharmaceutical manufacturer was able to:

- Save the product line and replenish the market supply
- Ensure an in-control, robust, and sustainable process
- Avoid millions of dollars of lost sales and costly damage to its reputation
- Gain deep process knowledge of the time-release product and all other related processes throughout their facility
- Acquire the PC&C methodology and tools skill set, which in turn can be applied across the breadth of the organization's products/processes.

TUNNELL
life sciences consulting

Tunnell was engaged to resolve recurring, product-threatening problems with dissolution rate failures.

For three years following the launch of a time-release product, the generics manufacturer encountered variation in the dissolution profile of the intermediate blend and the finished tablet. The variations, with high failure rates and large monthly fluctuations, included low and high release dissolutions and an increasing risk of product failure. Attempts to fix the problem by manipulating the process parameters, working with API and excipient suppliers, and by purchasing more expensive equipment all failed to produce sustainable results. Facing possible FDA shutdown of the product line and millions of dollars in lost sales, the company engaged Tunnell to:

- Return the product to production quickly with a highly capable process and new targets well centered within its design space specification limits
- Train the company's personnel on the methodology and tools, enabling the application of this new skill set to other products/processes
- Develop longer-term recommendations that could further optimize the process and product quality.

Tunnell's Process Capability & Control methodology provided a structured, qualitative and quantitative approach to comprehensively address the dissolution issue.

Tunnell rapidly deployed a highly experienced team consisting of a formulation scientist, process engineer, statistician, data analysts, and a project manager to address the problem using the firm's proprietary PC&C methodology. (PC&C is a proprietary solution framework that delivers process understanding and robustness in line with the FDA's current thinking and guidance that addresses an array of critical business challenges [e.g. dissolution, stability, potency, yield] within Manufacturing, Product Development and Quality.) PC&C has been successfully applied in many settings 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.

Working closely and cross-functionally with the client, the Tunnell team:

- Developed a comprehensive database populated with historical data from batch records, lab analysis, in-process data, Certificates of Analysis (COAs), maintenance records, and other documentation
- Coordinated detailed process observations and process mapping
- Undertook a detailed review of previous investigations and annual product reviews (APRs)
- Conducted customized focus interviews with key personnel, from director level to research scientists to process operators
- Generated and refined hypotheses about causes of the problem, prioritized them, and assessed them against the scientific knowledge and the supporting statistical data analysis.

As a result of this work, the team initially concluded that the cause of dissolution variation lay in the interaction of three critical process parameters: spray rate, atomization air pressure, and process air volume. They were then able to use statistical modeling to determine the optimal design space – the possible combinations of the critical process parameters that would keep the product well within specification limits.

However, before embarking on the experimentation phase to test the model, the Tunnell team focused on operational variation rooted in differences in operator methods, equipment, and setup. The identification and resolution of these differences enabled the team to embark on more precise experimentation with greater confidence in the statistical models to be tested.

”

Tunnell's Process Capability & Control methodology provided a structured, qualitative and quantitative approach to comprehensively address the dissolution issue.

Figures 1 & 2 depict the spray rate performance before and after improvements leading up to the experimental designs. The “short” list of process improvement actions are listed on Figure 2, adjacent to the more highly controlled spray rate function.

Fig. 1. KCI - Historical Spray Rate Performance

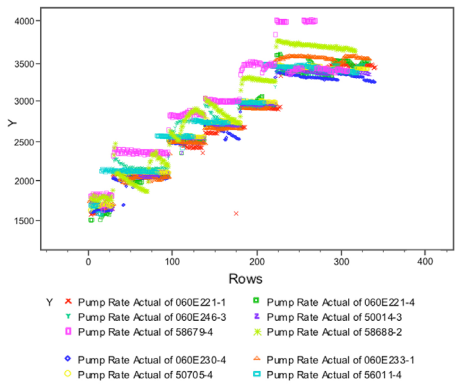
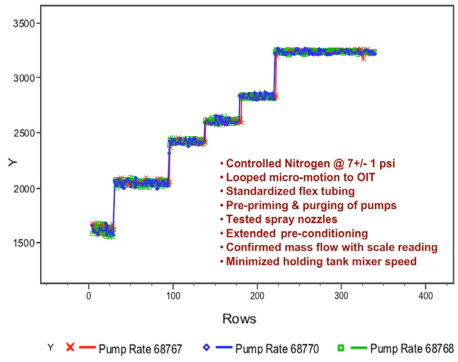


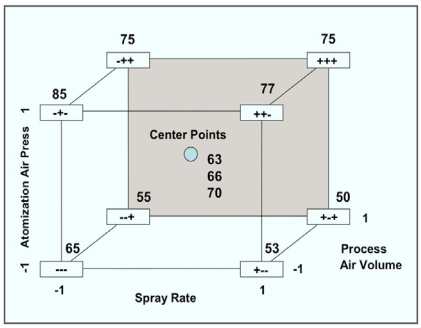
Fig. 2. KCI - Controlled Spray Rate Performance



The team conducted Design of Experiments (DOE) to test three process parameters, the interactions, and resultant impact on the dissolution release parameter in order to better define and optimize the design space.

Applying Design of Experiments (DOE) to avoid lengthy “one factor at a time” experimental approaches that fail to capture interactions, the team performed test runs to confirm the statistical model. These confirmation runs enabled the team to refine a statistical model that could accurately predict the effect of set point changes for spray rate, atomization air pressure, and process air volume on dissolution values of the intermediate blend and the compressed tablets. The refined statistical model was then used to optimize the process for the dissolution profile, increasing the capability of the process and thus its overall process robustness. (See Figure 3).

Fig. 3. KCI - DOE Results - 4 Hour Dissolution Time Point



Recommendations regarding equipment, procedures, set-up, material handling, and parameter ranges were also developed and implemented to mitigate or eliminate other common causes of variation. In addition, Tunnell’s PC&C methodology was transferred to key client personnel, and the technical knowledge was applied successfully to the client’s other processes and products.

The manufacturer reaped multiple business and financial benefits. With a more stable and predictable process, the manufacturer rapidly returned the product to production, enabling the company to:

- Replenish product supply to the market
- Reduce the risk of future shutdowns
- Realize savings in rejected-lot costs of an estimated $2 million annually
- Avert an average of 40 formal investigations per year and 2000 hours per year responding to them, resulting in significant savings in Quality Assurance and other tech support functions
- Avert loss of the entire multi-million dollar product contract
- Preserve the company’s reputation for quality manufacturing.

With its newly acquired knowledge, the company is realizing additional financial and business benefits by applying Process Capability & Control to other products and processes.

”

Tunnell’s PC&C methodology was transferred to key client personnel, and the technical knowledge was applied successfully to the client’s other processes and products.

TUNNELL
life sciences consulting

For over 60 years, Tunnell has provided both expert talent and consulting services to clients including Biopharmas, CDMOs, the US Government, incubators, investors and NGOs. We have experience across multiple platforms – including large molecule, vaccines, cell and gene therapy and small molecule – and our subject matter expertise focuses on regulatory, quality, GxP, pre-clinical/clinical, supply chain, manufacturing, CMC and product launch. To learn more, visit us online at http://www.tunnellconsulting.com.

1235 Westlakes Drive, Suite 280
Berwyn, PA 19312

t: +1 (610) 337-0820

tunnellconsulting.com