

SIMULATION



Lean(ing on) Six Sigma and Predictive Modeling

Monte Carlo simulation can allow drug manufacturers to gain new insight and drive further improvements across their organizations.

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THE PHARMACEUTICAL industry finds itself at the crossroads of change. Pharmaceutical manufacturers, which traditionally have enjoyed enviable margins even in times of economic downturn, are facing a number of emerging challenges that threaten to transform the industry paradigm moving forward. Challenges range from upcoming expirations of blockbuster drug patents, which can shift more than \$1 billion in U.S. sales within weeks, a dwindling pipeline of blockbuster drugs, increased pressure from generic drugs, and uncertainty about the future of healthcare reimbursement in the United States. In addition, merger and acquisition activity in the industry has seen a significant uptake in recent months, driving organizations involved in such activities to ponder how best to integrate and manage their new organizations (minimize time-to-value) and spurring organizations external to these activities to reassess their own strategies and operations to continue to compete effectively.

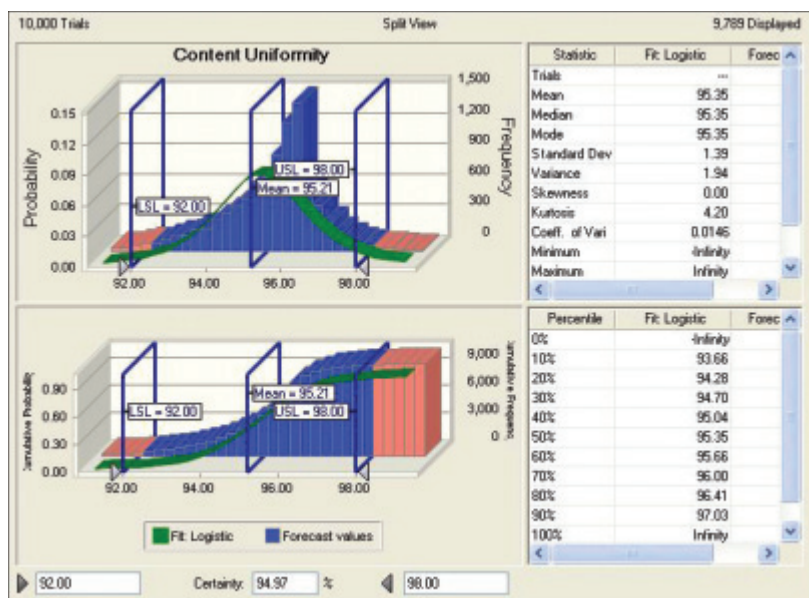
To position themselves for continued profitability, pharmaceutical companies of all sizes are taking a hard look at their organizations with an eye toward optimizing productivity, efficiency and quality across the enterprise. Manufacturing operations are far from exempt from the microscope's lens as pharmaceutical organizations seek

to drive down costs in every corner of the organization. To this end, progressive manufacturers are looking to extend the effectiveness of their Lean Six Sigma initiatives—which blend Six Sigma for quality and Lean Speed to enhance efficiency as well as reduce waste—with predictive modeling techniques, such as Monte Carlo simulation, to gain new insight and drive further improvements across their organizations.

BREAKING OLD HABITS

For a number of years, the pharmaceutical industry lagged behind other sectors in terms of manufacturing efficiency and productivity, largely because of the cost and burden involved in fulfilling regulatory mandates that require revalidation of processes following a change. The industry's focus on maintaining the *status quo* in its manufacturing environment has produced inefficiency and waste. It is estimated that the potential world-wide cost savings from efficiency improvement could be as high as \$90 billion [1]. Quality has also suffered under the *status quo*. The reject percentage in the pharmaceutical industry ranges from five percent to 10 percent (<2 Sigma), compared to 0.0001 percent (6 Sigma) in the semiconductor industry. This reject-percentage costs the

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A Monte Carlo simulation model gives maximum and minimum values of content uniformity, as well as a most probable value.

industry between \$4.5 billion and \$9 billion per year based on \$90 billion spent on manufacturing annually [2].

Pharmaceutical manufacturers, which historically have enjoyed consistently robust profit margins, have had little economic incentive to introduce change . . . until now. By some estimates, . . . drugs with sales of over \$73 billion from the largest 10 pharmaceutical companies will be initially exposed to generic competition over the next four years [3].

Fortunately, they have, in recent years, received some support for innovation from the regulatory community. The U.S. Food and Drug Administration (FDA) and other regulatory bodies are acknowledging that the industry has fallen behind other sectors in terms of efficiency and quality, and are now endorsing a Quality by Design model that contrasts with the industry's historical "quality-by-test results" approach.

As part of this shift, FDA launched its Process Analytical Technology (PAT) initiative, a risk-based guidance model that seeks to direct

pharmaceutical manufacturers toward consistent, predictable and higher quality levels. With PAT, manufacturers build in quality improvements on the factory floor through a deep understanding of how variable process attributes, as well as the relationship among raw material and manufacturing processes, affect product quality at a fundamental level.

As pharma seek to transform manufacturing operations in the industry's rapidly evolving business climate and embrace PAT, many are turning to or are expanding their focus on two highly regarded management approaches—Lean Manufacturing and Six Sigma—that have proven effective in other complex industries. Lean Manufacturing focuses on eliminating manufacturing waste, with the objective of making manufacturers more responsive to customer demand and market changes. Six Sigma is a business process methodology that focuses on minimizing variation in product and process to reduce product defects. When drug manufacturers

implement Lean and Six Sigma concepts, they have a powerful methodology to help them improve quality, compliance, productivity, costs and speed.

THE MOVE TO MONTE CARLO

With the PAT approach, manufacturers must understand how variations within core ingredients or manufacturing processes affect outcomes. Many manufacturers, however, still rely on traditional analysis of quality outcomes—which does not provide probability information on quality, cost and speed, all essential components to advancing PAT.

To effectively leverage PAT and the Lean Six Sigma methodology that supports it, pharmaceutical manufacturers require modeling tools that ideally help to improve quality long before a product is ever manufactured. These models enable predictive analysis that forecasts the impact of various changes to ingredients or manufacturing processes on the quality of the finished product. Monte Carlo simulation—a sampling technique that uses probability distributions as process inputs, as opposed to a single or average value—is one such modeling tool.

Monte Carlo simulation enables pharmaceutical manufacturers to establish a range-based view of the baseline (the current or "as-is" state) against which manufacturers can measure the effects of potential improvements (the future or "to-be" state). These predictive models are especially helpful when significant variation (or uncertainty) exists, and data is not available, of questionable accuracy, expensive to collect or difficult to measure in a reasonable amount of time.

This analytical method now enables pharmaceutical manufacturers to predict the probability of given quality in the final product with greater confidence,

and balance the quality demands of Six Sigma against the principles of Lean, which focuses on producing finished products faster and more cost effectively. As important, it can support lean initiatives at the manufacturing and business levels, allowing organizations to predict manufacturing demand as well as manufacturing cycle times.

With Monte Carlo simulation, pharmaceutical manufacturers can, in essence, quickly “produce” an almost limitless number of “virtual batches” of a drug, using the model to simulate outcomes based on variation adjustments.

When a Monte Carlo tool runs a simulation, it also analyzes the relationships between inputs and outputs to determine which inputs have the greatest impact on performance. This sensitivity analysis tool can help manufacturers to identify and understand which process steps are most critical to achieving the desired level of quality in the final product, such as cycle time and defects—letting them know where to insert the necessary controls. Sensitivity analyses are especially helpful when input distributions are abnormal, when output formulas are nonlinear and when the model contains large numbers of input distributions. Pharmaceutical manufacturers can then forecast the effects of proposed process improvements by updating the model, simulating the new version and comparing the results—all without wasting so much as a single capsule or pill.

TESTED AND PROVEN

To understand how Monte Carlo modeling can help pharmaceutical manufacturers improve product quality and reduce waste, we look to an example presented in a 2007 paper titled “Monte Carlo Simulations for

Risk Analysis in Pharmaceutical Product Design,” written by experts at contract manufacturer DSM Pharmaceuticals [4].


Content uniformity, which is the measure of the variation in the amount of active ingredients in the units of a batch, is an essential element to achieving consistent quality in pharmaceutical manufacturing. Ensuring consistent mixing of an active pharmaceutical ingredient (API) with non-active ingredients, however, is often a challenge due to many factors, including variation in particle density, shape and size—all of which, ultimately, affect uniformity.

In the DSM paper, the authors examined a pharmaceutical product that uses Dextrate, Silicon Dioxide and Magnesium Stearate as excipients, in addition to an API. DSM produced approximately 125 batches (consisting of 260,000 tablets per batch) of the 500 mg strength of this product (Product A) in 2006, some of which failed because of out-of-specification content uniformity.

To better understand what was occurring and improve the process and reduce waste moving forward, the team conducted a Monte Carlo analysis focusing on how the particle sizes of the API and excipients affect the content uniformity of Product A. DSM built a model based on the variability of the particle size of the API and the particle size of the excipients to understand the relationship between content uniformity and the input variables. The Monte Carlo simulation model enabled DSM to identify the impact of each variable, such as particle size of API and particle size of excipient, on content uniformity.

The DSM team also built a screening model by taking particle sizes of excipients and API as factors, and content uniformity as

a response. Upon fitting the model with the experimental data set, the team found that the particle size of API and excipient were not the only factors that affected uniformity, but there were also interactions between the particle sizes of API and excipients that had a significant impact on the outcome.

While Lean Six Sigma methodology and simulation models can help to improve product outcomes as in the example presented in this section, manufacturers can also apply the same approaches and tools to drive business process improvements, in terms of predicting customer demand and rationalizing it with manufacturing capability. Pharmaceutical manufacturers are fortunate that proven, easy-to-use commercial off-the-shelf applications for Monte Carlo and other modeling exist today, which is helping to support adoption of Lean Six Sigma in the pharmaceutical industry. 

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