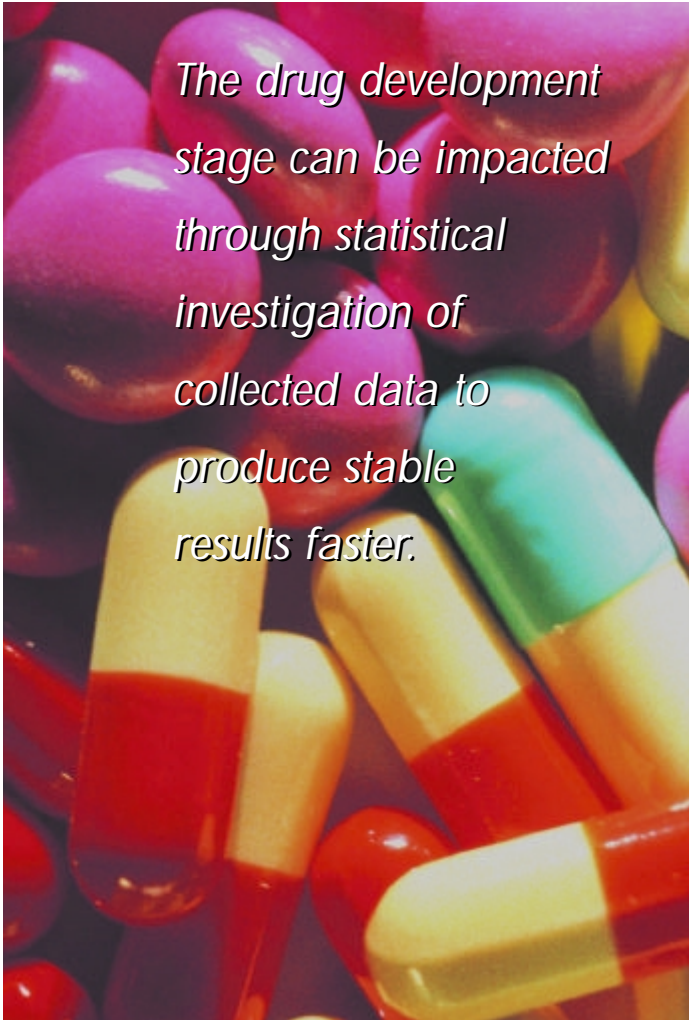




Amy Smith

GlaxoSmithKline Shortens R&D Cycle with JMP's Design of Experiments



The drug development stage can be impacted through statistical investigation of collected data to produce stable results faster.

Holding an estimated seven percent of the world's pharmaceutical market, GlaxoSmithKline (GSK) focuses its research in four major therapeutic areas — anti-infectives, central nervous system (CNS), respiratory and gastro-intestinal/metabolic. It is a leader in the development of vaccines and has a growing portfolio of oncology products. Consumer healthcare products augment the company's profile with over-the-counter (OTC) medicines, oral care products and nutritional healthcare drinks, all of which are among the market leaders.

GSK R&D is based at 24 sites in seven countries. Annually, about \$4 billion is dedicated to drug discovery and development.

This article explores how the drug development stage can be impacted through statistical investigation of collected data to produce stable results faster, thereby creating a higher conversion rate, improving yield, and decreasing time spent in pre-trial conditions.

Research Triangle Park, North Carolina

It takes on average 10 to 12 years to discover, develop, test, approve, market and deliver a new drug to the marketplace. With an associated price tag as high as \$800 million to deliver one drug to the public, it becomes critical to find ways to abbreviate processes and still ensure that pharmaceutical products are safe and effective.

The initial stage of drug development works to identify and isolate targets, which are chemicals in the body believed to be associated with disease. Once the characteristics of the targets are determined and the scientists understand how they influence a disease, compounds that interact with drug targets can then be

identified to help treat the disease.

Statistical Sciences at GSK collaborates with scientists and chemists during this preliminary stage of drug discovery and development. Once scientists select a target and identify a compound that interacts with that target, statisticians in Statistical Sciences help them by designing experiments to formulate a drug product and assure that the product has desirable properties, such as bioavailability and stability.

Mike Emptage, Assistant Director in Statistical Sciences at GSK, has worked with biologists, formulators and analytical chemists during drug development. "Robust assays are essential — they must give good results in both research and production settings," Emptage said. "These assays are used to evaluate multiple response variables — stability, concentrations of drug substance and impurities — and are developed by experimenting with various factors until a sensitive and specific assay is found."

Emptage utilizes JMP, a statistical visualization software tool, to analyze the effects of multiple factors, such as pH, concentrations and temperature, and find the settings that minimize the variability in the responses and produce a

'robust' assay. According to Emptage, JMP's graphing capabilities are very helpful. "There is no need to look at data in tabular form — JMP is a visualization tool that provides a significant amount of information on a single graph," he said. "JMP dynamically links tables to graphs so that outliers and trends in data are quickly identified."

JMP's Design of Experiments (DOE) facility allows statisticians

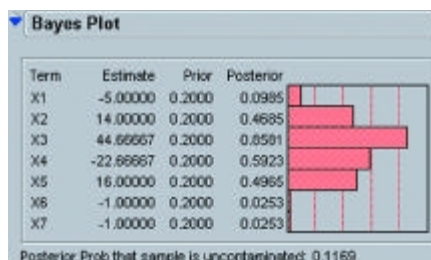
and scientists to design efficient experiments to fit their needs, reducing the number of experimental runs needed to obtain a good formulation or robust assay.

Below is an example of how JMP's DOE capabilities helped scientists and statisticians collect significant data in a minimal number of runs. It is a robustness experiment used in the development of a pediatric formulation of an AIDS drug. The experiment has nine runs, in which the levels of seven factors (X1 through X7) are varied (according to a Resolution 3 design from JMP). The factors include things such as wavelength, flow rate and volume of material injected onto the HPLC column. Two responses are Resolution and Retention time: Resolution must be larger than 2.00 and Retention time should be less than 20 minutes for the assay to be considered 'robust.'

In this example, high (1), low (-1), and middle (0) settings of the factors are tested to identify which settings cause the Resolution and Retention time to fail to meet their targets:

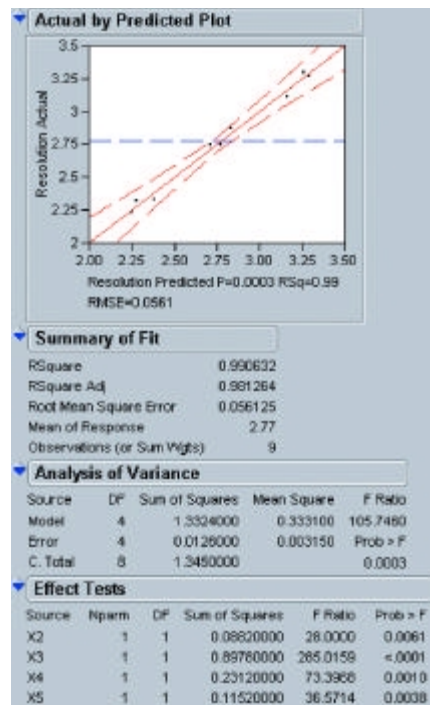
	X1	X2	X3	X4	X5	X6	X7	Resolution	Retention time
1	-1	-1	1	1	-1	-1	1	2.75	18.23
2	-1	-1	-1	1	1	1	-1	2.32	9.81
3	1	1	1	1	1	1	1	3.11	16.65
4	0	0	0	0	0	0	0	2.75	13.23
5	-1	1	1	-1	-1	1	-1	3.3	21.12
6	1	1	-1	1	-1	-1	-1	2.23	6.95
7	1	-1	1	-1	1	-1	-1	3.27	14.31
8	-1	1	-1	-1	1	-1	1	2.87	9.94
9	1	-1	-1	-1	-1	1	1	2.33	6.73

First, fit a model for Resolution with all seven effects in it, and look at the Bayes plot:



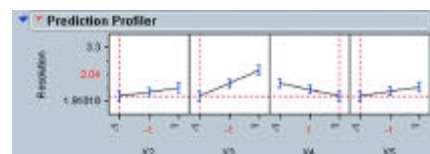
The longer columns in the plot indicate which effects are more likely to be statistically significant. They are X2 through X5.

Running a model containing only these effects gives the output:



All four of these effects are highly significant.

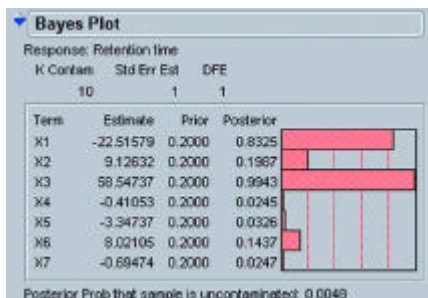
The next consideration is whether or not any combination of the settings of these four factors would lead to a Resolution less than 2.00. For this, the Prediction Profiler is the chosen tool:



This indicates that with X2, X3 and X5 at their lowest settings and X4 at its highest setting, the predicted Resolution is 2.04. So, no combination of these factor settings will cause the Resolution to fall below its limiting value.

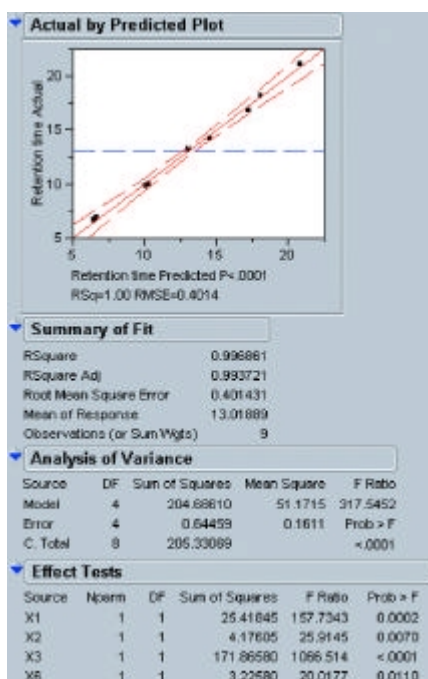


For the Retention time response, start with the Bayes plot:



Here we see that the possibly significant effects are X1, X2, X3 and X6.

Running a model containing only these effects gives:



We see that these effects are indeed significant.

The Profiler for this response is:



The predicted Retention time for X1 at its lowest level and X2, X3 and X6 at their highest levels is 20.79, slightly above 20 minutes.

The response is most sensitive to the X3 factor (steepest slope), so we decrease the setting of that factor a bit:



Any setting of X3 less than 0.829 gives a predicted response less than 20.00. (Actually, it may be safer to recommend that the upper limit of the range for X3 be reduced to something like 0.8 since the predicted response does have some variability.) So, as long as the range for X3 is reduced to 0.829 (or 0.8 to be safe), the Retention time will fall below the upper limit, and the assay is deemed robust.

abilities of JMP, enables statisticians to investigate multiple factors systematically. With DOE, this experiment was completed in nine runs.

Prior to the use of designed experiments, scientists would have conducted this same experiment using the OFAT method — measuring “one factor at a time.” Such an experiment would have required 15 runs. In this way, the use of DOE provides substantial cost and time savings for drug companies working to develop safe and effective drugs for the marketplace.

Another application of JMP's DOE and data visualization capabilities at GSK has been to optimize the chemical synthesis of drug substances — the active compound in a drug product — by increasing yields of the desired compound and minimizing the production of by-products. Since cost and time constraints force drug companies to make diffi-

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Validation of the robustness of an assay is essential as work on a drug moves from a research setting to a production environment. GSK has multiple international manufacturing sites, so the assay has to ‘give the same answers’ at these locations despite possible small variations in the factors from site to site. Based on FDA requirements, drug production must remain consistent to ensure the composition, purity levels, potency and overall quality of the finished product.

An experiment of this kind, utilizing the DOE and analysis capa-

cult choices about the number of drugs to investigate, use of JMP increases the resources available for a variety of drug research studies. The goal is to provide safe and effective drugs that can be used to relieve suffering from disease and provide a higher quality of life.

Amy Smith is a Corporate Communications Specialist at JMP, a business unit of SAS. Michael Emptage, Assistant Director in Statistical Sciences at GlaxoSmithKline, also contributed to this article. They may be reached at editor@scimag.com.