



DecisionSite Tames Risky Business

At Tularik, Spotfire® DecisionSite™ helps clinical pre-marketing risk analysts get a jump on spotting adverse event risks—before they adversely affect the bottom line.

Business Profile

Tularik is a biotechnology and drug discovery firm in South San Francisco, California, that focuses on developing therapeutics for cancer, inflammatory and metabolic disease.

Application Profile

A DecisionSite guided application designed for clinical trial risk analysis that helps analysts sort through clinical data across multiple phases for pre-marketing risk analysis.

Challenge

- Tularik's growing list of drug candidates under evaluation in clinical trials was creating a bottleneck in pre-marketing risk analysis
- Microsoft Excel-based statistical utility made it impossible to evaluate more than two variables at a time, slowing the analysis process of multiple laboratory, patient, and dosage variables
- Pre-marketing risk analysis procedures required better definition and lacked a process guide with exploratory capabilities to encourage informed decision making

Solution

- Spotfire worked with Tularik to develop a guided DecisionSite application designed for pre-marketing risk analysis
- Visualization interface enabled Tularik analysts to sort through multiple variables at once and easily spot relationships involving adverse events

Results

- Pre-marketing risk analysis bottleneck has been removed, as analysts can move much more quickly through the data
- Accuracy of analysis has improved due to comprehensive nature of data visualizations and ability to spend more time on each analysis exploring data relationships
- Identified risks are better managed as drugs progress through trials and unacceptable drugs can be removed from pipeline, saving money spent on trials

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– James Buchanan
Director of Drug Safety
and Surveillance, Tularik, Inc.

Tularik Inc. is a biotechnology and drug discovery firm located in South San Francisco, California, that specializes in drug discovery related to cell signaling and gene expression control. Promising Tularik drug candidates include T67, a drug that treats hepatocellular carcinoma, a primary liver cancer, as well as drugs that treat esophageal and gastric cancers, psoriasis, and diabetes.

Like any drug development company, Tularik performs clinical pre-marketing risk analysis on drugs passing through clinical studies. The goal is to identify adverse events and changes in laboratory values, physical findings and vital signs that might be related to the drug in question. It is essential to Tularik’s bottom line that adverse events are identified early in the development process in order to avoid the cost of further development. Early detection enables analysts to design study protocols and assess risk/benefit status before the company has invested significant funds on a particular drug. With timely and accurate analysis, drugs with an unfavorable risk/benefit assessment can be discontinued as early as possible. What’s more, drugs with defined risks that still offer favorable efficacy can be more appropriately managed, for example by controlling drug dosage and method of administration while avoiding use in at-risk populations.

The Business Challenge

Tularik’s drug development efforts have progressed to the point where the company has a dozen or more clinical trials in progress. This trend has significantly increased the workload for clinical pre-marketing risk analysis. James Buchanan, the firm’s lone analyst, was finding it difficult to keep up.

“We were quickly getting to the point where there was more data than I could sift through,” says Buchanan, Tularik’s Director of Drug Safety and Surveillance.

Because it was not yet feasible to hire another analyst, Tularik management agreed with Buchanan that a technological solution was in order. Up to that point, Buchanan had been using Microsoft® Excel spreadsheets together with add-on statistical utilities. The main problem with this approach was that the statistical software allowed for the comparison of only two variables at a time. This made it time consuming to evaluate adverse event data by all the different criteria that might come into play, such as dosage, age, race, and sex.

Buchanan first investigated commercially available signal detection software, but he found that the packages were designed primarily for post-marketing adverse event data. “The post-marketing software is based on proportional reporting rates, so you’re basing your analysis on the rate at which clinicians report adverse events outside of the clinical trial setting, where reporting is only voluntary,” says Buchanan. With pre-marketing analysis, he says, data collection is more thorough. There is more limited patient exposure, but there’s a wider dosage range, and you need to take into account the availability of PK and laboratory data. “You have a variety of other data to sift through, including some highly visual information,” says Buchanan. Considering that many commercial packages were expensive and not appropriate for clinical safety data analysis, he soon realized that he was “back to square one.”

It didn't take long for Buchanan to realize that DecisionSite met all his key criteria. It was relatively affordable, it required minimal IT support and it offered strong analytical tools. What's more, its sophisticated and intuitive visualization environment eased the simultaneous evaluation of multiple criteria, and in such a way as to reveal trends and patterns that might otherwise have remained hidden.

The Spotfire Solution

At an industry conference, Buchanan had been intrigued by a presentation given by Lilly analysts on using Spotfire DecisionSite to analyze drug safety data. He decided that it might be possible to apply the same data visualization capabilities to clinical trial data. Fortunately, Tularik already owned DecisionSite licenses for use in the Genomics group, so he began working with DecisionSite to analyze clinical data immediately.

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After convincing management that DecisionSite provided the solution he required to accelerate Tularik's analysis performance, Buchanan contacted Spotfire and explained the type of signal detection application he wanted to design for analyzing pre-marketing clinical data. Spotfire representatives worked with him to design and test a guided application. Much of the application was created using Spotfire's Application Builder, which allowed Buchanan to record tasks that he commonly performed during a typical analysis.

"Spotfire quickly understood what we were trying to accomplish and provided some very useful guides," says Buchanan.

The application drew data from two main data sources: extracts from Tularik's clinical database, which were prepared as flat files, and in the case of data for which extracts had not been developed, Excel spreadsheets that Buchanan created himself. DecisionSite was flexible enough that Buchanan could easily modify the application for different phases of clinical trials. In Phase I, for example, there is far more laboratory data than adverse event data. "In Phase I we look for relationships between levels of drug exposure and adverse events or changes in laboratory values," says Buchanan. "For example, you may find that the people who have the highest drug concentration also have highest level of markers of liver damage. Although there are usually relatively few adverse events, you can start to examine the relationship between PK measures of exposure and various adverse events."

With DecisionSite, multiple factors can be evaluated dynamically using color-coded scatterplots and adjusting query-device sliders on-the-fly. "DecisionSite is useful for exploring pharmacodynamic relationships," he says. "It lets you specifically interrogate the data."

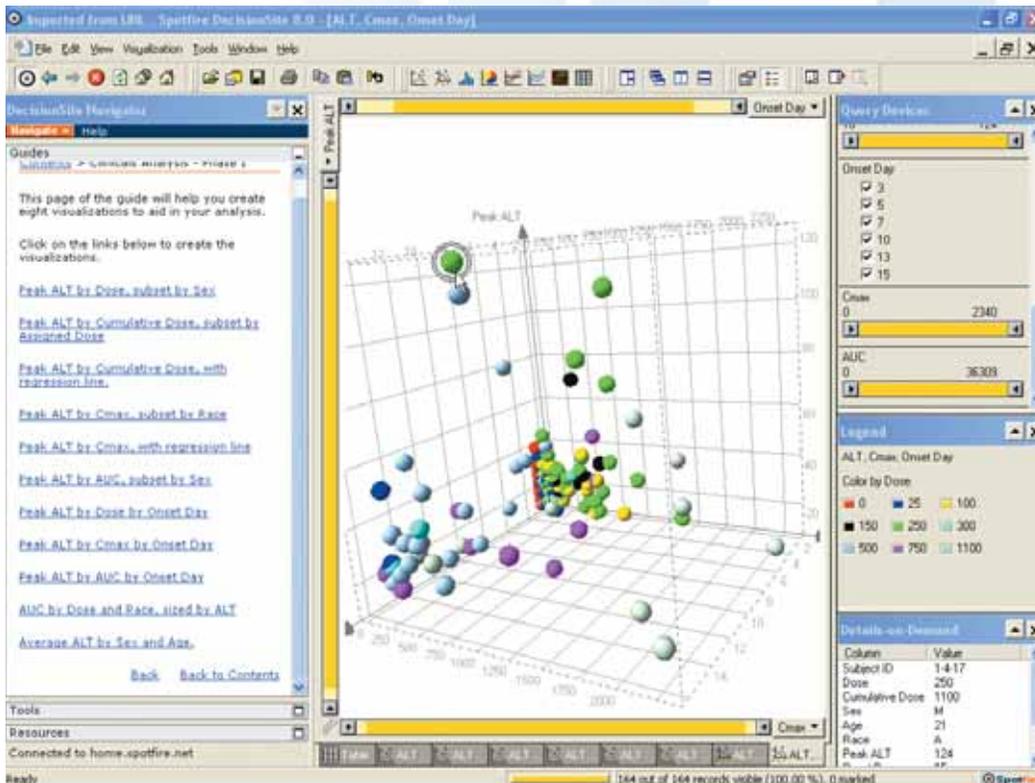
For Phase II trials, a slightly different set of visualizations and data sets are made available. Phase II trials include more subjects, more adverse events and more laboratory data, but PK measures don't play as large a role, as they are generally available for only a subset of subjects. There are also data from multiple groups, either placebo or active drug, permitting comparisons of adverse events between two treatment groups. Here Buchanan uses DecisionSite to evaluate patterns of adverse event frequency subdivided by parameters such as severity, gender, age, and duration on therapy.

Buchanan developed a different guide to handle Phase III trials. "With Phase III, there's not so much pharmacokinetic data," says Buchanan. "Phase III trials are characterized by very large patient groups, providing a wealth of adverse event and laboratory data. PK measurements, if done at all, are performed on only a small subset of patients. Instead, the general approach is to do comparisons between treatment groups." In this case, Buchanan uses the application to evaluate data for time-dependent patterns, for example, whether adverse events cluster shortly after dosing or accumulate only after a prolonged duration of exposure.

While most of these analyses are possible to perform with Excel, each comparison is a separate step. This is not only time consuming, but it makes it difficult to get the big picture of multiple interrelationships. "With Excel I can look at the drug concentration in blood and compare it to the level of liver markers, and run a correlation, but with DecisionSite, I can take it a step further. I can also include other markers, such as the time it took to develop, or I could color the data points by characteristics such as gender and race."

According to Buchanan, one of the greatest strengths of DecisionSite is the ability to visualize three or more variables at once. "One of our best visualizations we use is a 3-D graphic of a lab value by a drug exposure parameter (such as Cmax or AUC) by the time that lab value was recorded relative to day of first dose," he says. "This allows you to simultaneously see clustering or patterns of the lab value by exposure and by time. It's quite powerful."

Many such analyses, says Buchanan, were simply not done in Excel as a matter of practicality. "They would be too tedious to set up and perform," he says. "These analyses can be readily performed using Spotfire. There are definitely relationships that can be identified in Spotfire that a spreadsheet analysis can't show you."



At Tularik, analysts use Spotfire DecisionSite to explore PK data along with clinical chemistry test results and patient demographic data. Following the guided workflow on the left panel, analysts work through data access, analysis and visualization steps to address specific questions. In the window on the right side of the application, dynamic filtering devices are assigned for every field of data that is retrieved. This fluid combination of filters and workflow steps allows analysts to discover new patterns in the data and define future analysis requirements.

Results

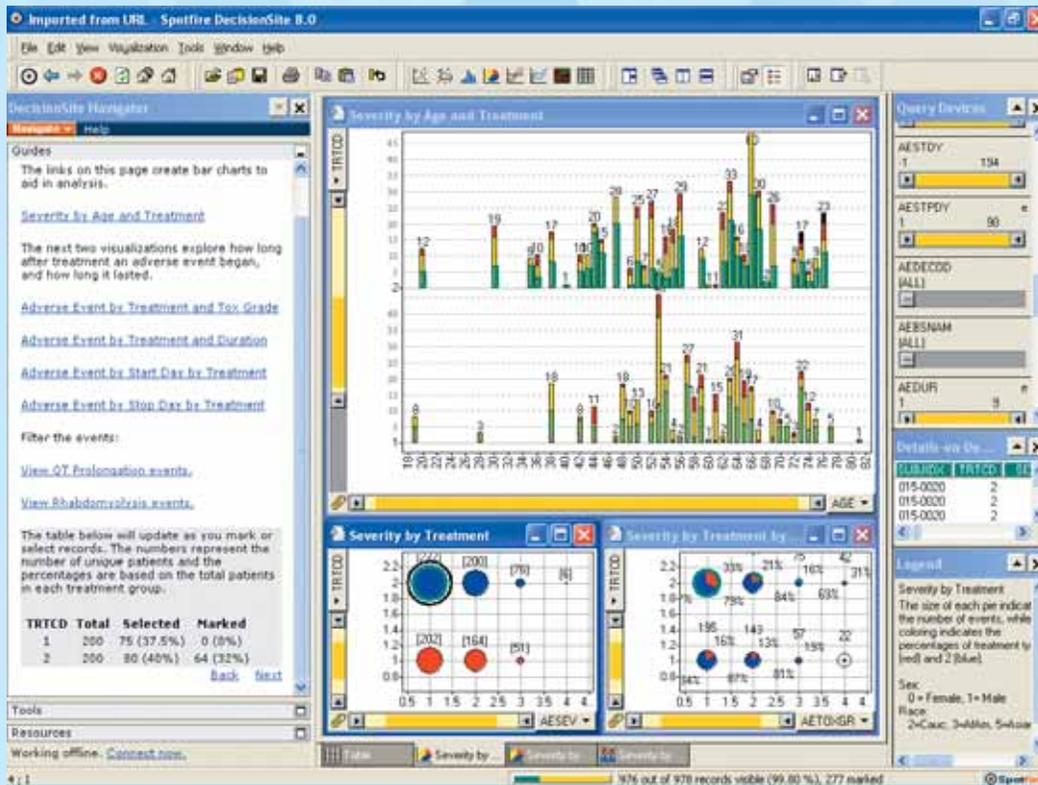
Having used DecisionSite for several months, Buchanan reports the software has been very helpful in developing adverse event profiles for drugs that support the safety information provided to regulatory authorities, study investigators and study subjects. “DecisionSite is valuable to signaling those adverse events,” says Buchanan. “It lets me analyze the data in more detail. It makes it more accurate.”

Because none of the Tularik drugs have reached market yet, it is difficult to judge return on investment. However, Buchanan has already seen the significant advantage DecisionSite has provided in terms of time savings. “The amount of time I would spend doing these analyses on a

spreadsheet is far greater than the time I would spend using Spotfire, and the results are more useful since there are analyses that I can’t do on a spreadsheet.”

Whereas DecisionSite’s use in drug discovery eventually shows up in boosting future profits, its implementation in clinical data analysis is judged more by how much it helps drug companies avoid financial loss. In the end, says Buchanan, ROI will be determined by how many mistakes you avoid, and how early you avoid them.

“If you have to kill your drug, you need to know that early on,” he says. Tularik has yet to kill a drug outright due to DecisionSite, but Buchanan feels more confident that he will be able to pass



In Phase III analysis, linked visualizations are presented that reflect membership in a particular demographic, such as age group. Using color assignments, this data is further broken down by severity and treatment group. A Guide lets analysts filter down on adverse events associated with a particular event such as QT Prolongation. Analysts can explore trends between adverse events and demographics in either stepwise or ad hoc fashion.

on the bad news – with authoritative proof – if the need arises. “Clinical trials cost millions of dollars, so you don’t want to have to terminate development of a drug only after conducting multiple trials and incurring that expense. It’s an enormous cost in terms of dollars and time.”

As for the future, Buchanan is planning to use DecisionSite’s dynamic data import capabilities to create a direct connection to the database rather than working with a data extract. “If you’ve got a trial that’s going on, it would be nice to have a live link,” he says. He’s also interested in exploring DecisionSite Posters, an interactive and visual report that supports

archived discussions, to disseminate the analytic results to members of the clinical teams. In the meantime, he’s happy that he now has the time to do his job to the very best of his abilities.

“It really comes down to a function of my time,” he says. “With Excel it took at least 10 times as long to set up and utilize the data as it does with DecisionSite.”

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About Spotfire, Inc.

Spotfire, Inc. provides interactive, visual data analytics applications and services that empower enterprises and their end-users to make fast, accurate business decisions. Over 25,000 users in more than 800 organizations around the world use Spotfire DecisionSite software to analyze their business information in an intuitive, visual environment that speeds analysis and drives confident decision making. The company maintains U.S. headquarters in Somerville, Mass., and European headquarters in Göteborg, Sweden. Additional information can be found at www.spotfire.com.