

IMPLEMENTING A MODERN ARCHITECTURE FOR ADME DATA MANAGEMENT

BEFORE 2000, STUDIES SHOWED THAT 40% OF DRUG CANDIDATES FAILED DUE TO POOR ADME (ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION) PROPERTIES. DRUG DEVELOPERS HAVE AIMED TO DECREASE THIS FAILURE RATE BY MAKING BETTER USE OF INFORMATION ON HOW COMPOUNDS MOVE IN THE BLOODSTREAM, WHERE THEY APPEAR IN THE BODY, AND HOW THEY ARE METABOLIZED AND EXCRETED. THESE EFFORTS ARE HAVING AN IMPACT, WITH RECENT SURVEYS REPORTING ADME FAILURE RATES BEING REDUCED TO JUST 10%.

The tests used to understand ADME characteristics in *in vitro* experiments are extensive, from P450 inhibition studies to permeability and transport experiments to metabolic stability testing. They are also becoming more numerous. At Boehringer Ingelheim Pharma, a leading pharmaceutical company based in Ingelheim, Germany, the number of ADME experiments performed increased four- to five-fold between 2003 and 2008. During this scaling of experimental throughput, Boehringer Ingelheim relied on Microsoft Excel spreadsheets—a favorite tool of biologists—to capture, manage, and share ADME results.

“There’s a really good word for the strategy of using spreadsheets as a data repository: spreadmart,” said Thomas Arnhold, lab head in the Department of Drug Discovery Support (DDS) at Boehringer Ingelheim. Unlike datamarts, which serve up data to scientists on demand, spreadmarts serve up spreadsheets, which isolate experimental data in worksheets and are difficult to access and use in the context of a typical research workflow.

“In our opinion, ADME spreadmarts weren’t storing our detailed data in a reusable way—they were burying it in a data grave,” Arnhold said.

The drug metabolism and pharmacokinetics (DMPK) group within DDS at Boehringer Ingelheim recently decided to abandon spreadmarts in favor of a modern software architecture comprising two custom databases and Symyx Assay Explorer. Together, the three systems eliminate time-consuming cutting and pasting and the endless maintenance of VBA (Visual Basic for Applications) macros that had come to dominate every aspect of planning, running, and analyzing assays. Not only does the DDS group capture information in an accessible and reusable format, scientists can now pass experimental ADME data efficiently from one task to the next, decreasing cycle times and giving scientists more time to spend on assay design, technology development, and data validation.

“Since 2004, we’re handling 20–25% more assay requests per year in my lab with the same number of bench scientists, while also implementing new technologies and assays each



year,” Arnhold said. “We can analyze one assay in as little as half an hour, and I would estimate we save up to 45 minutes of analysis time per assay run. Plus, the whole process is less error-prone.”

CUTTING OUT THE COPYING AND PASTING

The *in vitro* DDS DMPK group at Boehringer Ingelheim serves dozens of research programs covered by different DDS project representatives, which presents several informatics challenges. The dataflow is complex, requiring the group to coordinate and communicate among requesting scientists and members of the DDS service units while also organizing compound logistics and making appropriate data transfers to the corporate database (see Fig 1). Moreover, the group generates a substantial amount of data. A single run of a P450 inhibition assay (which the DDS group calls one LabProject) comprises 10 compounds plus a positive control at four concentrations in duplicate with five enzymatic reactions, each run on a separate plate.

The complexity was exacerbated by the group’s decision to use Excel for



managing all assay data. “Excel is a great tool for managing certain types of data as long as the assays you are managing are not routinely applied,” Arnhold explained. “But the fact is our scientists had to create a separate spreadsheet each time they ran a new assay. This meant that it was virtually impossible to compare detailed assay information—such as negative or positive control values—across different runs, unless scientists wanted to open sheet after sheet, find the data they needed, and copy and paste it into another worksheet to view it side-by-side.”

Analysis was similarly complicated. Relevant calculations for each assay type were also stored in spreadsheets. “We used templates, often with 10–20 different worksheets and, of course, plenty of cell relations referring between them,” Arnhold described. Consequently, whenever scientists made changes to an assay, the change had to be propagated through the corresponding assay templates.

Additionally, the DDS group was maintaining two separate data archives. The group had created a custom expert database called DDSBase to handle and communicate the various

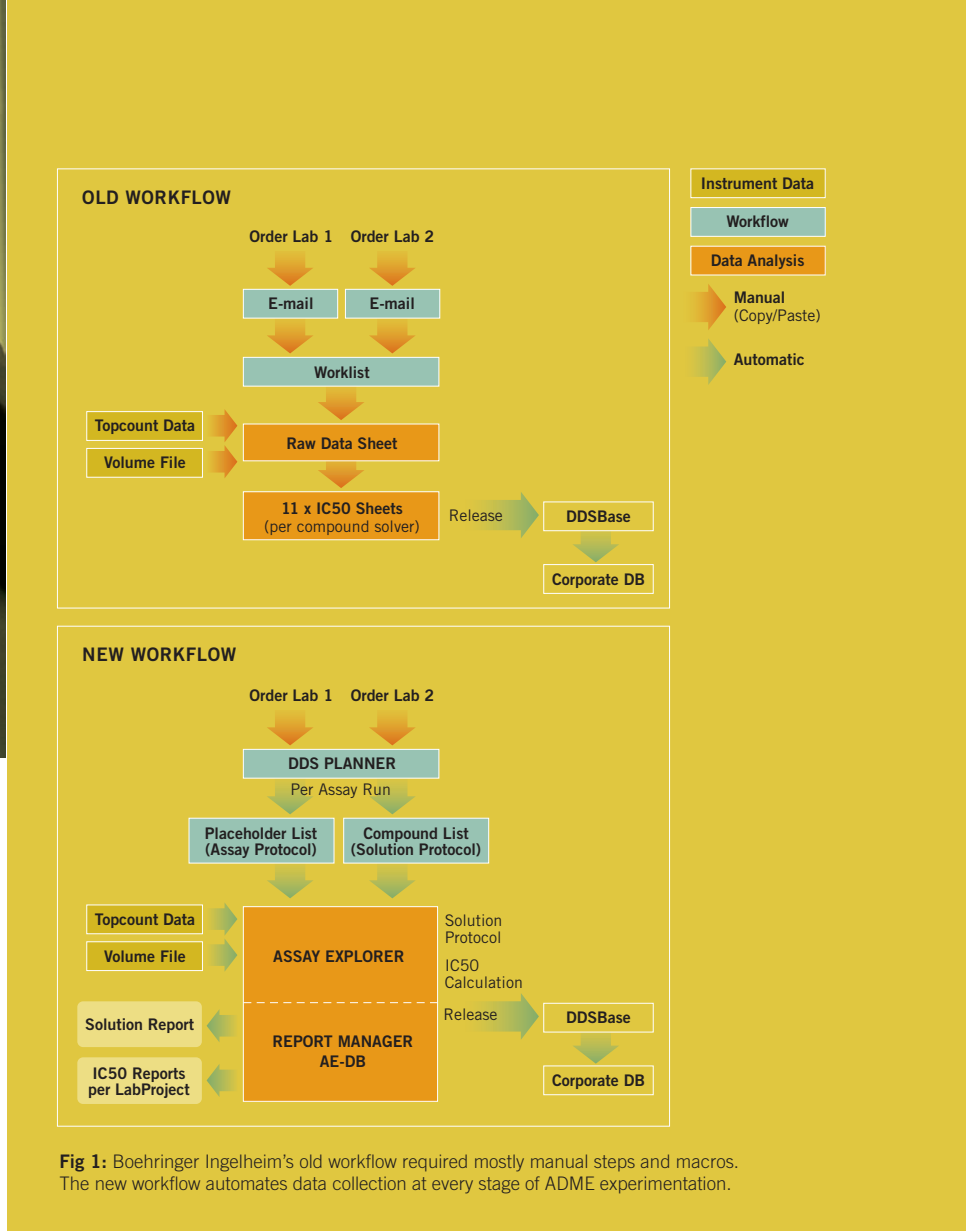


Fig 1: Boehringer Ingelheim’s old workflow required mostly manual steps and macros. The new workflow automates data collection at every stage of ADME experimentation.

key parameters associated with the research DMPK decision process of a compound, such as IC50s for P450 inhibition, metabolic stability half-lives or Caco-2 permeability coefficients. While VBA macros were used to transfer results from the spreadsheets to the database, maintenance of these macros created additional work for research informatics support.

Even with the macros in place, scientists still had to handle many data transfer tasks manually. Researchers received work requests by email and manually completed worklists in Excel. Once an assay had finished running, researchers

manually created a raw data sheet by cutting and pasting information from three sources: a volume file and topcount data file, both of which were produced after the assay was run, and a part of the worklist. A macro then used this data to create separate IC50 summary sheets for each compound run. A second macro obtained the IC50s from each sheet and imported them into DDSBase.

According to Arnhold, running just one standard inhibition assay required lab staff to perform a minimum of four cut and paste actions and 25 clicks to launch macros—not counting actions like

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saving and closing files. And that was *before* releasing any information to the corporate database.

“We had two primary goals in streamlining our workflow,” Arnhold summarized. “First, improve communication between our service units and the requesting scientists. Second, and equally important, get rid of the spreadsheet-based templates that were complicating our process and isolating our experimental results.”

NEW WORKFLOW PUTS FOCUS ON SCIENCE

The new workflow implemented by the DDS DMPK group introduces Symyx Assay Explorer and a custom system that together eliminate the old workflow’s manual steps. The DDS Planner, a communications platform between the DDS service labs and requesting scientists, was developed by local research informatics support team members along with external partners. DDS scientists use the DDS Planner to track experimental requests, plan experiments, source materials, and schedule and configure experimental apparatus. Once an experiment has been planned, the system generates a single file that sets up a new LabProject and provides Symyx Assay Explorer with the information required to run the assay and collect experimental results. The DDS DMPK group chose Symyx Assay Explorer after evaluating available commercial

options. Instrument manufacturers sometimes offer their own solutions, but most of these lack flexibility, as they are geared toward certain experiments, such as EC50 or IC50 experiments. This limited how easily the tools could be applied to the diverse experimental needs of the DDS DMPK group. Other primary commercial tools can handle multiple assays, but still use spreadsheets for certain data handling tasks. “Symyx Assay Explorer was the system that gave us the flexibility to handle all the assays as desired while allowing us to migrate entirely away from spreadmarts,” Arnhold explained.

Assay Explorer handles all assay management and data analysis tasks, streamlining communication within the DDS group. As assays are run, the topcount data and volume files are automatically collected by Assay Explorer and associated with the appropriate experiments. The system also automatically generates reports for each LabProject, enabling scientists to quickly review assay performance across the project. Crucially, Arnhold notes that an alert now prompts him to review analyzed data for release to DDSBase and subsequently to the corporate database. “The streamlined workflow leaves me free to focus on some of the other work done in my lab or within the entire organization,” Arnhold explained.

While scientists were initially skeptical of the new system, they

have since become convinced of its utility. Since implementing the new system in 2007, scientists have set up a range of P450 inhibition assays within Assay Explorer. Other assay types, such as microsomal stability, Caco permeability, transporter, and plasma protein binding studies are planned for 2009. “We have been very pleased with the flexibility of Symyx Assay Explorer and its ability to handle the types of ADME experiments that we want to conduct,” Arnhold said.

Because industry-standard components with a programmable interface are serving as the basis for this system, extensions and integration are relatively easy to implement. Currently, the DDS DMPK group is implementing TIBCO Spotfire for data review and “graphical” communication, and they are also considering whether to combine the three databases into one.

“Our aim was to provide our scientists with a spreadsheet-free environment that would enable us to extend our ADME work to make this data even more readily available across our organization,” Arnhold concluded. “Using Symyx Assay Explorer with our existing custom systems has given us a predefined framework that improves throughput and allows us to leverage our ADME data to enhance our research pipeline support.” 