Electronic Study Management

New Tools for Improving the Efficiency of Pre-Clinical R&D

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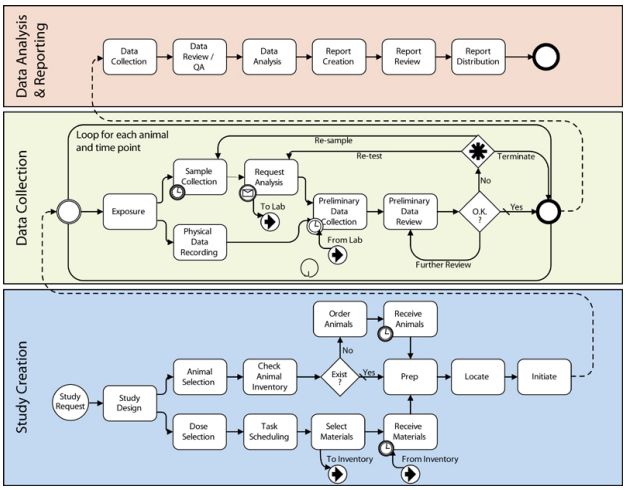
Back in the late 1970s, I was working in a biology research institution evaluating the metabolism of antipsychotic drugs by performing *in vivo* animal studies. To manage these studies, our team took pen to paper and tracked subjects, controls, observations and analytical results in a bound laboratory notebook. We soon discovered and purchased the new IBM personal computer. No longer did we have to vie for time on the mainframe; we could now write our own programs to trend and analyze data. However, due to a shortage of time to write code and the lack of commercially available software, we retained our notebooks to design studies and capture raw data. We began to use the PC for the creation of final reports, attempting to decipher each other's handwriting along the way.

Now move the clock forward almost 30 years. Computers have become significantly more powerful, software more sophisticated, and analytical instruments pour out more data than ever before. But one thing hasn't changed — the majority of *in vivo* animal studies are still created, managed and organized via bound notebooks or loose-leaf paper. Spreadsheet software, like Microsoft's Excel, is commonly used in conjunction with paper, but often the output is printed and glued in a notebook. This is despite the fact that for several years, the majority of biopharmaceutical pre-clinical laboratories have been using laboratory information management systems (LIMS) to track samples and collect data from rooms full of LC/MS instruments. These analytical results are often printed from the LIMS and pasted into a notebook, along with the design of the study and physical observations. Other raw data, amassed in spreadsheets of varying formats, are scattered through the organization locked away in researchers' computers.

We estimate that over 80 percent of *in vivo* animal studies are managed using a combination of paper and Excel. This is somewhat surprising, given the current state of R&D in the biopharmaceutical industry. Despite ever-increasing expenditures on R&D — over 40 billion U.S. dollars in 2004[1] — the number of new chemical entities approved by the U.S. FDA has remained fairly constant since the early eighties when R&D investment totaled less than 5 billion dollars per year.

Also, the time for discovery and development of a new molecular entity (NME) has gone from approximately 4 years in the early 1960s to over 14 years today. This has reduced the marketable patent life of new drugs to its lowest point in history with off-patent medications now comprising over 50 percent of U.S. pharmaceutical sales. R&D must be more efficient to release a higher number of quality compounds sooner.



Example Pre-clinical Study Workflow. Note the multiple data collection, review and decision steps.

Need for pre-clinical testing

Pre-clinical pharmacology and toxicology animal studies are needed to determine a potential new drug candidate's efficacy and safety before testing can begin in humans. New technology, such as *in silico* prediction and pathway simulation, are in their early stages of development and have yet to have a significant impact on the need for late stage discovery and pre-clinical *in vivo* investigations. Using primarily mice and rats — 99 percent of mouse genes have analogues in humans — these studies complement *in vitro* assays, which look at a compound's specific biological activity in a homogeneous environment. The large number of leads from *in vitro* high throughput screening assays is reduced to a set of potential drug candidates through a series of *in vivo* studies to examine their whole-body pharmacological properties. These studies explore questions such as:

- Is the compound effective? What is the effective dose?
- What are the pharmacodynamics of the compound? Does the formulation reach target levels to exert a desired biological activity on the therapeutic target?
- What are the pharmacokinetic characteristics of the compound? How does it get absorbed, distributed, metabolized and excreted (ADME) though the body?
- Are there toxicological effects? What is the level of chemically induced toxicity?
- Are there side effects? Are there any carcinogenic or reproductive effects?

Each compound must undergo multiple studies with only 5 out of 250 compounds that enter the pre-clinical development stage making it to human clinical trials. These studies can last from weeks to years and can be very complex in their design, involving a

matrix of variables that must be explored and analyzed. They also can be very costly. According to Tufts University,[2] in 2000 an animal study cost from 20,000 U.S. dollars for an acute rat toxicity study to 2 million U.S. dollars for a two-year rat bioassay. In 2002, it was estimated that 12.5 billion U.S. dollars were spent on pre-clinical R&D alone.[3] To reduce the costs associated with GLP compliance and to determine failures earlier in the process, there has been an increase in the number of *in vivo* studies performed in late-stage discovery.

Paper vs. electronic study management

Due to a study's complexity and matrix of variables, paper and Excel have been used for their inherent flexibility. Until recently, software specifically designed for the management of the study lifecycle did not exist. Commercial LIMS systems, which perform admirably to track samples and collect test results from the analysis of blood, urine and tissue samples within the pre-clinical laboratory, have not had the flexibility required for study design, collection of non-laboratory data (i.e. animal body mass, growth and behavior), data annotations, reporting, or the management of animal inventory. Additionally, with over 10 percent — and growing — of pre-clinical work outsourced to contract research organizations, biopharmaceutical companies have been faced with consolidating data from different sources and formats, making paper a necessity.

Nevertheless, the flexibility afforded by manual methods has led to an overall decrease in organizational effectiveness. This has lengthened the time it takes to complete a study. We estimate that between 5 percent and 15 percent (dependent on the study type) of time is spent in unproductive activities. Inefficiencies are caused by:

- Data not being accessible in real time, delaying important decisions until final data is reported. A study could have been modified during its course if data was readily available. For example, an animal became sick, exhibited unusual behavior, or had unexpected metabolites requiring a change in design or the addition of new animals.
- Transcribing data from one source to another. Information transfer is not timely, is error-prone, and requires additional QA steps. Data collection worksheets must be transcribed to spreadsheets, spreadsheets to notebooks, notebooks to visualization and statistical packages, and notebooks to final reports.
- Merging data from multiple data sources. This requires significant review and QA. Different styles of documentation and handwriting require interpretation and re-transcription. Excel spreadsheets in dissimilar formats must be painstakingly merged.

- Study design time being longer without the tools to algorithmically determine controls, time points, necessary treatment groups, needed phenotypes, dosage, and so forth.
- Tracking information locked in a researcher's computer or a technician's worksheet — creating "islands of information."
- Manually tracking the progress of a study and determining areas that require additional resources or capabilities.
- Manual work scheduling and investigation of resource workloads.
- Multiple technicians and researchers working with the same animal, causing overlaps in work practices.
- Manual creation of final reports. Without a central database for annotation and commentary on data, study directors must have more conversations, e-mail exchanges, and meetings than are necessary.
- Collecting data from multiple CROs or disparate geographic research centers. Data gathering is slow and not in real time.

We also see the introduction of data quality and compliance issues with traditional approaches:

- Without the application of a consistent ontology among researchers, data is left open to interpretation making it difficult to correlate data from diverse sources.
- Compliance is appreciably more time consuming with numerous spreadsheets and documents that must be controlled.
- The lack of a consistent audit trail for data traceability leaves an organization vulnerable to regulatory investigation.
- An absence of security exposes an organization to data theft, alteration and loss.
- Data can be inconsistently formatted without the enforcement of standard conventions.
- Equations in individual spreadsheets are not standardized between researchers, leading to induced calculation errors.
- Data points can be lost or not entered on paper forms without an automated enforcement of data collection and consolidation practices.

Enter new tools for study management

To change traditional study management procedures, and to provide a compliant environment for sharing information, new software products have been introduced during the last two years. These systems, designed specifically for managing the lifecycle of a study, are known as electronic study management or ESM (ESM also includes those systems specifically designed for human trials). ESM products have modules for study design, data collection, information management, task assignment, scheduling and reporting. Some products go a step further, offering animal inventory,

breeding, husbandry and drug management. One of the new breed of "crossover" informatics products, ESM includes capabilities customarily found in electronic laboratory notebook (ELN), LIMS and scientific data management systems. They possess technology to manage structured data like a LIMS and annotate and comment like an ELN. Their data-capture capabilities are for both at the animal cage and from within the laboratory, although most products claim they will interface to an existing LIMS for the integration of laboratory results.

Two of the companies that have made investments in ESM technology are ID Business Solutions (IDBS, Guilford, U.K.) and iAdvantage Software (Cary, NC). iAdvantage's eStudy system was born from the company's parent, AAS, a contract research organization that developed the software for their internal use and for use by customers. Recognizing the need for this technology industry-wide, AAS spun out iAdvantage in 2003 to promote and enhance the eStudy product. IDBS has decided to enter this space by announcing they will be shipping their enhanced BioBook ESM in early 2006.

The iAdvantage and IDBS products are ELN-centric in their design. IDBS is building their BioBook ESM around the recently acquired Deffinity ELN (now called IDBS E-Workbook) and is integrating the product with new technology and with software that already existed in the IDBS portfolio. iAdvantage's eStudy is a Web-based, thin-client product with an XML form designer for the entry of study data using a notebook paradigm.

Moving from paper to an electronic environment

Embrex (Research Triangle Park, NC), a biotechnology company and manufacturer of poultry vaccines and delivery systems, has been struggling with the flood of paper required for regulatory submissions. "It has been highly inefficient to manage our studies this way," says Lynn Murray, director of trial data management and QA for Embrex. "Eighty to ninety percent of our study data has been recorded on notebooks and paper forms. We are unable to perform meta-analysis across multiple studies without considerable work re-transcribing data into other systems. We want to have real-time access to information and to immediately determine the bottom-line of a study as it progresses. We also spend significant time in quality assurance deciphering hand-written notes."

Embrex worked with iAdvantage to modify their software for use with Embrex's complex workflows and variables. Since the company has to evaluate the effect of vaccines in multiple stages from *in ovo* through animal maturation, this created a complex data

model. Embrex has been beta testing the modified eStudy software for several months. "We have learned that it is imperative to understand your workflow, prepare detailed requirements, and manage scope and resources. Getting the variables correct upfront before you install software is critical," notes Murray. "It is equally important to partner with a quality vendor who understands their product, is responsive to your needs, and is willing to work with you to progress the technology."

A large Midwest U.S. agricultural biotechnology company (who by company policy declined to be identified) has been using the iAdvantage software for almost two years to manage their remote studies. Because data is entered once in the remote locations, several QA steps have been eliminated that were previously necessary to review the transcription of data between systems and reports. "We reduced the time for regulatory submission by an average of three to six months by using the system," says the company's manager of regulatory studies. "Due to all the transcription steps and the requirements of multiple QA reviews, we would have to wait until the completion of trials to develop the necessary reports. We can now review the progress of a study in real-time and make adjustments when needed. In the old days, a transcriber had to work with a researcher for several years just to understand their handwriting!"

The challenge of culture

For any system of this type, cultural resistance is the biggest barrier to technology adoption. Paper has been around a long, long time and the majority of personality types are reluctant to change. Users must see what the technology can do for them and how it can simplify their work. There must be a complete organizational change with full management support to successfully implement a system — which is not easy. According to Murray "You have to make the system be a part of the user's job description. There is a transition period where users can become frustrated until the system contains sufficient information to demonstrate real benefits. After that period, adoption is much easier."

Vendors are providing tools to help users with the transition to an electronic environment. For example, iAdvantage has built wizards to make it easier to design a study. These wizards guide a user, who may only use the software on an infrequent basis, through all the steps necessary to create and initiate a study. Because study directors are familiar with Microsoft's Word and Excel, the company has also designed their eStudy Publisher to automatically create final reports by pushing data from the common repository into those applications on-demand.

With over 80 percent of *in vivo* studies being managed by paper, companies will be challenged with the transition to electronic

study management for several years to come. To be competitive, organizations will have to modify existing work practices and look at ways to increase efficiency, reduce costs of quality and compliance, and build a collaborative work environment. This requires a total organizational commitment, but for those companies investing in ESM technology, they are already reaping the benefits. In the future, as personalized medicine and pharmacogenomics becomes the norm, it will be critical to monitor data in real time and to provide seamless data integration between animal and human trials. Eliminating paper bottlenecks is one way to move this vision forward.

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