BY GREGORY SAMOIL

OVERCOMING THE ADME/Tox PROFILING BOTTLENECK

BRUNO BUDROVIC /GETTY IMAGES

If you're still relying on spreadsheets to manage ADME results, you're wasting valuable time and resources on data manipulation instead of focusing on the science that can help bring a new drug to market faster.

Failing a drug once it reaches clinical trials is a costly exercise that companies are striving to avoid by looking to technology to innovate their processes. On the other hand, failing a compound *early* in the drug development process will result in a reduction of the overall cost and risk of developing those drugs with a higher probability of reaching clinical trials (see chart on page 40).

As translational medicine ("Bench to Bedside") becomes one of the fastest-growing areas in drug discovery, the focus on the discovery and development of biomarkers is at the center of the adoption of translational studies.

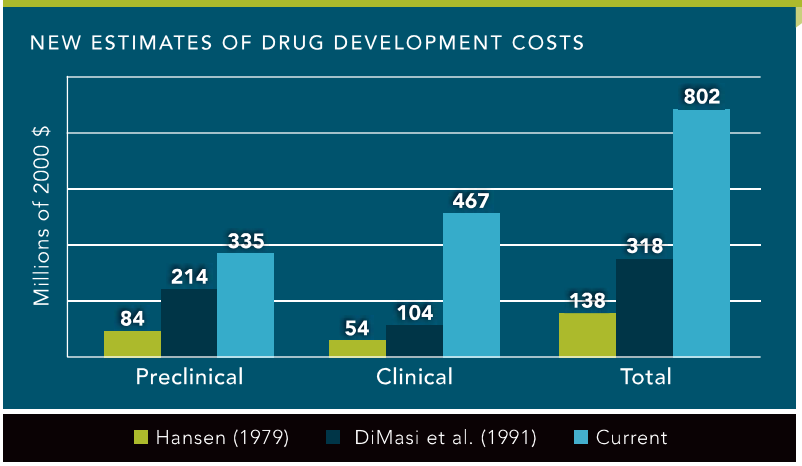
Together with newly identified biomarkers, data from ADME/Tox (Absorption, Distribution, Metabolism, and Excretion)/(Toxicity) profiling has permitted researchers to detect possible liabilities earlier in the development cycle.

Data points derived from ADME/Tox profiling experiments can be used as key indicators of a compound's performance later in clinical phase animal studies, and are at the foundation of building reliable, predictive in silico ADME models.

Companies are continually looking to optimize the processes for using a compound's in vitro ADME properties as indices of potential failure in the drug development pipeline, and to develop new predictors through experimental assay development.

As a result of this optimization, the industry has seen an increase in the number of different ADME/Tox experiments being developed as scientists are discovering new ways of interpreting current indicators, while the discovery of new indicators to identify lead candidates is ongoing. One pharmaceutical company reported that the number of ADME experiments performed increased four- to five-fold between 2003 and 2008. Each new assay has the potential to generate enormous amounts of drug metabolism data, which is then used to promote a drug compound to the next step in the drug development process or to prevent it from being developed further. Adding to the complexity of this strategy is the increasing number of chemical compounds in line for ADME/Tox screening as libraries of compounds are introduced into the screening process. While the synthesis of molecules through combinatorial chemistry has increased the number of potential lead compounds being discovered, it has also revealed potential backlogs in processing ADME/Tox profiling data. These key factors have created bottlenecks in the processing of ADME data, and have driven the industry to take a hard-line look at how it can more effectively manage data and turn it into knowledge that the organization can use for efficient drug candidate selection.

THE PRICE OF INNOVATION

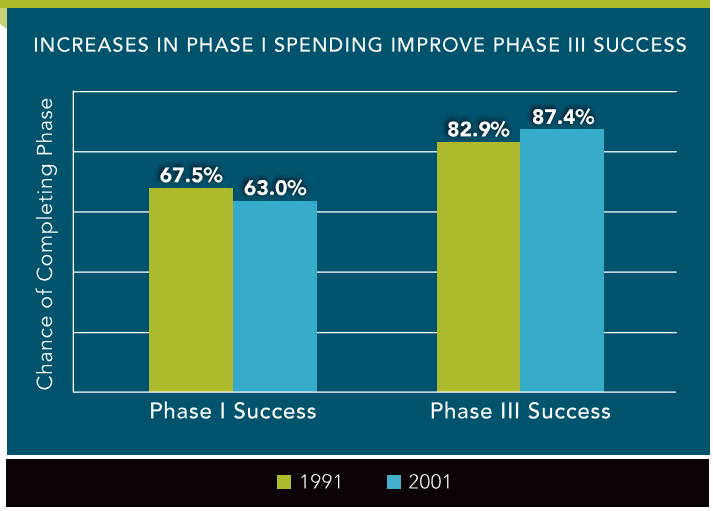


SOURCE : *JOURNAL OF HEALTH ECONOMICS*

Data Deluge

In today's economic climate, as resources are very carefully scrutinized and scientists are being asked to do more with their existing resources, pharmaceutical companies are looking for ways to ease the data deluge facing their drug development groups by addressing key areas of throughput, storage, and analysis. The techniques of data management using file-based processes, or spreadsheets or distributed data systems, are no longer considered appropriate solutions to handle the amount of data being generated. While spreadsheets have had their distinct advantages over the previous use of calculators and paper notebooks, scientists have increasingly experienced limitations in using spreadsheets as the amount of generated data has increased. These outdated and inefficient processes require manual and time-consuming manipulation of the data, often executed by scientists whose expertise is better spent on the science of drug discovery. Primarily through the use of high throughput screening, ADME/Tox profiling requires that single measurements be generated in parallel, which are then condensed, analyzed, and translated into knowledge about a compound's ADME properties. The spreadsheet- and paper notebook-based systems cannot efficiently pass data from one task to the next, and instead result in increased cycle times, which translates into scientists having less time to spend on assay design, technology development, and decision making. To efficiently pass data between tasks requires that the data be readily available, organized, and accessible. Performing these actions with spreadsheets is costly and time-consuming, and provides no audit trail or traceability. The use of spreadsheets may also require data transcription, increasing the chance of human error

WEEDING OUT FAILURES EARLIER



SOURCE : *JOURNAL OF HEALTH ECONOMICS*

and jeopardizing the integrity of the data. Using spreadsheets also contributes to the lack of standardization of experimental methods and procedures required to reproduce the data at a later date. Spreadsheets used for this type of data analysis do not provide a central and secure area where this data can reside and be readily accessible.

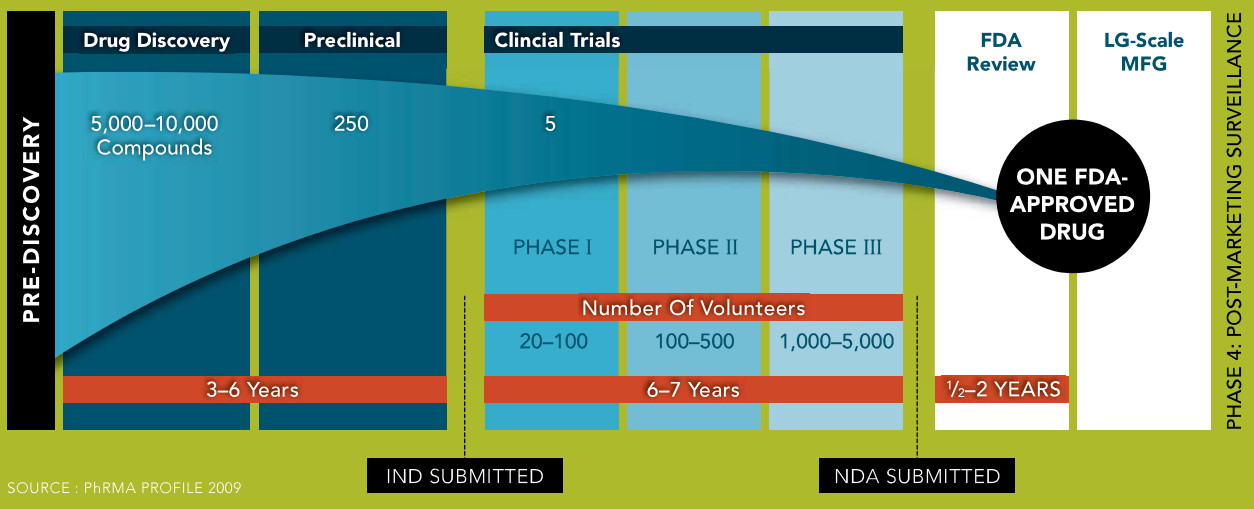
As advances in technology are generating more compounds and subsequently more ADME profiling data, it has also exposed the parallel opportunity to advance technology in the management of that data through advanced informatics systems. Today's data management systems can help scientists manage ADME/Tox profiling data faster and more efficiently, and by reducing the need to handle the data multiple times and eliminating the risk of transcription error, scientists have greater confidence in their findings. These advanced software solutions are equipped with security and auditing that adds another layer of quality assurance to the data that was not available with spreadsheet-based systems. The added security and audit capabilities have significant implications for time and cost savings as scientists spend less time reviewing the data and more time on the science of drug discovery.

Paper Passé

Electronic file-based systems have been the de facto standard in many companies and have offered moderate solutions to addressing the management of ADME/Tox profile data by automating single step data analysis. However, they do not address multiple step processes in an efficient manner and leave the data vulnerable to user modification and manipulation. File-based systems, lack of security leaves the data open to unwanted access and modification, which jeopardizes the integrity of the data. With secure software systems in place to prevent unwanted modification, pharmaceutical companies have more confidence in their data, which leads to quicker decision making and the ultimate goal of decreasing the time and cost of bringing a new product to market. The implementation of data management systems has resulted in the storage and organization of data in central and secure repositories. New generations of software solutions utilize

THE R&D PROCESS: LONG, COMPLEX, AND COSTLY

INCLUDES MANY STEPS, NUMEROUS DISCIPLINES, AND AN ARMY OF PEOPLE



SOURCE : PhRMA PROFILE 2009

databases that control access, enable an auditing layer, and prevent unwanted changes to the data. By guaranteeing this security layer, scientists are able to spend less time and resources reviewing the data. This controlled access also can be viewed as a key benefit in maintaining the integrity of the data and ensuring accuracy. With the growing importance of translational studies has come the realization that data originating from multiple disparate analysis systems needs to be localized in order for it to provide value to downstream analysis, and that disparate systems, spreadsheets, or other paper-based systems are no longer sufficient to manage the level of data generated.

Pharmaceutical companies, recognizing the need to address this bottleneck, are looking to better manage their ADME/Tox data by implementing software systems with workflow capabilities that guide analysts through established procedures and impart a high level of confidence that their data is a result of scientists following current operating practices. By implementing a data management system that facilitates use through experimental templates and simplistic user interfaces that promote rapid data review, one global pharmaceutical customer of Thermo Fisher Scientific was able to increase the number of compounds being screened to over two thousand compounds a week for their Tier 1 ADME screening. Their experience indicates that point solutions, such as stand-alone spreadsheets and graphing tools, are inefficient, prone to errors, and can lead to inconsistent results—the lack of a central repository results in data scattered in disparate locations without traceability and lacking value beyond its immediate use. Being able to maintain consistency with established operating procedures across an organization helps reduce the complexity of operations, thereby ensuring compliance, improving quality, and reducing drug development costs. As operating procedures are changed, the risk exists that users will continue to use outdated processes in lieu of the new process because of resistance to change. While there may be clear advantages to the new process, users might still continue to opt to use their familiar systems. However, systems that enable consistency in operational processes lead to greater predictability in levels of data integrity, imparting confidence that all users are generating data in a consistent manner.

Data management systems enable companies to increase throughput and decrease overall costs by automating the ADME process from initial data acquisition through analysis and review to the ultimate acceptance of the data. Data management systems are equipped with features that automatically import instrument data and decision-making tools, based on predefined acceptance criteria, which simplifies the review process. Data management systems also accelerate the decision-making process by utilizing visualization tools that present data in a simple and meaningful manner. The soft-

ware system presents each dataset in a thumbnail graph, which contains an indicator flag that quickly relays to the user if the data is questionable and requires further review.

By reducing data review times, scientists can spend more time interpreting results and focusing on the science of drug discovery.

Informatics

The increased volume of ADME/Tox studies and the data they produce, which is generated as the result of an increased focus on combinatorial chemistry and failing compounds early in the process before they reach clinical trials, has created a real need for informatics. Today, pharmaceutical companies that rely on spreadsheets to manage their ADME results waste valuable time and resources on data manipulation instead of focusing on the science that can help bring a new drug to market faster. Software systems are needed to replace the existing antiquated file-based systems, and drug development organizations need to rethink their current way of operating. These new systems address this need by providing a centralized database where results are processed and maintained, making the information available to ADME scientists and also downstream to colleagues performing in vitro studies. These systems offer improved efficiency by automating workflows, managing processes through harmonization of methods, and ensuring data security and traceability through auditing—thereby enabling scientists to focus on the science of drug discovery.

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