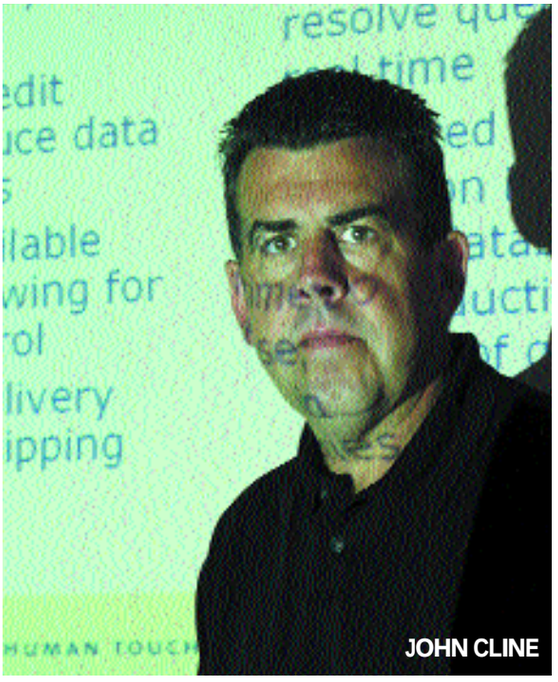
BY TARENGROM

PUSHING Past the Paper

ELECTRONIC DATA CAPTURE IS JUST THE TIP OF THE TECHNOLOGY ICEBERG when it comes to collecting, managing, and analyzing the enormous amounts of information needed to support the development of just one new drug.

While adoption of a paperless approach by pharmaceutical companies has been gradual, Forrester Research, based on a recent survey of 400 pharmaceutical professionals, is projecting that 24% of all new clinical trials will be Web-enabled by 2004.

Integrated electronic application, many say, is the next step in the evolutionary process. The effective and efficient use of integrated enabling technology solutions can impact every stage of drug development from discovery to preclinical, through clinical to post-marketing, and ultimately to commercialization, including direct-to-consumer promotion. Companies that continually strive to maximize successful product development are, albeit slowly, starting to develop EDC-based performance metrics, and deploy strategies for building clinical data warehousing and archiving, while meeting regulatory requirements.



The future is having a **FULLY INTEGRATED ELECTRONIC ENVIRONMENT** for the development of drugs.

Dozens of companies that address the electronic capture of data have sprung up in recent years, and more are expected to emerge, as the pharmaceutical industry grapples with strategic imperatives to streamline the clinical-trial process. The electronic data capture market is expected to almost triple from a revenue base of about $55.7 million in 2000 and the first quarter of 2001 to more than $165 million by 2004.

Pharmaceutical companies will, according to estimates, have to produce four to six new drug applications per year to maintain a competitive position. Industry observers say integrated technology applications could be the way to achieve these milestones.

Paul Bleicher, M.D., Ph.D., founder and chairman of Phase Forward Inc., says the future is a complete integration of electronic data capture with the libraries and capabilities of a traditional data-management system as well as the real time, interactive, transactional online, review, cleaning, and locking of databases.

"That is where the real power of enterprise technology is, and it extends to using data for a number of different applications," Dr. Bleicher says.

"The pharmaceutical company of the future that's going to win is the company that can put together a technology platform that can go from the molecule to the money," says John Cline, president of etrials. "People concentrate,

in my view, way too much just on the electronic data capture piece. To me, that misses the excitement. The future is having a fully integrated electronic environment for the development of drugs."

A fully integrated electronic environment would involve processes that can be implemented at the end of the preclinical phase, the stage at which companies begin modeling. The next stage is Phase I studies. Integrated technology would allow companies to optimize the best trial design with the greatest probability of success. Technology could then be used to automatically develop electronic protocols, electronic patient recruitment technologies, electronic IRBs, and electronic investigator meetings, leading up to the electronic data capture of patient information. The next phase would involve sophisticated database technologies, clinical-trial management systems, and analytical and reporting tools. All come together for the electronic submission of a new drug application or biologic license application. After submission, integrated systems would assist companies with marketing strategies, including patient registries and conducting post-marketing studies.

"There is a continuum of solutions that, from my perspective, offer the opportunity to very substantially reduce costs, reduce time to approval, and consequently accelerate revenue from newly developed drugs," Mr. Cline says.

EDC enables physicians to record trial data on site using software instead of paper forms. The software can validate the data at the point of entry, communicate it to a central service, and raise queries arising from the entry.

"Technology is about improving the quality of the data, improving timeliness and responsiveness, improving the patient's safety because companies can see and view safety issues as they happen, sooner rather than later," Dr. Bleicher says. "Electronic capture and management of data from investigative sites is the dominant wave of the future, it's the direction every company is moving in, or hopes to move in the near future. The enterprise solution to electronic clinical data management is very different than what most people think of as EDC and what the large majority of companies that are offering EDC or clinical-data-management software are doing today."

According to an IBM Global Services report, EDC's appeal is wide-ranging. In addition to verifying patient information as it is input against predefined criteria, thus ensuring fewer invalid patients and improved data quality, the information in the database is either real time, or near real time, making data available to the sponsor's data managers, clinical research assistants, and management — thereby overcoming the traditional delay period.

"The most important issue is not how the data are collected, it's being able to use incoming data to be able to manage the study well," says Michael Rosenberg, M.D., MPH, president and CEO of Health Decisions Inc. "When EDC is viewed as simply collecting data, it really represents what I consider incremental technology, rather than technology that improves processes. It is incremental in the sense that it applies technology to what remains fundamentally a paper-and-pencil process."

Dr. Rosenberg adds that the "slow adoption" of EDC is related to the experience of not improving bottom-line results. Sponsors may focus on getting data in quickly with EDC, but because of other complicating factors, they can't actually make real-time use of the data. As a result, the study doesn't go any faster, and EDC is frequently viewed as a "failed" technology.

Currently only about 5% of clinical trials use EDC technology, which leaves 95% of clinical trials paper-based. This reliance on paper-based process for recording patient information during a trial, according the IBM Global Services report, results in a three- to four-month

A Brief on the Benefits

According to a March 2002 report from IBM Global Services, written by Colin Spink, life sciences industries' specialist, there are several benefits that can be attained as a result of data entry at site and data validation at input, and the availability of near real-time access to trial information.

EFFECTIVE MANAGEMENT OF CLINICAL TRIALS — Improvements in data validation at the input stage ensure that fewer invalid patients are initially signed up for the trial.

IMPROVED TIME TO MARKET — In addition to reducing the trial length through efficient patient recruitment, the availability of accurate information in real time also enables the pharmaceutical company to rapidly undertake statistical analysis of the trial results as soon as the last patient has completed the study.

IMPROVED UTILIZATION OF RESOURCES — This information immediacy enables a company to pull the plug on unsuccessful trials earlier in the process, ensuring costly resources can be effectively deployed elsewhere.

IMPROVED PERCEPTION — Investigators, as doctors, are also prescribers and as such their perception of a pharmaceutical company can be influenced during participation in a clinical trial.

IMPROVED DATA QUALITY — On-site checking through data validation at the point of entry and rapid query response makes this possible.

As the figures to the right show, the benefits achieved in real world EDC deployments are significant. These results were collected from 10 Phase III studies, which together involved 6,700 subjects and were conducted over 3 1/2 years. IBM provided consultation, deployment services, and support for half of these studies.

	EDC	PAPER
Percentage of enrolled subjects that are invalid	7.50%	15%
Cost of raising and resolving a query	$10.00	$60.00
Number of queries/subject	0.25 to 1	5 to 20
Percentage of data requiring correction	0.05% to 0.1%	1% to 2%
Percentage of queries caused by missing data	0%	48%
Percentage of queries caused by inconsistent data	5%	35%
Percentage of queries caused by out-of-range data	0.10%	8%
Percentage of queries requesting clarification	0%	6%
Percentage of queries due to invalid data	0.05%	0.10%

Note: Query percentages are based upon number of queries raised when using paper.

Source: IBM Global Services, March 2002, Pharmaceutical Clinical Development, Electronic Data Capture (EDC) as a means for e-clinical trial success; Colin Spink, life sciences industries' specialist

lead-time before information becomes available. Not only does this delay the overall trial process, but it also leaves pharmaceutical companies vulnerable to flaws in the trial process that can go unnoticed for several months.

"The drug-development process within the pharmaceutical industry is inefficient compared with product development in other industries," says James J. Conklin, M.D., president and CEO of Araccel Corp. "This presents one of the great challenges for pharma. More than 20 years ago, the financial community began electronically transferring a trillion dollars a day, and they didn't lose a penny. Yet our industry seems incapable of making a similar type of transition."

According to industry experts, a number of converging factors — managed care, regulatory changes, Medicare and Medicaid, generic competition — will require that the pharmaceutical industry adopt technology at a faster rate than it has done to date.

"The final factor is that there has been no effort to change processes because the industry essentially ran on a cost-plus basis, with the highest gross margins of any industry in the world," Dr. Conklin says. "When all of the proceeding factors are added to the need to more rapidly handle the new drug targets coming out of proteomics and genomics, the industry is going to have to automate. The industry has been very good at automating the drug-discovery process, creating what I call an industrialized biology application, but it comes to a screeching stop with the clinical-trial process. Companies need to be able to provide a capability for quick kills as well as accelerating compounds that are going to be moved on throughout the rest of the process."

In addition, managing paper-based clinical trials is becoming increasingly more expensive.

"The secondary value of technology is the ability to manage large volumes of data more cost effectively," says Barry Turnbull, VP of biometrics at CareStat Inc. "Managing paper is prohibitive. Aside from reducing the costs associated with the storage and acquisition of paper, scanning electronic images can save companies up to 30% in data-management labor. If the Pfizers and the Mercks of the world calculated their cost in paper and their return on investment, they could save billions of dollars a year by moving to electronic technologies. Eventually the industry is not only going to move to electronic capture but to electronic source documents. It may take a decade, it may take 15 years, but it is going to come. Technology will speed ahead of acceptance."

According to John Freshley, director of business development at Statprobe Inc., "the struggle for sponsors is to not only identify whether there is an opportunity to benefit from using more technology for a study, but how to apply the technology and which technology to apply.

"Sponsors are interested in doing things better, faster, and cheaper, but it's difficult for them to sift through all the layers to determine which tool to apply to which study," Mr. Freshley says.


DR. PAUL BLEICHER

Technology is about **IMPROVING THE QUALITY OF THE DATA**, improving timeliness and responsiveness, and improving the patient's safety.

Overcoming Resistance

Pilot studies using EDC have been successful, yet pharmaceutical companies have not yet implemented EDC across the majority of their clinical trials. According to the IBM report, companies are constrained by a lack of strategic planning, the varying requirements of each trial, the relative immaturity and fragmentation of the EDC software market, and the need to address both process and organizational change.

"Companies risk losing out on substantial efficiency opportunities that can be gained through the change in the drug-development process," says Albert J. Siemens, Ph.D., CEO, vice chair of the board of FHI and president and CEO of PharmaLinkFHI. "It's not just adoption of EDC, but restructuring the entire clinical-trial process. Companies can markedly reduce the time that it will take to bring a product to market if they fully capitalize on the strength of this technology and process revolution. Companies can reduce cycle times and become more efficient overall."

There is considerable hesitation on the part of industry executives to move from molecule to market using a single unified paperless process, mainly because of the silo structure of companies and due to legacy systems in use.

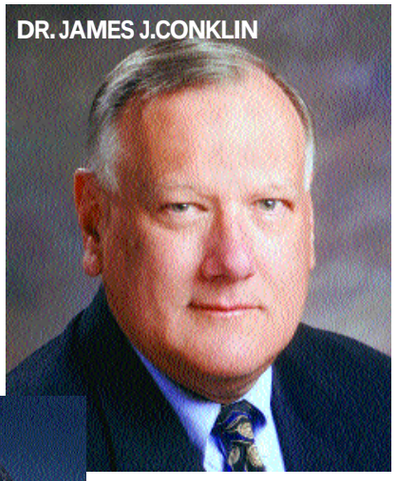
"There's also less reason right now to centralize all this information," says Munish Mehra, Ph.D., chief information officer of Medifacts International. "Every unit has its own systems and the processes around them. The preclinical teams use different systems. Clinical research groups use their own set of tools. And, the databases used by the pharmacovigilance groups are still different systems. It's still far-fetched to be believe that a single knowledge base can transfer and manage data from the hospital's database on the first patient treated through the FDA approval process and into post-marketing surveillance."

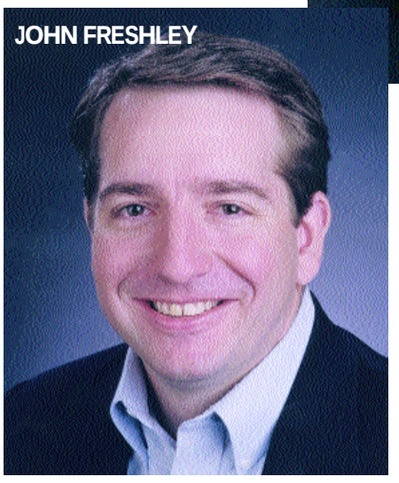
The clinical-trial process has remained virtually unchanged in the past 30 years. Companies have become very comfortable with paper processes, which is one of the biggest contributing factors against embracing new technologies.

"There's a comfort with the paper processes," Dr. Conklin says. "There has never been senior executive-level support to institute technology, and, more importantly, reengineering processes within their companies before now."

"One of the major challenges facing the industry today, is what I call 'change management,'" says Chris Couch, VP and chief operating officer at Perceptive Informatics Inc. "Pharmaceutical companies as well as the sites are accustomed to handling paper-based trials. EDC represents a different way of doing business — a better way of doing business. As we well know from other industries, companies that simply automate without changing processes just pave cow paths. Pharmaceutical companies need to understand how EDC works and then tweak their processes for query management, data management, and monitoring to best allow for the power of EDC."

Companies face the challenge of restructuring and re-building while continuing to support legacy systems. It is virtually impossible


DR. JAMES J.CONKLIN


JOHN FRESHLEY

The customers are the sites and the site coordinators. **THESE PEOPLE ARE OFTEN LEFT OUT OF THE EQUATION.**

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to switch overnight from doing everything on paper to adopting an electronic approach.

Edna Stoehr, project manager/National Registry of Myocardial Infarction at Genentech, is well-versed in adopting an EDC solution midstream.

"I think we were one of the first studies at Genentech that had to transition from paper to electronic during the course of the study, which is like changing a tire on a moving car — you can't stop, you have to keep going," she says.

Launched in 1990, NRMI is an observational, cross-sectional database designed to collect presentation, treatment, and outcome data on patients with acute myocardial infarction (AMI). Since then, more than 1,600 hospitals have participated, more than 1.8 million patients have been enrolled, and more than 160 scientific abstracts and articles have been published based on NRMI results. Among the areas NRMI examines are trends in treatment, length of hospital stay, mortality, and variations among specific patient populations. To date, three NRMI studies have been conducted, and NRMI 4 is currently ongoing. Launched in July 1999, NRMI 4 was designed to meet the 1999 Revised ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction. Currently, more than 130,000 patient records have been entered into the NRMI 4 database using EDC.

Making a switch is a difficult decision and process for many companies, because the EDC technology being implemented is in isolation from other corporate initiatives or there is not a long-term strategy for EDC implementation across the product pipeline.

"These are two concerns, the other is cautious skepticism within pharmaceutical companies of whether EDC is going to be a long-term benefit," Dr. Siemens says. "In fact, the benefits will not be fully visible until a company changes its entire clinical development process. It's not simply a question of technology, there needs to be a corporate-wide commitment to changing how clinical research is managed, and how information is developed and distributed, and then utilized."

Companies have become very good at managing paper case report forms, and therefore are resistant to changing the status quo.

"Companies have achieved reasonable time lines for collecting the information on paper, getting data into coordinating centers or data management groups, issuing queries, cleaning the data, and locking the database, in some cases two to eight weeks after last patient out or last patient visit," Mr. Turnbull says. "I don't think remote data capture is any faster than that. It's the secondary value of EDC that is important — storing documentation and having instant access to paper case-report forms are huge advantages."

"We've been able to extend the deadlines for our sites by at least a week," says Susan Morris, Ph.D., senior project manager/National Registry of Myocardial Infarction at Genentech. "In addition, we're finding that the reports are more complete. They don't have outstanding DCF so the clean data are entered into the database more quickly. Once the sites get the information in and respond to the electronic edit checks so that it is clean, it's available for analysis. EDC has really sped up the process of creating a clean and complete database."

Standardizing the software, systems, and equipment for all sites is essential to receiving consistent, comparable results, says Scott Burcham, director of centralized spirometry at Biomedical Systems Inc.

"If a company were to rely upon individual sites to use their own equipment, a sponsor would have to validate and compare every device at each site to ensure they are using identical equations and software methodologies," Mr. Burcham says. "By centralizing the data and standardizing the equipment, the sponsor can ensure their data are being captured by globally identical software. The other advantage is that the sponsor can customize the software at each of the sites specific to its clinical trial."

For example, including forced fields, which kick back inaccurate data upon input, can reduce the number of queries required to clarify data.

"Certainly, when a site is recording multiple visits over long periods of time, this becomes very important," Mr. Burcham says. "We require each site, especially in the international studies, to become certified before it can begin enrolling patients. The real weight

of this rests with the sponsors, with the pharmaceutical companies, or the CROs. We have found that by requiring our sites to perform practice testing and transmitting data before patient enrollment, we can identify training inadequacies and ensure sites are comfortable with equipment operation and protocol requirements. Ensuring flawless data transmission and capture up front is essential to getting a new trial off to a good start."

According to Mr. Freshley, it is critical to remember who the customers are when it comes to EDC, and they are not the sponsors.

"The customers are the sites and the site coordinators," Mr. Freshley says. "These people are often left out of the equation. Site coordinators have to do extra work to become a data-entry person. The best systems and the best sites understand this. We've been involved in eight different EDC projects, and some have been quite successful and some have been quite unsuccessful. The measure of success is usually based on how well the study takes into consideration the role of the sites."

Companies remain reluctant to take a 300-person, 500-person, or 1,000-person data-management or clinical-management organization and reorganize it based on electronic data capture.

"Without making the necessary process changes ROI, quality, and patient safety can't be achieved," Dr. Bleicher says. "So there is reluctance, internally, by pharmaceutical companies to make the process change commitment. However, the momentum is building as there are probably now half a dozen companies that are committed to 100% electronic data capture in all their clinical trials."

Removing the barriers

"The first EDC system was launched 20 years ago, and one of the barriers to adoption was that the technology was relatively immature," Dr. Conklin says. "For the integrated electronic process to be effective there needed to be a technology convergence — robust software and database capabilities — low-cost, high-performance computing technology, as well as distribution throughout the entire drug-development world, including investigator sites. There also needed to be a worldwide telecommunications infrastructure for the data to ride on. The final barrier to adoption, I believe has been the perception that costs are increased, which according to reports is not true." (See box on page 21 for more information.)

Mr. Cline notes a one-time barrier to EDC adoption, the FDA, is no longer a roadblock.

"The implementation of 21 CFR Part 11, which dictates the parameters of electronic data compliancy for FDA reporting standards, allows sponsors to audit vendors to make sure they are following regulations," Mr. Cline explains. "Before 21 CFR Part 11, EDC systems were at a disadvantage because there wasn't a standard that helped to guarantee the FDA would accept the data. With other systems, if it looked like paper and felt like paper, the FDA would accept it. But there was less history with EDC. A pharmaceutical company that spent upwards of $500 million to get a crown jewel prepared for submission wasn't going to take a chance on the agency responding, 'maybe we'll take it, maybe we won't.' Thankfully, 21 CFR Part 11 has eliminated this as a concern by standardizing the data format for FDA submissions." ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmalinx.com.

Experts on this topic

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