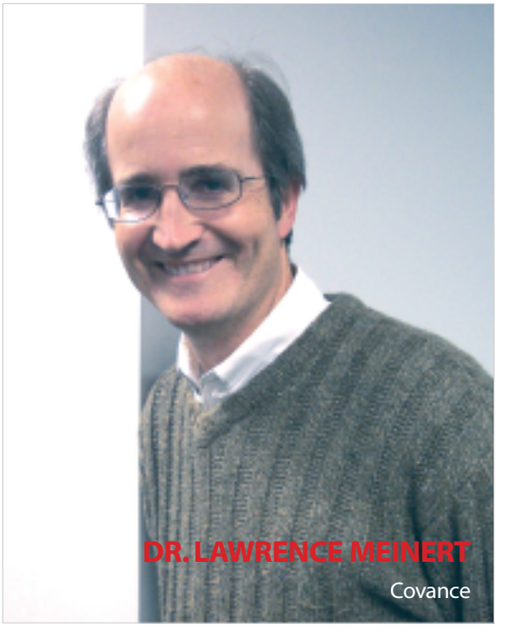
IN THE CLINIC
Trials & Tribulations

Stakeholders involved with drug development and the clinical-trial process are rising to the challenges to improve efficiencies, reduce costs, and accelerate time lines.

Systematic elegant approaches borrowing from areas such as intelligence analysis are at hand. Enhanced product characterization will be achieved with reduced investments. The solution is less about technology and more about a cognitive paradigm shift.


DR. LAWRENCE MEINERT
Covance

▶ RESEARCH AND DEVELOPMENT

New medicines that win approval from the FDA required an average of 8.5 years to move through the clinical and approval phases between 2002 to 2004 period, and on average it costs about $900 million to move through the clinic. Yet, drug discovery remains the foundation for innovation, and industry experts agree that the process needs to be improved in terms of both cost efficiencies and time lines.

MEINERT. The drug-development story of the past 10 years has been a decline in productivity. At every stage of the development process, more complexity and greater sample sizes have been seized as the path to improve product characterization. But the emergent story is that bias in virtually every aspect of the process degrades as much as two-thirds of the effective information content achievable from studies. Systematic, elegant approaches — borrowing from areas such as intelligence analysis — are at hand. Enhanced product characterization will be achieved with reduced investments. The solution is less about technology and more about a cognitive paradigm shift.

WILLIAMS. Cephalon applies an integrated compound pipeline strategy that balances the risks of internal drug discovery in the areas of oncology and CNS disease research with extensions to existing marketed products, acquisition of new compounds, and collaborations with industry partners. The strategy provides the financial wherewithal needed to sustain a commitment to the many challenges of the drug discovery process. The combination of new extensions to existing products, acquired late-stage compounds, and Cephalon's own drug discovery and predevelopment research activities provides the means to maintain a pipeline of new compounds that can be advanced from the laboratory to the marketplace, creating tangible value for both patients and the company.

EHLERS. Increasingly, pharma and biotech companies are developing biomarkers as companion diagnostics during the preclinical and clinical drug-development process. This raises several critical issues. Appropriate biomarkers are usually codiscovered with drug targets inside pharma and biotech. Moreover, sponsors can usually develop early-stage, experimental assay procedures for novel biomarkers for use in preclinical and sometimes early clinical development. But for later-stage clinical development, there is usually a need to hand these assays over to a specialty central lab capable of undertaking the tech transfer, validating the assays, and performing the testing at a level suitable for FDA submissions. Biomarkers can be conventional biochemical markers, genomic/proteomic markers, or imaging markers, which means a diversity of specialty labs or diagnostic companies must be brought

into the picture. Even more problematic is the scenario when the biomarker becomes a fully fledged companion diagnostic to be co-approved with the therapeutic and to be used postapproval in a theranostic approach. This requires decisions about who develops, manufactures, and markets the diagnostic; who controls the IP; and how all this is coordinated with development of the therapeutic. The evolution of targeted therapeutics and theranostics is a true paradigm shift that is now underway and that will force pharma and biotech companies to make some tough decisions.

BRUNO. In my opinion, one of the biggest issues in 2006 will revolve around the continued need for the timely generation of pediatric data for products. As many sponsors request deferrals for generating pediatric data until there is clear efficacy and safety data in the adult population, the speed of generating pediatric information is limited. Also pediatric studies are often challenging in terms of enrollment and retention for longer-term clinical studies, and this affects the timely nature of generation of data in pediatric populations.

IN THE CLINIC — FAST FACTS

RESEARCH SUGGESTS THAT a pharmaceutical product with $1 billion in peak annual sales can forgo as much as $2.5 million for every day that suboptimal clinical trials delay product launch.

Best Practices LLC, Chapel Hill, N.C.
For more information, visit best-in-class.com.

THE PORTION OF THE PHARMA AND BIOTECH IT budget that is spent on addressing regulatory compliance needs will grow by 5% over the next 12 months. New and replacement investments in enterprise regulatory content management systems will be an important component of this spending.

Life Science Insights, Framingham, Mass.
For more information, visit lifescience-insights.com.

NEW MEDICINES THAT WIN APPROVAL from the FDA required an average of 8.5 years to move through the clinical and approval phases in the 2002 to 2004 period. This contrasts with a steady decline in combined clinical and phase timelines since the passage of PDUFA in 1992, from a high of 9.4 years in 1990-1992 to 7.2 years in 1999-2001.

The Tufts Center for the Study of Drug Development.
For more information, visit csdd.tufts.edu.

PHASE I TRIALS COST about $5,500 per patient; companies spend about $6,500 per patient in Phase II trials ; and Phase III trials cost more than $7,600 per patient. Research also revealed that each additional day a drug spends in clinical development could cost companies $600,000 for a small or niche drug and upward of $8 million for a blockbuster in lost revenue.

Cutting Edge Information.
For more information, visit cuttingedgeinformation.com.

BIOPHARMACEUTICALS

Biopharmaceutical products are considerably more expensive to manufacture than traditional ones, largely because of the high-cost technology required for production. According to Frost & Sullivan, apart from the various investments in the development and registration of new drugs, meeting regulatory specifications can take eight to 12 years and the entire product launch can cost between $200 million and $500 million. To successfully introduce biopharmaceutical drugs, product developers need to be familiar with the intricacies of biologic behavior and should be able to define a regulatory path by working with regulatory agencies. Regulations for fine-chemical/small-molecule drugs have clearly delineated guidelines and precedents that can be relied upon to advance a development program. But distinct advantages of biopharmaceuticals include fewer side effects and a more potent effect on target cells.

ADITYA. Once biopharmaceutical developers thresh out a solution for meeting stringent regulatory requirements by hiring expert personnel and installing sophisticated facilities, the biological manufacturing processes — especially for monoclonal antibodies — are expected to become a lot simpler. This will encourage the development of several new biopharmaceuticals. While new technologies for identification of novel biopharmaceuticals will continue to emerge, a variety of supportive production technologies enable a growing pipeline of novel therapeutics. Developments in bioprocess technology have resulted in high outputs, thereby minimizing cost and time. Advances in biopharmaceuticals have coincided with a drop in the number of innovations in the area of traditional small molecules. While the number of approvals for new small molecules is waning, there has been a marked increase in the approvals for biopharmaceuticals. Although the inherent simplicity of operation of small-molecule therapies has given them an edge over newer ones such as stem cell therapies, the latter's ability to eliminate concerns over viral or prior contamination

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during organ replacement has gained a lot of popularity. Stem-cell therapy is also a cheaper and faster route to repairing damaged or diseased tissues, since it involves the use of some of the patients' own cells to grow replacement parts on biodegradable scaffolds. The research also makes it possible to produce immortalized cells derived from stem cells for research, biologics production, and therapeutic applications. Differentiated cells derived from stem cells have enormous potential for replacing dead or damaged cells in patients to treat a long list of disorders for which effective therapies currently do not exist.

E. MILLER. While biotech is heating up all over the world, we are continuing to make amazing advances in the United States, and it will be important for us to communicate and share this research globally. We have made tremendous strides in personalized medicine and pharmacogenomics with the hope of bringing better, tailored therapies to cure myriad diseases from cancer to

BIOCHIP TECHNOLOGY REDEFINES PROCESS OF DRUG DISCOVERY

Biotechnology firms are now successfully performing certain functions of drug discovery that were previously considered the domain of large pharmaceutical companies.

Biochip manufacturers are providing novel and effective solutions in drug discovery, thereby encouraging the acceptance of new technologies by end users.

In turn, drug-discovery companies are gradually evolving to adapt innovative biochip technology into their product pipeline with the aim of bringing down attrition rates and reducing drug pipeline time lines. Such objectives are being supported by advances in biochip technology such as multiparameter testing, miniaturization of chip technology, and the increasing flexibility of array technology.

Biochips rapidly identify and prioritize drug targets based on their ability to corroborate a multitude of gene expressions in parallel. The concept of doubling information content while contracting feature size is being developed with the help of technical know-how drawn from semiconductor technology.

"With the recent FDA guidelines on pharmacogenomics and steady growth potential anticipated in the biochips markets, companies can expect to see a boost in their revenue and market share holdings, if they focus on developing mainstream applications with genomics/proteomics technology," says Charanya Ramachandran, healthcare analyst at Frost & Sullivan.

Biochips rapidly identify and prioritize drug targets based on their ability to corroborate a multitude of gene expressions in parallel.

As competition escalates, the provision of value-added services will be critical for success. Initiatives to ensure better value propositions will include an improved understanding of the customer's requirements, budget issues, and regulations, as well as comprehensive knowledge and management of technical aspects and assured quality standards.

While biochip technology is undoubtedly innovative and adds real value to the drug-development chain, its cost continues to pose a major deterrent to more widespread uptake. End users remain sceptical of the financial rewards yielded by investments in such chip-based solutions. Here, cost-effective solutions can promote their use in routine product development practice.

"In terms of working out a cost-effective solution, some chip companies are following an open platform model, wherein chips are compatible with most of the other instrumentation available in the market," Ms. Ramachandran says. "This strategy should attract all end users: the academic research base that forms a major chunk in the biochip community, as well as pharmaceutical and biotech companies that consider this open technology a valuable tool for their targeted applications."

In 2004, the European biochip market accrued nearly **$126.9 million**. Standardization of array platforms reinforced by a strong bioinformatics infrastructure will push the biochip market into the next phase of the product life cycle resulting in revenue of about **$500.3 million** in 2011.

Projected to grow at a compound annual growth rate (CAGR) of **25%** during the period 2004 to 2011, the protein chips segment will experience higher growth than the DNA chip segment as most drug targets are proteins. Because of strong growth in the protein chip sector, the DNA chip segment, which currently accounts for almost **90%** of overall revenue, will witness a marginal drop in its market share over the long term.

The competitive landscape of the highly fragmented and aggressive European biochip market is in the process of being transformed. Despite the mounting rivalry, companies are entering into alliances and partnerships. Such strategies are bolstering the trend of biochips being rapidly adopted into the drug-discovery process. At the same time, alliances between chip companies and pharmaceutical firms are driving market growth, in addition to underlining the positive impact of biochips as a complementary technology.

"Although many teething technical problems are limiting their penetration into routine target validation and compound screening phases of drug discovery, a synergistic climate in the coming years, along with the strong double-digit growth rate estimated at nearly **21.6%** during the period 2005 to 2011, offers a promising outlook for biochips," Ms. Ramachandran says.

Source: Frost & Sullivan, New York. For more information, visit healthcare.frost.com.

immunologic disorders. These areas are only in their infancy and hold tremendous promise for the future of medicine. The United States also continues to lead in many global research initiatives. Global collaboration in biotech research is exemplified by the International HapMap Project, a mapping of genes and genetic variations that affect human health and disease, which has exceeded all expectations in terms of the speed with which it has been compiled and the in-depth data that have been made available via the Internet.

SYSTEMS BIOLOGY INVESTMENTS WILL TRANSFORM THE DRUG DEVELOPMENT PROCESS WITHIN FIVE YEARS

Pharmaceutical and large biotechnology companies are actively investing in systems biology for both discovery and development, according to a recent study published by Life Science Insights, an IDC company. Analysts contend that these investments will lead to direct improvements and increased efficiencies, potentially transforming the entire drug-development process.

"Systems biology is beginning to play a prominent role in the drug-development process," says Alan Louie, research director at Life Science Insights. "As systems biology approaches increasingly become an integral part of drug companies' research programs, both users and vendors need to recognize and respond to the evolving research and commercial landscape."

As drug development expands, systems biology companies are playing an increasing role in bringing together the biological knowledge available today. Systems biology companies will need to adopt an emerging technology approach to achieve long-term success. With technology maturation and market pressures, the commercial landscape will significantly change from what it is today within five years.

Source: Life Science Insights, Framingham, Mass.
For more information, visit lifescience-insights.com.

NANOTECHNOLOGY

While there have been some early success stories, few nanotechnologies with life-sciences applications have made the transition from the laboratory to the marketplace. Experts discuss the short- and long-term prospects for nanotechnology.

MOFFITT. Nanotechnology offers a revolutionary new way to affect an extensive and disparate list of industries, including materials, diagnostics, and pharmaceuticals, and therefore the long-term effect of nanotechnology will be wide and substantial. Short term, however, the impact of nanotechnology is the responsibility of companies, such as Nanosphere, to channel this potential into reality, into a shippable product. The potential of nanotechnology resides within the fact that existing materials behave differently on the nanoscale versus terrestrial level. Leveraging these nanoscale properties into real-world products will not only improve the performance of these materials, but also enable previously unimaginable applications and performance, bringing next generation products to life.

SELIGMANN. Nanotechnology is a relatively loose term. Miniaturization of assay processes will continue, and in the process nanofabrication will be used. But research is a complex process, and therefore whole scale overnight "nanosization" is not practical. I believe the technology will be adopted when and where it makes sense and can deliver benefits that outweigh the cost.

MOFFITT. In the case of diagnostics, the industry is ripe for a new, disruptive technology. Each wave of diagnostics is predicated by a new discovery, a new technology that enables

BIOPHARMACEUTICAL MANUFACTURING CAPACITY TO INCREASE 48% BY 2010

The production capacity for biopharmaceutical manufacturing will expand an average of 48% during the next five years for mammalian and microbial production systems, according to a report by BioPlan Associates Inc.

The industry's current five-year projection of production capacity expansion is now significantly lower than in 2003. In that year, the survey's five-year projection indicated capacity would expand **69%** by 2008.

BioPlan's recently released report, 3rd Annual Survey of Biopharmaceutical Manufacturing Capacity and Production, provides details and comparisons of production by biotherapeutic developers and contract manufacturing organizations (CMOs).

The industry's current five-year projection of production capacity expansion is now significantly lower than in 2003.

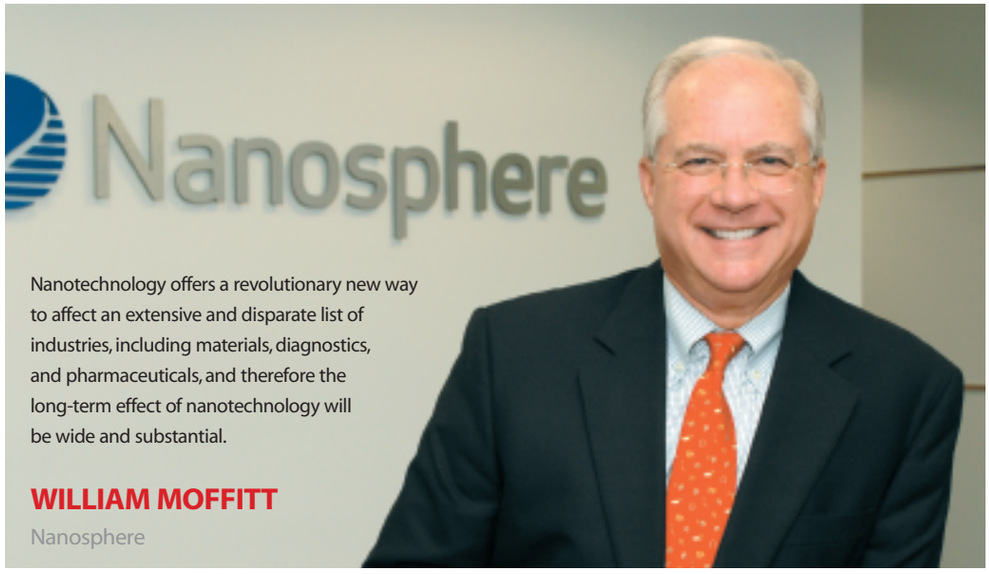
The report found that for CMO respondents, a major factor is expected to be lack of financing for production expansion, which was indicated by **52%** of CMO respondents. Key areas to address to avoid capacity constraints included: optimizing cell-culture systems to increase upstream performance (noted by **54.2%** of respondents) and improving downstream purification performance (**43.8%**).

Recently, overall capacity utilization by biopharmaceutical developers and contract manufacturers has declined. In 2005, use of existing capacity decreased **8%** compared with 2003. The decrease is a result of continued industry expansion and improvements in yield at existing facilities. Despite this, some segments of the industry, including larger biopharmaceutical developers, continue to experience capacity constraints.

Capacity utilization for all biomanufacturers using mammalian cell-culture systems is currently **68.8%**. Capacity utilization for microbial fermentation is **60.5%**. As a comparison, the U.S. Federal Reserve Statistical Release showed that capacity utilization for all U.S. industries in July 2005 was **79.7%**.

Source: BioPlan Associates Inc., Rockville, Md.
For more information, visit bioplanassociates.com

additional facets of disease to be identified and monitored. Such disruptive technology is then commercialized and subsequently optimized to its fullest performance. Over the past few decades, the enzyme-linked immunosorbent assay (ELISA) is an example of a similar technology that enabled efficient protein detection and has been commercialized and optimized, creating a multibillion-dollar industry. But modern medicine continually demands more and has generated a backlog of need for access to ultrasensitive protein detection. Nanotechnology-based technology, known as Biobarcode, enables proteomic detection with sensitivity three to four orders of magnitude greater than ELISA. In the short term, nanotechnology will present a solution to this medical need; in the long term, it will enable the maturation of a billion-dollar opportunity similar to the ELISA story. Today's diagnostics also incorporate genomic information. Such molecular diagnostics are based upon target amplification technologies such as PCR. Although creating an initial market, such technologies have slowed widespread market acceptance because of the high costs of required technology and highly skilled personnel needed, characteristics originating from the core technologies themselves. Again, a technology (PCR) enabled the creation of a new set of diagnostics but has reached a plateau period of development. Nanotechnology may now provide the next jump in technology necessary to bring molecular diagnostics to the masses, with the ability to provide genomic detection in a significantly lower cost embodiment, not requiring highly skilled personnel or infrastructure. The short-term gain will be the fulfillment of an immediate medical need, with the long-term benefit of enabling a widespread evolution in molecular medicine, with the simultaneous expansion of a commercial opportunity.



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WILLIAM MOFFITT
Nanosphere

CLINICAL OPERATIONS

From patient recruitment to end of trial accountability, experts discuss how processes, strategies, and project management can be improved on an enterprisewide level, as well as for tactical executions.

DRISCOLL. Even the best-planned patient-recruitment campaign can go awry when callers or referrals get lost in the follow-up process. There are several contributing problems, including calling when the referral is not home or having a large number of potential referrals and not enough time to call each person. Patient referrals can be excluded from a study simply because the site was unable to make contact. Follow-up calls should be made within 24 to 48 hours of the initial call; the longer the site waits to call, the more likely it is that the person will lose interest. The follow-up process is often overlooked while planning the patient-recruitment strategy. The advertiser has made the phone call, and the call center has screened and referred the appropriate callers. At that point, many firms consider the job done. But sites often need assistance reaching all the people who have been referred. Whether calling to confirm interest or to find out why someone did not show up for an appointment, this contact is very important for maximizing enrollment. Without follow up, many referrals simply fall out of the process. Ample money is spent making the phone call and sending referrals to the sites. It is needless for people to get lost in the process. Follow-up can maximize the investment in a patient-recruitment program.

NOFFKE. From an enterprise perspective, companies should dedicate and empower skilled project managers — internal or external — to lead the process of complex drug-development efforts. Focused solely on process, not content, the project manager's role is to ensure that team members, often across functions and sometimes across companies, accomplish activities according to an agreed plan. Companies are consistently lagging in three areas, all of which can be addressed by skillful project management. Companies often are not meeting their time lines — frequently because of miscommunication between different functional silos. For example, the technology development team may not fully understand the clinical program requirements, so materials may not be ready at the right time or in sufficient quantity. A seemingly obvious critical functional interdependency that requires diligent management, yet is still a prevalent problem that delays projects and costs companies big money. Second, companies depend upon alliances for innovation and yet are not managing them adequately. It is reported that a full 50% of all alliances fail to meet expectations, costing billions, largely because of inadequate alliance management. Often, the deficit occurs at the project level — multiple projects across functions, companies, geographies — without sufficient coordination and, often more importantly, without an objective party trained to bridge cultural, communications, and process divides. And third, companies are not preparing sufficiently for product launch. With the intense pressure on preparing an application for regulatory submission, launch planning often falls to the wayside, delaying market entry for months and sometimes longer postapproval. This can mean millions of dollars lost while playing catch up.

NOWAK. The benefits of alliance management include having clear objectives, ensuring that performance remains on track, and confirming that customers' needs are being met throughout. In 2006, for major customers, we will continue to assign a dedicated project manager and develop a schedule for business managers and executives to collaborate to achieve success.

ENGLISH. During the planning stage for labeling, packaging, and distribution, it is imperative to consider the "end of trial" accountability, reconciliation, and the destruction of investigational product (IP). Oftentimes, we are so narrowly focused on study start that we do not take into consideration the added and unforeseen costs of the end of study IP reconciliation and destruction. Waiting until all costs have been submitted and a budget has been approved is not the time to ask whether a procedure for IP has been addressed and budgeted for. It's impor-

By automating study design, data capture, and data movement, companies will ensure uniform data collection, significantly reduce transcription errors, and improve data quality, which will result in major efficiency gains and reduced development time.

DR. LAFAYETTE THOMPSON
iAdvantage

The benefits of alliance management include having clear objectives, ensuring that performance remains on track, and confirming that customers' needs are being met throughout.

PAUL NOWAK
Symyx Technologies

MONICA ENGLISH
Covance

During the planning stage for labeling, packaging, and distribution, it is imperative to consider the "end of trial" accountability, reconciliation, and destruction of the investigational product.

SCOTT FREEDMAN
Monitorforhire.com

Both sponsors and CROs are favoring strategic outsourcing in an effort to reduce costs and minimize risk, in other words, do more with less. EDC and other related clinical technologies continue making larger trials more efficient, but the equation remains the same: a large multicenter study still requires a team of monitors.

CLAIRE DRISCOLL
Claire Driscoll & Associates

Even the best-planned patient recruitment campaign can go awry when callers or referrals get lost in the follow-up process. There are several contributing problems, including calling when the referral is not home or having a large number of potential referrals and not enough time to call each person.

CORT GREY
Dendrite Clinical

Against the backdrop of the widely distributed nature of clinical-trial sites and participants, as well as the varying frequency and consistency of trial operations, clinical-trial technologies are increasingly for rent, not for purchase. In most of these technology considerations, Web-based access is now a low-end threshold, not a nice-to-have.

tant to research what the end-of-trial business practice is regarding the remaining IP. This process can be streamlined by incorporating the returned IP into an interactive voice response system (IVRS). Not only can the IVRS track all released IP, it can also handle IP returns. Personnel at sites, warehouses, and/or depots, who are already familiar with the IVRS, can enter what a subject has returned, including the date the IP was destroyed. The entire reconciliation from packaging to destruction can be easily accessible at any time. This reduces many hours of reconciling various documents manually, which ultimately reduces costs. By proactively addressing the process at the beginning of the trial, trials are more likely to stay within budget and studies closed out with the all-important final disposition of IP.

FREEDMAN. We're seeing all the indications

for a positive outlook in 2006. The finite pool of qualified CRA talent continues to be stretched by large sponsor pipelines and an increased demand for postmarketing studies. Both sponsors and CROs are favoring strategic outsourcing in an effort to reduce costs and minimize risk, in other words, do more with less. EDC and other related clinical technologies continue making larger trials more efficient, but the equation remains the same: a large multicenter study still requires a team of monitors.

HOLLINGSWORTH. By looking at current state business processes, companies can quickly determine where reengineering is necessary before attempting to automate it. By creating a collaborative and holistic environment, the adoption of the right strategy will change how clinical data management is accomplished. Once gaps are identified and issues fixed, the team can move to define software and training requirements. Most importantly, good implementation needs to incorporate change management. Data managers may soon become project managers, clinical directors will need to maximize the benefits of the new CDMS, and research departments will be adjusting the way they operate. Planning and the realization of organizational changes will guarantee victory and collaboration along the way in support of return-on-investment goals for a global clinical data management strategy.

MEINERT. Much of the pharmaceutical drug-development investment is directed toward verification and repair of investigator perfor-

GLOBAL REVENUE FOR CONTRACT MANUFACTURING AND RESEARCH TO REACH $168 BILLION BY 2009

Not so long ago, big pharmaceutical companies turned to contract manufacturing organizations (CMOs) solely to achieve efficiencies in cost, capacity, and time-to-market or to obtain a specific expertise not available in-house.

Today, these factors still also play a role, but the most dynamic driver behind the use of CMOs is now rapidly becoming the unique, innovative, and state-of-the-art process and production technology they offer. More and more pharma companies are leaning toward outsourcing to concentrate on marketing their products and spending less time in drug discovery and manufacturing. This applies to those virtual companies that exist by the simple fact that they can rely on the contract manufacturers and researchers.

According a report from Business Communications Company Inc., the global revenue for contract manufacturing and research for the pharmaceutical industry is estimated at just more than **$100 billion** in 2004 and is expected to rise at an average annual growth rate (AAGR) of **10.8%** to **$168 billion** in 2009.

Contract research organizations (CROs) assist biotechnology and pharmaceutical companies in designing, implementing, and managing clinical testing. Contract manufacturing organizations manufacture chemical or biosynthetic bulk pharmaceutical chemicals or intermediates for clinical testing or commercial use, or they may produce dosage forms such as tablets or injections.

Of the three market segments, the market for contract manufacturing of prescription drugs for 2004 was estimated at **$26.2 billion**, which is expected to rise to **$43.9 billion** by the end of 2009. Contract manufacturing of OTC and nutritional products is the largest and fastest growing segment, expected to rise at an AAGR of **11.3%** to **$102 billion** by 2009. The contract research market is expected to reach **$21.9 billion** by 2009, rising at an AAGR of **8.6%** from **$14.5 billion** in 2004.

Within the contract manufacturing segment, the cardiovascular drugs are the largest among all other application categories, with worldwide revenue of about **$2.56 billion** in 2004. It is rising at an AAGR of **8.7%** through the forecast period. Analgesics seem to be rising at the highest pace in the contract manufacturing business with the expected annual average growth rate of **11.9%** over the period of five years.

Many CMOs have gone far above and beyond the immediate needs of their customers to create innovative homegrown processes and to implement the latest, technologically advanced equipment technology that frequently surpasses that available at big pharma's own facilities. The total cost of pharmaceutical production includes not only the cost of building new plants. It includes the cost to maintain them, stay up-to-date on equipment advances, and to maintain a workforce of highly skilled operators — operators with more than just the knowledge to run them, but with the expertise and experience necessary to continually update and improve them.

WORLDWIDE REVENUE OF CONTRACT MANUFACTURING AND CONTRACT RESEARCH ORGANIZATIONS, THROUGH 2009

	2002	2003	2004	2009	AAGR % 2004-2009
Contract manufacturing of bulk drugs and dosage forms	$21.4	$23.8	$26.2	$43.9	10.8%
Contract manufacturing of OTC drugs and nutritionals	$48.6	$54.2	$59.8	$102.0	11.3%
Contract research	$12.5	$13.2	$14.5	$21.9	8.6%
TOTAL	**$82.5**	**$91.2**	**$100.5**	**$167.8**	**10.8%**

Note: $ in billions
Source: Business Communications Company Inc., Norwalk, Conn.
For more information, visit bccresearch.com.

Source: Business Communications Company Inc., Nowalk, Conn.
For more information, visit bccresearch.com.

mance in a clinical trial. One particular area that is not only reflective of inefficiency but a substantial degradation of scientific validity is "data cleaning." There is a growing body of literature in the survey and census community that suggests that even when obvious errors are repaired, the scientific validity of the aggregated data set is more degraded than if never edited. That which looks correct often has equal possibility of being wrong; selective repair creates an overwhelming bias. Furthermore, the clinical truth of a patient encounter is often ambiguous, and the concept of a differential diagnosis reflects that ambiguity. Much of the data-cleaning process is directed toward clarification of ambiguity. Techniques that summate individual ambiguous states to a superior aggregated understanding will start to prevail over traditional methods. Going forward, these developments may radically change the scale and scope of the clinical data management role.

THOMPSON. Electronic study management systems will expand the scope of ELNs/EDC by incorporating study design, dynamic electronic laboratory notebooks (ELN) design, analysis, and reporting into an integrated package that is compliant with federal regulations. The next logical progression will be to systems that are 100% Web-based. The impact of such systems on industry costs and time lines will be significant as companies experience benefits similar to, or greater than, those becoming evident in synthesis/discovery and clinical. By automating study design, data capture, and data movement, companies will ensure uniform data collection, significantly reduce transcription errors, and improve data quality, which will result in major efficiency gains and reduced development time. Web-based systems will provide transparency and enhance communications throughout the organization. Data will be reviewed, analyzed, and reported easier, faster, and with greater accuracy, so that compounds moving beyond the preclinical process will have a greater chance of success. Go/no-go decisions will be empowered with accurate, easily accessible information. Ultimately, decision makers will be able to better assess the probability that a compound might fail in clinical trials or, worse yet, fail commercially, helping them avoid making costly mistakes.

GREY. Against the backdrop of the widely distributed nature of clinical-trial sites and participants, as well as the varying frequency and consistency of trial operations, clinical-trial technologies are increasingly for rent, not for purchase. In most of these technology considerations, Web-based access is now a low-end threshold, not a nice-to-have. The application service provider (ASP) model presents an attractive pay-as-you-go approach while providing the vast distribution capabilities inherent in the Web.

▶ CROS AND OUTSOURCING

It has been suggested that pharmaceutical companies are backing away from end-to-end, full-service contracts with CROs and instead are selecting providers based on their capabilities in distinct service and technology categories.

MINOR. Historically, people have tried different approaches to outsourcing with varied success, and the functional model seems to be the latest fad. In my late-phase group, the majority of our engagements are still at the project level, and we expect this to continue because it is most efficient and cost effective. But over the past year, Icon has participated in a variety of different approaches to outsourcing from different sponsors — from FSP (single functional service providers and services typically reserved for sponsors only), reverse auctions involving CROs and contract staffing agencies (new competition for CROs), to complete full-service programs. Each requires different competencies on the part of the sponsor and the vendor. For those partitioning services into functional pipes, the traditional outsourced project management (PM) interface of PM to PM has become inverted. This means multiple sponsor departmental staff must take on the role of mini-PM or outsourcing manager for that service, a competency they probably do not have. It remains to be seen if the efficiencies in a functional service model are greater than the entropy required to keep processes separated and managed independently. I believe that there will be some consolidation of FSP strategies so that there are fewer internal managers required.

HIGGINBOTHAM. In 2006, we will see the trend of strong growth continuing in outsourcing of Phase I-IV clinical development and regulatory services. Estimates from industry analysts Goldman Sachs and Jefferies show the total CRO market opportunity ranging

IMPACT OF PHARMA'S SHIFTING CLINICAL OUTSOURCING STRATEGY

In an effort to reduce the cost and time spent conducting clinical trials, pharmaceutical companies such as Wyeth and Pfizer are overhauling their relationships with CROs and forcing significant change in the clinical outsourcing market.

According to Life Science Insights (LSI), shifting sponsor sentiment toward alternative sourcing approaches represents a call to action for CROs offering end-to-end contract research services.

"A shake up is occurring in the clinical outsourcing market," says Ellen Julian, research director for pharmaceutical outsourcing markets. "Companies are reexamining the ways that they work with CROs and other outsourcing providers as they seek to increase efficiencies in the coming years."

LSI finds that many pharmaceutical companies are backing away from end-to-end, full-service contracts with CROs (despite the positioning of large CROs) and instead are selecting providers based on their capabilities in distinct service and technology categories.

OTHER KEY FINDINGS INCLUDE:

▶ **THE ROLE OF CLINICAL OPERATIONS EXECUTIVES** will change depending on the type of outsourcing approach chosen.

▶ **CONSULTING AND RESEARCH PROCESS OUTSOURCING** will increasingly be facilitated by a mix of service providers, including business process outsourcing vendors, who are experienced in evaluating the processes of clinical development organizations to drive operational improvements, and clinical staffing and project management firms. These and other outsourcers will continue to ramp up and more aggressively market their clinical development domain expertise.

▶ **CROS WILL FOCUS ON** a narrower range of best-of-breed services offerings and divest areas in which they are not soon to be a leader.

Source: Life Science Insights (LSI), Framingham, Mass. For more information, visit lifescience-insights.com.

SIMON HIGGINBOTHAM

Kendle

In 2006 we will see the trend of strong growth continuing in the outsourcing of Phase I-IV clinical development and regulatory services.

from $15.4 billion upward to $17.2 billion in 2006. The late-phase arena will continue to provide significant growth opportunity in response to calls for increased drug-safety testing and more patient data. Large, simplified registry trials and post-marketing approval and surveillance trials, in addition to regulatory and safety expertise, will be areas of strong incremental growth in 2006 and the coming years.

GOLDBERG. The definition of a good outsourcing partner to smaller bio/pharma companies will continue to evolve in 2006 and beyond. For instance, it will be increasingly important for CROs to streamline communication with their clients, taking advantage of appropriate technologies. The challenge is that clinical trials are characterized by the use of numerous, and potentially disparate, technologies, such as electronic data capture (EDC), clinical trial management systems (CTMS), interactive voice response systems (IVRS), and electronic patient reported outcome (ePRO) solutions. Given the number of technology vendors that may converge in the conduct of a single trial, it is important for the CRO partner to play a leadership role in ensuring that the various data streams can be integrated. To do so, the partner of choice should clearly understand the roles and capabilities of the various systems and be able to determine which systems will provide what data. In the end, it is essential that the relevant data be aggregated and surfaced to drive timely decisions. While larger pharmaceutical companies may have critical mass to invest in and standardize on one or more technologies, this is less likely to be the case for smaller companies that tend to choose solutions on a study-by-study basis. Consequently, each new trial tends to present new integration challenges. From a technology perspective, we expect to see a continued trend by smaller companies toward the use of hosted or application service provider (ASP) models. The benefits of the approach include the ability to avoid dedicated infrastructure, support, and maintenance costs.

ARMSTRONG. Genaera has used CROs in the past at varying levels, from pretty much full-service clinical to monitoring ourselves. In our Phase III studies, we are using more of the full-service model, based on capability and cost-effectiveness. We continue to source things such as API and drug product manufacture with the appropriate experts. In all cases, we staff our studies with highly qualified internal people who work closely with and monitor the CRO activity.

HUGHES. Sponsors are looking to work hand in hand with vendors to standardize the approach used by different therapy groups and suites of studies. In the past many of these groups have had very specific, individual requirements, which has meant that there have been numerous customers within a single organization who all have different needs from the technology solutions that they deploy. Now, internal client champions of technology are beginning to exert their authority to make processes and systems work harder for their own organizations, and vendors are assisting with this process by helping drive the standards while remaining flexible enough to accommodate necessary study-specific customizations along the way.

ARMSTRONG. The trend in big pharma will be toward splitting the work among several CROs and managing the work more closely internally. The CRO industry has experienced significant turnover and cost pressures from higher wages. The key people at a CRO are at least a major part of the decision process for pharma, and those people are the same individuals who are most likely to be part of the CRO turnover equation. This will cause the industry to modify the full-service contract and to manage the process differently.

MURPHY. Pharmaceutical companies are demanding the highest level of scientific and regulatory expertise be applied for their drug-development projects. With new technologies such as pharmacogenomics, proteomics, and biomarker discovery being applied as a more strategic way of developing drugs, many are looking to outsource to those with core competencies in these select areas. With few exceptions, most CROs are not equipped to address the needs of pharmaceutical companies that want to take advantage of this new burgeoning approach to development. Pharmaceutical companies are now faced with the build-or-buy decision, and most realize that their own internal expertise is around the discovery and licensing of new chemical entities. This has created an opportunity for niche players that have both the scientific and regulatory expertise to carry out clinical trials using this important new approach to drug development. The publication of "Guidance for Industry: Pharmacogenomic Data Submissions" by the FDA in March 2005 codified the use of pharmacogenomics and gene-based clinical trials for the pharmaceutical industry. Certainly, additional guidance documents addressing other emerging and specialized areas such as proteomics, expression analysis, and metabolomics will follow. In 2006, we

JACK ARMSTRONG

Genaera

The trend in big pharma will be toward splitting the work among several CROs and managing the work more closely internally.

might expect that pharmaceutical companies will cycle back to doing what they do best and leave the burden of using these newer approaches to those companies that are pioneers in bringing this novel approach to mainstream drug development.

HIGGINBOTHAM. Kendle did not see a trend away from end-to-end, full-service contracts during 2005; if anything we have seen significant growth in requests for this type of contract during the year. But, it is true to say that pharmaceutical companies are exploring different models to complement this approach. Importantly, in both models, distinct skills, innovative approaches, and global capabilities are paramount to successful delivery. Some of our biopharmaceutical customers are moving to a functional service provider model, identifying a few best-in-class providers to assist in noncore competency drug-development services. Many others are pursuing a more traditional strategic outsourcing model, developing relationships and preferred provider agreements with a select group of CROs to which they outsource full-service projects or even entire development programs. This approach leverages the full skills and expertise of the CRO, creating significant efficiencies through a centralized point of accountability and integration of their Phase I-IV drug-development needs.

EDC

The percentage of pharma and biotech companies using EDC in trials is expected to increase from only 7% in June 2005 to more than 18% in the next 12 months. (Some estimates have EDC adoption as high as 40%.) Another 30% of pharma and biotech companies are expected to use EDC in 50% to 90% of their trials in the next 12 months.

GREY. While the numbers on adoption of EDC across the clinical-trials market space range widely depending on the source, there is little doubt that adoption is experiencing an upswing from its historically terrapin-like pace. Major pharma companies are more seriously investigating options, and heretofore autonomous research entities within companies are finally recognizing the need to centralize and standardize data-collection techniques electronically. This hopefully means a wider understanding of the critical need for sponsors and CROs to develop, support, and retain satisfied and loyal investigators. The wise players will recognize the catharsis the shrinking pool of investigators represents, especially in light of the increasing demand for more studies with more subjects over more time. This recognition will prompt these forward thinkers to put the high-touch activities of investigator relationship management offerings and hopefully a wider understanding of the critical need for sponsors, into the hands of a provider who can make the promise of investigator selection, training, and satisfaction a reality.

RICHARDS. We see the market at an inflection point. The industry has been in a perpetual piloting mode for several years. We see this year as a commitment inflection point; those that were piloting programs are now looking to implement enterprise solutions. We are being told that the service model is quite expensive to implement in the enterprise. CRO customers seem to be more discerning about the total cost of ownership and are very aware of their underlying costs. Our customers are using our new hybrid paper and electronic data-management solution to reduce the cost of training and to consolidate their back-end processes. Because they are using the same system to support paper and EDC, they don't have to support two separate systems. This allows them to be much more competitive and at the same time maintain a certain level of flexibility. CROs need to reduce their costs, improve profit margins, and maintain a competitive edge, and now that our CRO customers are beginning to realize these goals the pharma companies are beginning to follow.

CLAYPOOL. In Phase I trials — paper-based trials — the sponsor has relatively little visibility into results while the study is in progress. The costs and processes associated with changing direction often inhibit creativity in the trial process. EDC provides quicker access to trial data so that the sponsor can identify when a compound is not working as intended or, possibly, if there is another application where it may be more effective. If the trial uses an EDC system, the data are available in a usable form more quickly than a paper-based trial. For example, if the sponsor is testing a medication, the sponsor may find a greater adverse experience profile for women, even before the study blind is broken. Study progress and particularly subject safety can be managed far more efficiently

As more users involved in the clinical-trial process are brought online, the opportunity to move to a more business process management focus will emerge.

NICK RICHARDS
DataLabs Inc.

using EDC than using paper. EDC also enables the sponsor and trial staff to monitor more effectively the enrollment, drug usage, and any number of study metrics, including financial grants administration in the study. With an EDC system, the sponsor may be able to automate reporting with less time investment and lower cost. Safety issues can be managed and reported more readily to the appropriate agency. Since Phase IV trials are becoming more common, look for EDC to play a major role there. Phase IV trials tend to be simpler and more long term than Phase II or III and are perfect for EDC.

HUGHES. Many sponsors are looking to work in partnership with technology vendors to streamline their workflow and gain greater efficiency through the integration of systems that have traditionally worked in isolation of each other. The electronic collection of patient self-report data continues to be a fast-growing requirement in the clinical space, and sponsors are turning more and more to the use of interactive voice response and handheld device technologies to collect accurate and cost-effective patient data.

STAFFORD. Quintiles has witnessed the rapid expansion of EDC firsthand. Our own experience mirrors that of the IDC findings regarding EDC market penetration accelerating through 2006. Many sponsors have preconceived notions about what EDC can and cannot provide so we work with them to make sure all of the benefits and potential obstacles are identified and explained thoroughly. We have found that once pharma or biotech companies have multiple EDC trials under their belt, they are much more comfortable with the process and technology and can fully appreciate the tangible benefits of EDC. Quintiles has been designing paper and electronic CRFs across therapeutic areas for more than 20 years, and we can say, without a doubt, that EDC is meeting expectations. It is our belief that the evolution of EDC will have a significant

It has been our experience that staffing for EDC trials requires candidates with the same level of expertise but places emphasis on very different skill sets from those required for paper-based trials.

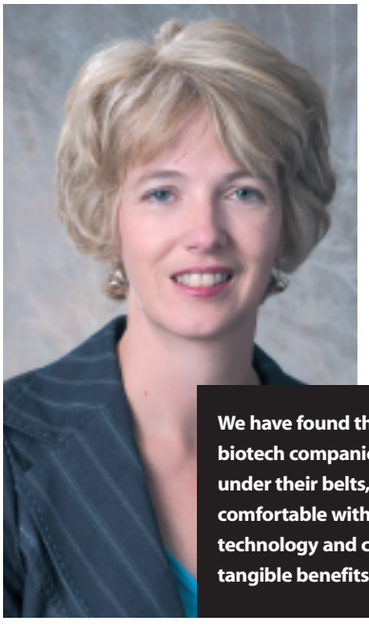
MARYSASSER HOLLOWAY
ClinForce

PATRICK HUGHES
ClinPhone

The electronic collection of patient self-report data continues to be a fast-growing requirement in the clinical space, and sponsors are turning more and more to the use of interactive voice response and handheld device technologies to collect accurate and cost-effective patient data.

EDC has huge potential to improve the performance in both the accuracy and speed of regulatory submissions. But EDC is not going cure the underlying conflict between these two goals or relieve the temptation to take shortcuts in data evaluation.

ELLEN BARROSSE
Sychrogenix Information Strategies



PAULA BROWN STAFFORD
Quintiles

We have found that once pharma or biotech companies have multiple EDC trials under their belts, they are much more comfortable with the process and technology and can fully appreciate the tangible benefits of EDC.

impact on not just clinical data management, but on the entire clinical-development process.

RICHARDS. The adoption of EDC is connecting more and more users every day via a standard Web browser and an Internet/Intranet connection. As more users involved in the clinical-trial process are brought online, the opportunity to move to a more business process management focus will emerge. Pharmaceutical companies will begin to invest in technologies that address the entire clinical process and particularly those solutions that help tie technologies together. There will never be an all-in-one solution; companies will need to develop a strategy that allows them to tie best-of-breed solutions together that meet their specific needs. Technology standards such as XML and service-oriented architectures, along with industry standards such as HL7 and CDISC, are laying the foundation for a higher level of interoperability.

MINOR. Icon recognized some time ago that EDC is a tool that offers unique advantages to projects demanding accurate, reliable, and timely data collection. While the majority of our projects still use paper, the interest in this technology has nearly doubled as measured by the number of requests for EDC costing in 2005 compared with 2004. We expect this trend to continue. Overall, electronic data capture has a significant place in our global data-management strategy, and most systems meet our expectations when used. We find it especially useful for studies requiring interim analyses or rapid database closure and for late-phase studies with little or no onsite data verification requirements.

DE VRIES. We're witnessing that once a sponsor decides to make the commitment to EDC, it aims to have 90% or more of its new trials up and running on the technology within 12 months to 24 months. After selecting a vendor, relatively fast implementations allow sponsors to leverage EDC's benefits and experience ROI across their portfolio. Additionally, very few sponsors are trying to add EDC incrementally and scale it to existing technologies; rather, sponsors are making deep commitments to new technology platforms for clinical data management.

HOLLOWAY. As the industry moves toward conducting higher percentages of EDC clinical trials, our clients ask us to identify candidates with prior EDC experience over those with traditional paper-based trial management experience. It has been our experience that staffing for EDC trials requires candidates with the same level of expertise but places emphasis on very different skill sets from those required for paper-based trials. For example, a data manager involved in an EDC trial needs to be savvy in the technical aspects of the study design and the database design. In an EDC trial, the data-collection tool is the entry screen, and the responsibility for designing that entry screen and conducting the user acceptance testing belongs to the lead data manager. Historically, that responsibility would be shared with other team members, such as the database programmer, the clinical monitor, and the CRF designer. With heavy emphasis on data testing and a shorter duration of time until the screens go live, the data manager must anticipate all possible data scenarios and accommodate those early on in the setup.

BARROSSE. Of course EDC has huge potential to improve performance in both the accuracy and speed of regulatory submissions. But EDC is not going cure the underlying conflict between these two goals or relieve the temptation to take shortcuts in data evaluation. Our company is focusing on leadership and regulatory communications to gain commitment across organizational groups to quality processes. Without this fundamental alignment around the mission of the organization the success of any toolset, electronic or otherwise, will always be restricted.

SCHWAB. i3 Statprobe is implementing a variety of EDC methodologies, including IVRS, ePRO, and Oracle RDC, for clinical databases. In addition, we occasionally work with third-party EDC providers to meet specific sponsor requests. To date our experience with EDC has confirmed that data are more readily available earlier and are cleaner than with classic paper studies. We also have benefited by locking clinical databases in a shorter amount of time when compared with classic paper studies. There continues to be a need for education and effective change management in the industry, which would allow us to move past the concept of applying a paper process to an EDC environment.

SHIELDS-UEHLING. The SAFE standard is supporting the increased use of EDC in clinical trials and other business transactions. Many of SAFE's member organizations, which include pharma companies, CROs, and other healthcare organizations, have begun implementation of SAFE credentials for use in EDC for clinical trials.

The industry has learned that even extensive clinical trials cannot replicate the full range of patient circumstances that exist in the world and that rare side effects often surface only after a drug has been launched and used by far greater numbers of patients.

DR. BARRY ARNOLD
AstraZeneca

DRUG SAFETY/ PATIENT SAFETY

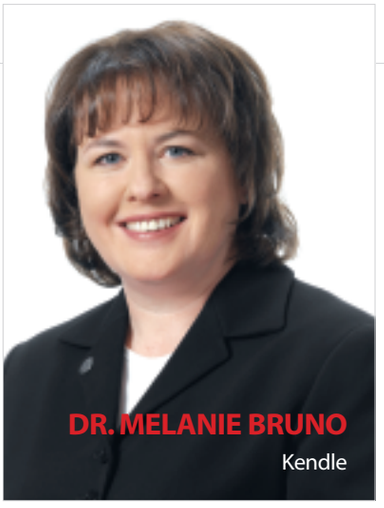
The vast majority of physicians and consumers (82% and 88%, respectively) believe that more should be done to monitor the safety of drugs after they are on the market. Pharmacovigilance risk-management technology is predicted to be one of the fastest-growing application areas in the drug-development arena as a tool for proactively addressing the drug-safety issue in marketed drugs.

MURPHY. Pharmacogenomics, the study of variable response to drugs based on the patient's genetic makeup, is focused in this area of drug safety. For drug companies to take advantage of this scientific application, they need to prospectively acquire a patient sample, for example whole blood, in order to bank the patient's DNA and look postapproval for genetic trends tied to those patients that show a common reaction. Rare traits that might be overlooked during development can then be reexamined for every patient who reports problems with the new treatment. Underlying genetic predisposition may not be the only potential cause of adverse drug reactions but it is a tool that regulators and patients expect drug companies to use in this new approach to drug development and postmarket surveillance. In March 2005, the FDA published the "Guidance for Industry: Pharmacogenomic Data Submissions" as a means to encourage and enhance the use of this science so that drug safety and efficacy issues can be identified much earlier in the development and approval process.

MENDRICK. Drug-development companies are beginning to embrace the concept of personalized medicine or the thought that "one size doesn't fit all." Drugs may show population-based safety and efficacy yet may not be safe or efficacious for each individual patient. New technologies, such as pharmacogenomics, are beginning to be applied in the drug discovery and development pipeline to determine if a more accurate assessment of patients' responses can be performed before a prescription is written. But implementation of such technology in the clinic will bring more pressure to bear on medical cost-containment measures since molecular diagnostic tests are predicted to be more expensive than some currently used tests, such as serum chemistry. From a patient and insurer perspective, the additional expense for molecular diagnostic testing would be offset by potentially fewer adverse events and better patient response to medications. Pharmaceutical companies could see more success because identification of appropriate responders — as to efficacy and safety — would improve their chances of regulatory approval for new drugs and potentially mean fewer drug recalls. To move this field forward, all involved in the medical-care system, including insurers, government agencies, and patients, will need to be educated about the benefits of using tests that promise to be more accurate than current approaches. Such tests will better enable physicians to prescribe the correct drug for each individual instead of the current trial-and-error process that can accompany the use of some prescription drugs.

MURPHY. Drug safety is very much in the public eye with articles in the lay press almost weekly about the dangers of certain drugs that were previously thought to be safe and effective. Should pharmaceutical companies have known about these, and did they have the tools to examine these relatively rare adverse events? Personalized medicine offers the hope to tailor medications to the patient's unique genetic profile. While it is not a panacea, it does offer a new approach to both drug development and postapproval prescribing. For pharmaceutical companies, pharmacogenomics offers an insurance policy enabling them to retrospectively

The nature of global studies requires sponsors to conduct trials in many different countries. At the same time, safety regulations require the reporting of adverse event data. The challenge is to create a system to mine and analyze the data collectively in the United States and other countries.



DR. MELANIE BRUNO
Kendle

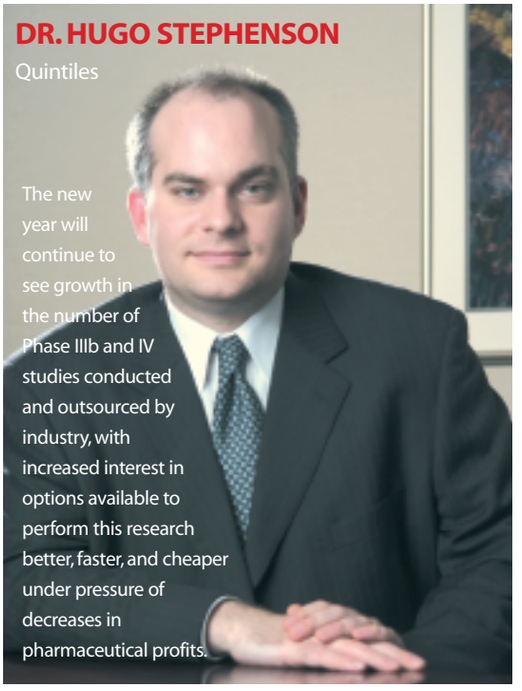
DR. JAY MASON
Covance

In the upcoming year, three dominant forces will reshape cardiac safety surveillance of new drugs and, thus, services offered by core ECG laboratories.

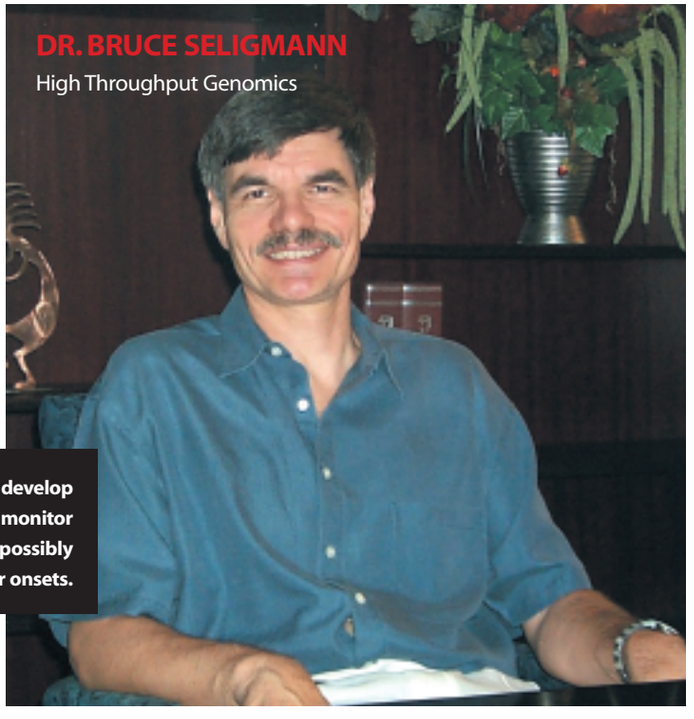
DR. DONNA MENDRICK
Gene Logic

New technologies, such as pharmacogenomics, are beginning to be applied in the drug discovery and development pipeline to determine if a more accurate assessment of patients' responses can be performed before a prescription is written.

DR. HUGO STEPHENSON
Quintiles



The new year will continue to see growth in the number of Phase IIIb and IV studies conducted and outsourced by industry, with increased interest in options available to perform this research better, faster, and cheaper under pressure of decreases in pharmaceutical profits.



DR. BRUCE SELIGMANN
High Throughput Genomics

There is a need in the industry to develop more reliable and precise ways to monitor adverse side effects of drugs and to possibly predict their onsets.

DR. WILLIAM CLAYPOOL
Phoenix Data Systems

One of the most important trends to follow in the coming year will be greater scrutiny over drug safety as exemplified by the Vioxx withdrawal. As a rule, drug testing will take longer and be more costly.

examine trends that have an underlying genetic component. For this to be feasible, they must undertake large-scale DNA banking initiatives so that a sample is taken from each patient enrolled in clinical trials. The challenge inherent in this approach is to educate patients, investigators, and institutional review boards (IRBs) about the value of doing this; it ensures that there is a means to evaluate all possible reasons for why some patients demonstrate safety or tolerance issues while others do not. The public and the regulatory agencies expect pharmaceutical companies to use all means possible to ensure that only drugs that are safe are approved and prescribed. Pharmacogenomics and other post-genomic technologies offer additional tools that can detect inherited predisposition to drug toxicity. These technologies have moved from the research lab into the clinical setting with a number of highly specialized companies offering these services in a regulatory compliant setting so that the data can be integrated into drug submissions much like tradi-

tional safety data, such as therapeutic drug monitoring.

MASON. Three dominant forces will reshape cardiac safety surveillance of new drugs. First, the ICH E-14 QT Guidance is in effect and will reach step 5 (final adaptation by regulatory agencies) early in 2006. The guidance clearly states that nearly all new chemical and biological entities must undergo thorough assessment of their effects on repolarization in humans by means of a definitive QT study (DQTS) in which a large number of ECGs must be recorded in a carefully controlled environment under a complex study design and read by an expert. It is clear that a large number of DQT studies will be performed in the next few years, which will strain pharma budgets and core ECG lab capacity. Second, there is a growing effort to drive down the cost of electrocardiography, especially that mandated by the E-14 Guidance, by reliance on automation of ECG interval measurement. Because of the large number of ECGs processed in a DQTS, it would be advantageous to increase the speed and decrease the cost of QTc measurement. Thus, pharma, ECG core laboratories, and academic investigators are actively pursuing opportunities to accomplish this with both existing and newly developed technology. It is likely that a semi-automated approach will gain the strongest foothold. This strategy relies on being able to separate those ECGs that cannot be accurately measured by a computer algorithm from those that can and directing only the former to an expert human reader. Third, there is a growing recognition that the coronary vascular adverse effects of new agents are at least as important as adverse repolarization effects. Now that it is clear that not only COX-2 inhibitors but other classes of drugs may cause entirely unexpected adverse vascular effects, resulting in coronary, cerebral, and other-organ ischemia and infarction, it is also clear that pharma will be encumbered with the need to clear its pipeline drugs of this adverse effect. Sensitive animal models must be developed to detect this propensity before clinical studies are initiated, and detection of the vascular change itself, or of the resultant ischemia and infarction, must become a routine safety component of Phases I-IV.

CHAN. The FDA and the industry should use a wide array of data resources, including electronic claims databases, to monitor the safety of drugs after they are on the market. Recent contracts announced by the FDA are an important step toward proactive study through high-quality data sources and scientific expertise to monitor drug safety. We have built data systems that can allow users, including the FDA, to quickly evaluate the usage patterns and safety profiles of newly marketed drugs. The major benefit is that this information is available earlier in the postmarketing phase than information generated using more traditional methods for collecting safety information. In turn, this allows informed risk-management decisions to be made on a more timely basis.

SELIGMANN. There is a need in the industry to develop more reliable and precise ways to monitor adverse side effects of drugs and to possibly predict their onsets. Having diagnostic platforms and tests that can provide such warnings, based on biomarker assays, will enable the industry to address the demands of patients and physicians. Currently, the Critical Path Initiative and the pharmacogenomics initiatives of the FDA are helping to achieve these goals. The idea is to develop diagnostic assays to better align patients with drug therapy. This includes patients who will not benefit from drug therapy, are not treated, and therefore avoid drug risks. For those patients who will benefit from therapy, if there is a greater certainty of benefit, then risks may be more acceptable. HTG is developing its multiplexed quantitative Nuclease Protection Assay (qNPA) technology platform as a diagnostic to accurately measure gene-expression changes as biomarkers of efficacy and safety. The assay will enable clinicians to identify the earliest changes before overt toxicity is observed, as well as allow physicians to determine when patients enter a progressive disease path. Identifying the genome of each person may permit those with increased risk of disease to be recognized, but will not identify which patients actually are, or when they begin, developing the disease. When patients begin to develop diseases, it can only be determined by monitoring the biomarkers associated with the actual diseases, such as changes in gene expression, which will be possible using qNPA-based diagnostics.

CLAYPOOL. One of the most important trends to follow in the coming year will be increased scrutiny over drug safety, as exemplified by the Vioxx withdrawal. As an evolving trend, drug testing will take longer and be more costly. Some of our sponsors are telling us that three-year trials may now take six years to complete. Sponsors are increasing the length of trials, particularly Phase III, and are looking for ways to build efficiencies into the process to control costs and end unproductive trials sooner. EDC solutions will play in important role in helping sponsors build efficiencies into the process.

FDA SELECTS I3 APERIO TO MONITOR SAFETY OF NEW DRUGS

The Food and Drug Administration in September 2005 selected i3's Aperio drug registry for postmarketing drug surveillance.

Dr. Terry Madison
i3 Drug Safety

These proactive efforts should enhance the FDA's ability to identify and assess issues and potential risks related to pharmaceutical agents in a more timely fashion than ever before.

i3, an Ingenix company, will work with the FDA to monitor the safety of new drugs, as well as conduct ad hoc safety studies on established pharmaceutical agents.

"These proactive efforts should enhance the FDA's ability to identify and assess issues and potential risks related to pharmaceutical agents in a more timely fashion than ever before," says Terri Madison, Ph.D., MPH, president of i3 Drug Safety, which will lead the program.

I3 Aperio, a drug-registry tool launched in April 2005, allows drug manufacturers and regulators to access data on the safety of newly introduced drugs. The registry pairs i3's technology and scientific expertise with the Ingenix database of de-identified healthcare experience and provides faster access to data.

Through its parent company, Ingenix, i3 has access to longitudinal and integrated prescription, laboratory, and general medical experience from more than 10 million individuals. i3 Aperio offers both quarterly and annual reports of the drugs in the registry.

Source: i3, Basking Ridge, N.J.
For more information, visit i3global.com.

EHLERS. The pharmaceutical industry must continue to encourage transparency of clinical-trial data and to report all clinical-trial data, whether positive or negative. Further, there needs to be a stronger commitment to post-marketing studies to evaluate long-term safety and efficacy and full disclosure of results in a timely fashion. There will be increased regulatory, societal, and interest-group pressure to comply with these requirements. The codevelopment of companion diagnostics will occur with greater frequency, and this is expected to have a material impact on drug safety. Companion diagnostics can identify groups and individuals who will respond to a drug, thereby increasing the success rate of a drug and reducing needless exposure in patients not likely to respond. There also will be the development of biomarkers that can identify subpopulations at increased risk for adverse events, which will further reduce the incidence of adverse events in the general population.

ARNOLD. The industry has learned that even extensive clinical trials cannot replicate the full range of patient circumstances that exist in the world and that rare side effects often surface only after a drug has been launched and used by far greater numbers of patients. Hence, we continue to monitor our medicines extensively after approval and launch, and throughout their time on the market so that we readily become aware of side effects that were not identified during clinical development. AstraZeneca has a comprehensive system for detecting and rapidly evaluating such effects and for taking any action that may be required. Reports of possible side effects are collected from doctors and healthcare professionals, patients or their families, medical and scientific journals, and our own ongoing clinical trials. We maintain a dedicated drug-safety database designed to gather this information centrally for those responsible for drug safety across the organization and for regulatory agencies. Each of our products, whether in development or on the market, has an assigned global drug-safety physician who, supported by a team of drug-safety scientists, is responsible for that product's continuous safety surveillance.

STEPHENSON. The new year will continue to see growth in the number of Phase IIIb and IV studies conducted and outsourced by industry, with increased interest in options available to perform this research better, faster, and cheaper under pressure of decreasing pharmaceutical profits. These studies will be aimed at monitoring safety, such as Phase IV commitment studies and active postmarketing surveillance, but also benefit/risk studies in special populations and clinical settings. Increased investment in the latter studies will help restore prescriber confidence by helping physicians identify patients who are likely to benefit from treatment the most and, in turn, reinforce the concept of calculated risk rather than absolute drug safety. At the same time, facing an ongoing battle against cancer, autoimmune diseases, diabetes, AIDS, and a possible flu pandemic, reg-

FDA PLANS PUBLIC HEARING ON COMMUNICATION OF DRUG SAFETY INFORMATION

In October, the Food and Drug Administration announced that as part of its ongoing effort to continue to improve how it communicates information about the risks and benefits of drugs, the Center for Drug Evaluation and Research (CDER) will convene a public hearing December 7 and 8, 2005, to discuss CDER's current risk communications and outreach strategies.

FDA believes it is critical that risk communication be timely, accurate, and easily accessible, and it must recognize health literacy limitations and include the needs of a multicultural population.

The purpose of the public hearing is to obtain public input on CDER's risk communication tools, identify stakeholders for collaboration and implementation of additional tools, and obtain understanding of the strengths and weaknesses of CDER's existing risk communication.

The Part 15 public hearing will address six questions related to documents currently distributed by the FDA.

The Part 15 public hearing will address six questions related to documents currently distributed by FDA. The questions being posed by FDA will help the agency learn which tools are effective and how these risk communications can be improved. These tools include Patient Information Sheets, Healthcare Professional Information Sheets, Public Health Advisories, Press Releases, the MedWatch Listserv Safety Updates, Patient Safety News, CDER Educational Campaigns, and the CDER Internet site.

Examples of questions that CDER intends to ask include: do these tools provide the right kind and amount of risk and other information that healthcare professionals need to make informed decisions about whether to prescribe drug products, and do these tools provide what the public needs to make informed decisions about whether to use those products?

CURRENT FDA-APPROVED PATIENT LABELING

PATIENT PACKAGE INSERTS

For some prescription medicines, FDA approves special patient materials to instruct patients about the safe use of the product. These materials may be given to patients by their healthcare provider or pharmacist and are considered part of FDA-regulated product labeling.

MEDICATION GUIDES

FDA may require distribution of Medication Guides, FDA-approved patient information for selected prescription drugs that pose a serious and significant public health concern.

MEDICATION GUIDES WILL BE REQUIRED IF THE FDA DETERMINES THAT ONE OR MORE OF THE FOLLOWING CIRCUMSTANCES EXIST:

- **PATIENT LABELING** could help prevent serious adverse effects
- **THE DRUG PRODUCT HAS SERIOUS RISK(S)** (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product
- **THE DRUG PRODUCT** is important to health and patient adherence to directions for use is crucial to the drug's effectiveness

Source: Food and Drug Administration, Rockville, Md.
For more information, visit fda.gov.

ulators and industry are challenged to accelerate patient access to new treatments. And companies are already spending an enormous amount of money on drug development; they don't want to increase costs. Regulators are very aware of this and don't want to add greater complexity and cost to the drug-development process. Many have suggested a conditional approval that would give patients access to new medicines under tightly controlled conditions, allowing the manufacturer to recoup some of the costs of bringing the drug to market while continuing to study the drug for safety.

ARNOLD. Our system helps identify whether particular types of patients may be more susceptible to the risks associated with a particular drug and what the early indicators of this might be, so that side effects can be avoided or minimized in these people. In addition to routine safety reviews, our monitoring system can highlight events that require immediate attention. If information received suggests that there may be an effect upon a medicine's benefit/risk profile, our actions, alongside appropriate discussions with regulatory agencies, can include carrying out further clinical studies, modifying prescribing information, and communicating with healthcare professionals and others who need to know of the change. In certain situations, it may be appropriate to stop an ongoing clinical trial or withdraw a product from the market.

BRUNO. The nature of global studies requires sponsors to conduct trials in many different countries. At the same time, safety regulations require the reporting of adverse event data. The challenge is to create a system to mine and analyze the data collectively in the United States and other countries and to locate relevant safety signals from all the "noise," especially for rare events or events that manifest themselves as common human ailments. In addition, the proactive use of various drug safety review boards, staffed by those without a vested interest in the drugs under review, can lend a level of analysis that benefits sponsors and consumers. Risk-management technology has been used for decades in preclinical studies. The application of these technologies for clinical-trial work brings a level of prethought and analysis to the collected data. Earlier detection of safety issues and understanding any therapeutic limitations of a drug's use are additional benefits that can come from this technology. One of the challenges facing our industry is the inability of the various technologies to work together between countries, allowing us to analyze the data in its entirety. Because there is no common database, reviewing the data with independent systems does not yield consistent results and can miss rare serious safety signals.

▶ REGULATORY

According to some industry estimates, the portion of pharmaceutical and biotechnology IT budgets that are spent on addressing regulatory compliance needs will need to increase by 5% over the next 12 months.

BAKALOV. Respondents to Ernst & Young's (E&Y) recent eighth annual Global Informa-

RECENT DRUG RECALLS LEAVE PHYSICIANS AND CONSUMERS CONCERNED ABOUT PRESCRIPTION DRUG SAFETY

In light of recent prescription drug recalls, physicians and consumers alike are concerned about drug safety.

Physicians agree that more should be done to monitor drugs for side effects after they are approved for market to ensure their safe use, according to the results of a recent study of more than 100 U.S. physicians and 500 U.S. consumers conducted by Accenture.

THE STUDY RESULTS FOUND THAT

▶ **80% OF DOCTORS SAY** more should be done to monitor the safety of prescription drugs after they are on the market.

▶ **TWO-THIRDS (67%) OF DOCTORS** and one-third (32%) of consumers have become more concerned about the safety of prescription medications since the recent removal from the market of the popular COX-2 inhibitor class of pain relievers.

▶ **THE VAST MAJORITY OF PHYSICIANS AND CONSUMERS** (82% and 88%, respectively) believe that more should be done to monitor the safety of drugs after they are on the market.

▶ **EIGHT IN 10 PHYSICIANS (80%)** said regulatory agencies should increase monitoring after drugs are approved for use, and more than three-quarters (77%) said regulatory agencies should improve monitoring feedback capabilities.

▶ **ONLY ONE-THIRD (32%)** of physicians said they were extremely or very confident in the current postmarket monitoring system.

▶ **TWO-THIRDS (66%)** of physicians surveyed said they believe that electronic medical records could help address postmarket drug surveillance. Doctors who participated in the study expressed confidence that new medical information technologies have the potential to help improve the existing system of drug-safety monitoring.

▶ **VIRTUALLY ALL CONSUMERS (93%)** surveyed said they believe that prescription drugs can have a positive impact on their health, and 87% said pharmaceutical companies provide an extremely or very valuable service to society.

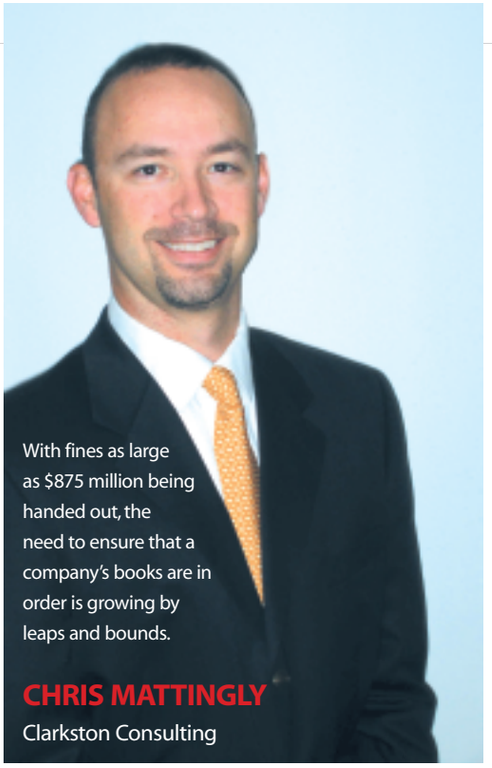
"The positive news here for the pharmaceutical industry is that consumers continue to believe strongly in the value and efficacy of prescription medications," says Philip George, a managing partner in Accenture's Health & Life Sciences practice. "But consumers and physicians expressed a lack of confidence in the postmarket safety monitoring systems currently in place for prescription medications in the United States. It appears that recent high-profile product withdrawals have intensified this concern."

Source: Accenture, New York.
For more information, visit accenture.com.

MICHAEL MURPHY
Gentris

Demonstrating to regulators that companies have sufficiently examined all areas around drug safety will be one of the more challenging issues facing the pharmaceutical industry in 2006.

tion Security Survey indicated that they will support regulatory requirements by creating/updating policies and procedures (100%) and training and awareness (76%). On the other hand, only 12% indicated that they will reorganize the information security function. We are concerned that policies, procedures, and training are not enough to sustain regulatory compliance. Long-term changes, such as reorganization of the information security function, are needed and are more likely to achieve sustainability. Specifically, survey data suggest that one of the areas for improvement is closer alignment of the information security and regulatory compliance functions; 41% of the respondents indicated that these are separate functions. This is an issue for pharma where many of the regulations — 21 CFR Part 11, Annex 11, and so on — are directly related to information security controls. With proper organizational alignment and delivery, information security can make significant contributions to the organization's strategic initiatives and overall risk management. Organizations that employ information security in this way continuously involve business, IT, and information security leaders in identifying specific areas where information security can contribute to strategic initiatives, such as mergers and acquisitions, outsourcing, and product launches. Yet most organizations continue to concentrate their information security activities on operational and tactical issues at the expense of addressing strategic concerns. They are not doing nearly enough to adapt, even though awareness about information security has risen as a critical issue among boards and executive management. For example, 88% of the respondents indicated they are proactively involved in improving IT and operational effectiveness compared with only 12% involved in mergers and acquisitions (69% are not involved in M&A at all). Most would agree that M&A activities are becoming a common practice for pharma to strengthen the product pipeline. Even more surprising is the fact that only 47% indicated that they are proactively involved in protecting intellectual property — a key information asset for any pharma or biotech company — compared with 41% who have no involvement at all and 12% who show reactive involvement. So if information security is not involved in strategic initiatives, how do they spend their time and budget? Survey data indicate 40% of the time is spent on routine operations (38% of budget), 24% of the time on compliance support (28% of budget), and only 18% on strategy.



With fines as large as $875 million being handed out, the need to ensure that a company's books are in order is growing by leaps and bounds.

CHRIS MATTINGLY
Clarkston Consulting

BOLLWAGE. As we enter 2006, the industry faces compliance challenges both new and old. There are several compliance issues that are expected to face industry in the coming years. One is monitoring the safety of newly approved drugs. Recent experience suggests that the close monitoring of newly approved drugs will be critical to achieving compliance with regulatory reporting rules and labeling requirements, as well as to staunch the product liability actions that may ensue when previously unidentified risks become apparent after market introduction. Another issue is compliance with the EU clinical trials directive. While the directive required that EU member states apply CTD provisions locally by May 2004, a number of states have yet to finalize their local regulations, fostering an atmosphere of uncertainty and nonuniformity across states within the EU. In this atmosphere, assuring compliance with all member states requirements and the FDA's standards may continue to prove uncertain. Local representation that monitors CTD implementation plans on the member state level is considered essential. A third issue is informed consent in clinical trials with pharmacogenomic evaluations. Clinical trials that incorporate genomic research must now focus on fulfilling three sets of informed consent requirements: FDA's Protection of Human Subjects (21 CFR 50), The HIPAA Privacy Rule administered by the Office of Civil Rights Protection, and CDC's Informed Consent Template. Three sets of requirements exist, some overlap, some compete, and some may appear contradictory. Numerous questions arise, such as will a single consolidated consent form be required or is it more prudent to have clinical-research subjects sign three separate consent forms covering the provisions of each of the three areas? A fourth issue is Part 11 electronic records and electronic signatures. The FDA issued a Scope and Application Guidance in August 2003 announcing its intention not to pursue enforcement of certain provisions of 21 CFR Part 11. This has afforded industry the ability to rationalize its approach to Part 11 compliance but in an atmosphere of uncertainty and continuing risk. The FDA has promised revisions to Part 11 regulations intended to clarify requirements, which will be welcome. One final concern is the FDA's quality system regulation (QSR) approach to GMP. FDA has announced its intention to expand the use of the QSR approach to GMP regulation beyond the medical-device industry and into the pharmaceutical industry. But as recently as October 21, 2005, the FDA was handed a setback in a decision by a federal judge in Utah that, if sustained on appeal, would undermine the foundation of the FDA's compliance and enforcement posture for medical device GMPs and cast uncertainty on expansion of QSRs to pharmaceuticals.

RICHARDS. It is important that vendors begin to integrate features within their solutions that help companies maintain compliance. Newer solutions will provide the ability to segregate studies to reduce the risk of impacting other studies if something goes wrong within a particular study. Large monolithic systems do little to protect against exposing other studies to compliance issues. In addition, companies will need to invest in solutions that help manage the dynamic nature of processes that become electronic. The management of documents, tasks, communications, and key metrics will become a critical part of addressing regulatory compliance needs.

The continued evolution of regulatory electronic information standards, such as eCTD, SPL/PIM, and CDISC, are offering new ways to gain efficiency through implementation of the accepted standards.

DAVID EVANS

Octagon Research Solutions

Consistent and quality data will improve both FDA and international regulatory submissions and approvals, and a sound strategy can help teams get correct budget approvals and establish benchmarks that will directly impact product life-cycle management.

TRAVIS HOLLINGSWORTH

Clarkston Consulting

EDSTROM. The regulatory environment is constantly changing, so keeping up with the changes and accommodating them in clinical and development plans is costly and staff intensive. This will not change, and as such, a company needs to find ways of accessing that information and incorporating it into its development plans. That's easy to say and hard and expensive to do.

MATTINGLY. Over the past decade, the federal government has imposed more than $2 billion in fines for improprieties, or irregularities, at companies that do business with them. In June 2005, the Office of the Inspector General reported that it has in excess of an additional $2 billion of investigations now under way. With fines as large as $875 million being handed out — individual fine values have increased dramatically over the past decade — the need to ensure that a company's books are in order is growing by leaps and bounds. It is also important to remember that fines are only part of the cost of OIG actions. Most include some kind of Corporate Integrity Agreement (CIA) that can span from revising Standard Operating Procedures (SOPs) to extensive, ongoing educational programs. There is no way to know just how much of an impact these agreements have on a company's bottom line, but it is safe to assume it is considerable and potentially greater than the fine itself over the life of the agreement.

MURPHY. Demonstrating to the regulators that they have sufficiently examined all areas around drug safety will be one of the more challenging issues facing the pharmaceutical industry in 2006. Late-stage drug failures are not only expensive but those that occur post approval such as Vioxx can create major liability cases for pharmaceutical companies. We now know in hindsight that sometimes a rare, life-threatening adverse event can occur unnoticed during drug development and before market approval. During development, these new compounds may be tested in only hundreds or thousands of patients leading up to the regulatory submission. Significant adverse events may only come to light after the drug is approved when hundreds of thousands or millions of patients start receiving treatment. Drug companies can enhance their postmarket surveillance by not only tracking adverse events but also by using new technologies that can demonstrate that the cause of these reactions to new drugs have an underlying genetic component.

EVANS. A recent study from Tufts indicates that clinical trials supporting the approval process are taking longer. This information, combined with the fact that R&D expenditures are outpacing approval rates, is weighing heavy on R&D organizations. But the continued evolution of regulatory electronic information standards, such as eCTD, SPL/PIM, and CDISC, are offering new ways to gain efficiency through implementation of the accepted standards. Some may see these standards as an additional cost of business, when in fact they offer a unique opportunity to intelligently redesign processes and information systems. The optimization of processes and systems can only begin with the adoption of industrywide electronic information standards, especially those that are necessary for electronic submission of information to the regulatory agencies. While information exchange standards serve as the foundational-level element, the nomenclature and content layer standards enable increased knowledge transfer capability across studies, compounds, departments, partners, organizations, and regulatory authorities. When the standards are successfully implemented, recurring efficiencies are captured across the organization, thus decreasing costs, increasing productivity, and shortening the time to market of new therapies. These unique market forces are driving companies to look at internal processes more closely to identify areas for improvement. An intelligent design approach to rethinking legacy practices, processes, and systems will provide an optimization of the methodology and science of clinical-research information collection, processing, reporting, and analysis. Companies are going to be scrutinizing internal processes and information systems, as well as partner offerings, to identify ways to shorten the overall time to market through effective partnerships and collaboration. Additionally, competitive organizations will begin to combine creative multisourcing strategies with innovative information technologies to support this goal. This is all possible now, but only if we all speak and embrace the same common language of information processing standards.

HOLLINGSWORTH. The formation of a unified data-management team will analyze the company's needs, review current processes, and define project goals with a risk-based approach often used for other regulatory systems. Consistent and quality data will improve both FDA and international regulatory submissions and approvals, and a sound strategy can help teams get correct budget approvals and establish benchmarks that will directly impact product life-cycle management.

PHILLIPS. Patient-assistance programs, research projects, and the device industry will all come under close scrutiny from the oversight agencies, especially the Office of Inspector General of the Department of Health and Human Services. States' attorneys general will become very focused on kickback and fraud issues driven by the legislative actions of state governments. All in all, the compliance pressures on our industry will continue to increase.