CRO Outlook & Market Trends

Innovation tied to globalization & collaboration

Photo courtesy of PPD

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As drug developers face intensifying pressure from generic drug firms, patent expirations, and increased scrutiny from the FDA, efficiency is more important than ever. The pharma and biopharma industry no longer approaches drug development alone, and after years of reduced R&D spending, numbers are on the rise. These dollars are increasingly being allocated to CROs. In their 2013 R&D Funding Forecast, R&D organization Battelle and *R&D Magazine* project that U.S. life science companies will increase R&D spending from $181.6 billion in 2012 to $189.3 billion in 2013.

Innovation efforts are increasingly tied to globalization and collaborative research. Efforts to advance drug development have greatly increased the frequency and value of strategic partnerships. Also, a careful combination of site-based quality, performance, and global distribution is driving efforts to impede escalating clinical costs and complexities. Additionally, the latest technology trends include more efficient methods of study execution and site selection to advance clinical development.

Among the latest industry trends: adaptive trial designs dominate development programs and healthcare reform is bolstering outcomes research activities; despite recent regulatory initiatives, biosimilar development for the U.S. market draws concerns; and on the global front, we're seeing major shifts as once burgeoning markets take a back seat while others rally.

Services, Markets & Trends

Increased outsourcing to CROs runs the gamut from small to large pharma and biopharma, and early to late-stage development. CROs are seeing continued growth in several service areas, such as adaptive trials and programs for personalized medicine and orphan drugs. Also, with major shifts in healthcare systems taking place as part of an effort to real in healthcare costs, a growing number of Phase III trials now include economic endpoints and conducting analyses alongside clinical studies with the goal of demonstrating cost effectiveness. As such, services for outcomes research and comparative effectiveness research (CER) have intensified.

According to Alistair Macdonald, chief operating officer, INC Research, "We are seeing a lot of growth in the rare disease and orphan spaces. Customers are looking to push the frontiers in these sectors and we see growth in them all. In dollar terms, the major growth is coming from the later stage development areas and post-approval commitments. The largest segment of our business is the mid-sized and large pharma/biopharma, but we do continue to see a great deal of business in biotech and small pharma. We are encouraged that the size of opportunities continues to grow as we ourselves grow. It's great for our teams to see a variety of studies in

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terms of shape, size and customer, and we enjoy strong relationships across a broad spectrum."

John Watson, corporate senior vice president; president, Strategic Partnering and chief commercial officer, Covance, said, "Covance is seeing growth in both early and late-stage development. Late-stage leans more heavily toward larger pharma, whereas mid-size and smaller companies are more focused on discovery. In late-stage we are seeing growth in both our central labs and clinical services, while increases in biomarkers and genomics are a by-product of a surge in discovery. Also, with commercial viability being the single biggest reason for a new drug's failure, there's definitely growth in HEOR (health economics outcomes research) as more and more clients pull market access economics earlier into their development process."

CROs are also forging partnerships to enhance capabilities in these burgeoning service areas. "One area of increasing growth is in adaptive trial design," said PPD's Niklas Morton, vice president of Global Biostatistics, Programming and Medical Writing. "Adaptive trials can help provide a better understanding of the treatment effect and dose response profile within Phase II (which subsequently should increase the probability of a successful
Phase III trial), but also can facilitate stopping an ineffective compound earlier within a Phase III trial. PPD has partnered with Berry Consultants to give clients access to an unprecedented level of knowledge on adaptive trial design and execution. PPD's license agreement to use Tessella and Berry Consultants' FACTS software tool expands our adaptive design capabilities by giving clients greater ability to use extensive simulations to investigate various study design options, which helps generate richer designs so clients can make better informed decisions about their trials."

Healthcare reform is also having a huge impact on the pharma/biopharma industry. HEOR has become an integral part of R&D, which has greatly increased demand for CRO services. John Doyle, vice president and practice leader of Consulting at Quintiles, said, "Helping
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companies improve population health and outcomes is an important trend. Payers and regulators are demanding a more integrated approach to drug development to achieve better patient outcomes. Payers also want demonstrable results. This will require pharma companies to work closely with regulators, payers and providers to design a model: a systems approach to drug development. The only way biopharma companies can improve patient outcomes — and validate the relevance of their products — is to focus on them from the outset of the development process, and view each decision through this lens. Biopharma companies recognize that they have engineered all the incremental value from the current development model and it now needs to transform to a systems thinking, value-driven industry."

So, do the objectives of outcomes research and CER programs conflict with incentives for R&D of innovative medicines? Do these aspects of healthcare reform impact sponsor portfolios and the drugs they develop? According to Neil Hawkins, vice president of Health Economics at ICON, said, "There are potential conflicts arising due to differing evidential requirements between the regulatory and reimbursement agencies. These conflicts are likely to become more pronounced both as the FDA tries to expedite the development of treatments for serious diseases with unmet need through its fast-track and accelerated approval processes, and reimbursement authorities attempt to target therapies to particular groups of patients based on estimates of effectiveness for subsets of patients within trials. The resolution of these conflicts will require careful consideration of the whole of the approval and reimbursement lifecycle by manufacturers and discussion between regulatory and reimbursement agencies regarding the interdependencies of their respective processes." Regardless of what the future R&D paradigm holds, CROs should continue to see growth in outcomes research as sponsors seek the value these services provide.

Regulatory Initiatives

Biosimilar development has been a significant growth area for CROs, however, the uncertainty around biosimilars regulation in the U.S. is holding back progress. Two main factors being considered by industry are development costs and interchangeability provisions associated with marketing a biosimilar product in the U.S.

Although the FDA published guidelines on biosimilar development in 2012, the need for a well-defined development process, beginning with characterization and then comparison to the attributes of the reference product, is crucial. Robert Wojciechowski, associate director of Regulatory Strategy at INC Research, said, "Even with the guidance, the amount of preclinical and clinical data needed for each application is not specifically spelled out. At this time, it's likely the FDA would require that a new biosimilar, even if it's a comparable product for the same indication, submit more preclinical and clinical data than is currently required in the EU. This would have to be done to address more thoroughly the similarity in safety and efficacy between the biosimilar and reference product. Unlike the EU and much of the rest of the world, the FDA does not take into account the cost of development. As a result, the current cost of developing a biosimilar in the U.S. is likely to be significantly higher than that of developing biosimilars in other regions."

"Early and follow-on consultations with the FDA are essential to establish the extent of the clinical comparator trial(s) required with the originator interchangeability of the biosimilar at approval," added Mr. Wojciechowski. "Considering the current basis for reimbursement in the U.S., the potential for not receiving automatic interchangeability designation may have a significant impact on commercial success in the market."

Tim Clark, vice president of Scientific Affairs at ICON, stated, "Uncertainty in the U.S., but also in emerging markets, is impacting the ability of companies to conduct global biosimilar development programs. For time, cost and ethical reasons, biosimilar developers want to run a single Phase III trial. However, it's not unusual for a study design that has been agreed with the European Medicines Agency (EMA) to be tweaked by the FDA, to the extent that a single trial is no longer possible. Developers are then faced with the decision to con-

duct separate studies with all the associated cost, time, and feasibility challenges, or make a choice between the U.S. and EU for the initial approvals. Some firms have already hit development difficulties with reports speculating that these delays are due to FDA trying to work out a route to interchangeable biosimilars. This uncertainty is being further confounded by the enactment of state legislation requiring doctors and pharmacies to clear additional hurdles before substituting an approved biosimilar for the original drug. Emerging markets can muddy the waters even further, with India, for example, largely following the EMA, but requiring local trials."

Even with the draft guidance for biosimilar development, the agency has not received any biosimilar applications to date. According to Deepa Dahal, MBA, principal consultant, Commercial Strategy, Biosimilar Intelligence Team, Quintiles, "Possible explanations for this could be that companies are still using other pathways for their products, e.g., 351(a) or 505(b)(2) or they have modified/streamlined their clinical development plans based on the new biosimilar guidelines. The recent suspension/delay of several rituximab biosimilar programs by Teva, Samsung, and Celltrion may be due to rethinking of the regulatory strategy moving forward or as a result of partnership agreements, as well as regulatory uncertainties." While these issues will be resolved in time, at the moment, a level of uncertainty and inaction remains.

Globalization & Market Shifts

Conducting trials in global markets is a necessary and rapidly expanding pursuit. However, favorability of newly established and emerging markets has shifted. For example, CROs are seeing a drop-off in India and somewhat improved conditions in China. Also, Japan has seen an uptick in CRO services this past year as a result of a shortened regulatory applications process.

R&D is on the rise, especially in China, where Novartis plans to invest $1 billion during the next five years and has invested $250 million in a new global technical center in Changshu. Covidien spent $45 million on a new R&D facility, and Johnson & Johnson and Medtronic opened innovation centers. The challenges associated with conducting clinical trials in China are, to some extent, abating. The opportunities for outsourcing R&D in China are starting to outweigh the constraints of slower regulatory review and quality concerns. While China provides many opportunities, the Association of Clinical Research Organizations (ACRO), continues to work with the government to provide shorter and more predictable timelines for clinical trial approvals.

According to Rick Cimino, executive vice president and group president of Clinical Development Services at Covance, "China sites and investigators are becoming increasingly more experienced in doing global clinical trials and meeting global quality requirements. Large global pharma companies that have set up large R&D centers in China (i.e., Bayer, AstraZeneca, GlaxoSmithKline, Roche, etc.) are outsourcing R&D in China, creating new opportunities for global CROs. R&D expenditure in China is growing at a much faster rate, driven by new products and new clients. In addition, more and more Chinese companies are increasing their R&D investment as they move from generic manufacturers to innovative R&D companies, targeting both China and global markets for their innovative products. We have an increasing number of Chinese companies in our service portfolio and we expect this trend to continue."

On the other hand, there's a paradigm shift where India is concerned. Garth Tierney, executive vice president, Asia Pacific at INC Research said, "India's Central Drugs Standard Control Organization (CDSCO) has approved less than 20 clinical trials to date in 2013, a small number compared to last year's 262 and 2010's peak of approximately 500. This sluggish start is in many ways caused by sponsors and CROs playing catch-up on new regulatory requirements. This will continue to evolve and is expected to improve once organizations have a clearer understanding of tighter regulations. This environment highlights how crucial it is to have local experts within an outsourcing partner who understand local and regional regulatory processes." For more, see this issue's India Report.

The reasons behind the significant drop off are equally substantial. According to John J. Lewis, vice president of Public Affairs, ACRO, "India is currently a very challenging environment for clinical research. The regulatory climate is very uncertain. There a few or no new trials being approved and the recent regulations surrounding compensation for clinical trial participants injured during a trial are very troubling. Unfortunately, the whole area of clinical research has become a political issue and the media is helping to fuel the fire. And there are significant issues around intellectual property protection and compulsory licensing that make sponsors wary of operating in the country. ACRO is continuing to work through the regulatory process and interacting with the Ministry of Health, but the short-term outlook is not good and interest in conducting clinical research in India is waning. This not only has an impact on the placement of global studies but also severely limits India's ability to become an innovator in the biopharma area, one of its stated goals." While hopeful the situation will improve over the next year or so, clinical activity remains stagnant.

Thanks to a sluggish and costly approvals process, Japan was hardly a hotbed of clinical research activity. However, increased interest and growth in Japan is attributed to recent advances in timeframes. Ken Faulkner, Ph.D., PAREXEL's corporate vice president of Medical Imaging, said, "Overall, there is a heavy emphasis on the entire Asian market. In Japan, the Ministry of Health, Labor and Welfare (MHLW) has made significant changes in recent years addressing the downward trend in new drug applications due to the lengthy and expensive processes for clinical studies and approvals, and shortening a lag in the availability of drugs compared to other developed countries. Currently, there is not a pharma/biopharma company with products on the market that is not trying to establish a foothold in Asia due to the region's rapid growth and expansion." During the past few years, PAREXEL expanded to four offices in Japan, including two in Tokyo, to further assist locally based clients with regional and global market access opportunities.

The pharmaceutical industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA), noted that Japan might be one of the world's best markets right now for foreign drug companies. Ray Hill, president, of inVentiv Health

Clinical Japan, has been experiencing what PhRMA has referred to as 'emerging market' growth rates, with sales growth in 2011 for the top eight multinational drug firms in Japan ranging from 12% to 31%. Additionally, the Pharmaceutical and Medical Device Agency (PMDA), which oversees the approval process for Japan's Health Ministry, has reduced review times over the last five years and increased the number of new drug approvals. Mr. Hill said, "inVentiv has had a long-standing presence in Japan and has worked on numerous programs including both local studies and global programs within Japan." In April 2013 inVentiv entered a strategic alliance with Bell Medical Solutions, one of Japan's top CROs, to offer comprehensive global drug development services to Japanese and international clients conducting studies in Japan.

Integrated Partnerships

Within the CRO landscape, the value of strategic partnerships has grown tremendously. We continue to see more multi-year, highly-integrated engagements between pharma/biopharma companies and CROs aimed at advancing clinical development programs by creating efficiencies, reducing the sponsor's level of oversight, decreasing costs, and providing access to highly specific capabilities. Notably, Quintiles and Merck Serono recently partnered to integrate their respective expertise with the goal of optimizing productivity in the design and execution of studies. Quintiles serves as sole primary provider of Merck Serono's outsourced clinical development services for its global programs, while Merck Serono gains expanded global reach to implement development programs around the world.

The latest partnerships are evolving to increasingly incorporate alignment in commercial incentives, deeper collaboration, and greater utilization of targeted expertise. Within the past year for example, Quintiles entered two long-term, strategic commercialization pacts, one with Sinclair IS Pharma to commercialize a portfolio of dermo-cosmetic products and medical devices in Mexico, and one with Almirall to promote Almirall's respiratory portfolio in the UK. These strategic partnerships deepen the relationship between the organizations and in this case, Quintiles conducts part of the clinical program and provides commercialization services to help navigate the complexities certain markets present.

According to Mr. Watson at Covance, "Maturing our partnerships is the focus of a lot of our activity now. Confidence and trust established in the early stages of a relationship lay the groundwork for a longer-term strategic partnership. With outsourcing being an increasingly proven approach to R&D, more clients are looking for an integrated solution. They're asking us to do more, looking for a partner to help with molecule selection to proof-of-concept, and proof-of-concept to NDA. Some want to test new models before they're required to do so by regulatory agencies. They're expecting more innovation in solving today's challenges and more tangible insights to prepare for future unknowns."

During these uncertain times in the pharma industry, the importance of CROs and the role they play has grown. This successful segment stays attune to the needs of its clients, evolving to incorporate flexibility and productivity at various levels to address ever increasing drug development cost and complexities. Joshua Schultz, corporate vice president of Strategic Partnerships at PAREXEL, said, "Over the past five years, a wave of strategic partnerships between large pharma companies and CROs has occurred, driving flexibility, reducing costs and optimizing expertise. These partnerships demonstrate improved efficiencies, decrease internal oversight, accelerate cycle times and provide access to global patient populations. In fully established strategic partnerships, speed-to-market can be accelerated by months and cost efficiencies can reach 25- to-30%, relative to transactional outsourcing."

In April 2013, PAREXEL issued a detailed Strategic Partnerships 2013 report that highlights the growing trend of biopharmaceutical companies engaging in strategic partnerships with CROs. The report found that 85% of executives interviewed believe that strategic partnerships improve the relationship between their companies and CROs. Participants in the study represent companies with 39% of industry R&D spend.

Overcoming Obstacles

Among the important ways CROs overcome the challenges and stay profitable with complex protocols and clinical trial budgeting trends, invariably incorporates identifying efficiencies based on site performance and utilizing eClincial technologies that provide near-immediate access to data.

An anticipated near-term trend is that, in an effort to simplify clinical trial complexity, sponsors and CROs will scale back the number of investigative sites they operate and the number of countries where they locate their trials. According to Alistair Macdonald, chief operating officer, INC Research, said, "Taking studies to fewer countries helps to reduce the costs of setting up and starting a trial, and we are seeing customers look more closely at this option. Our approach is to identify upfront sites that are not likely to perform well on a particular study for any number of reasons, and eliminate them from consideration. The key to strong site performance is to actively work with sites through the startup process and provide ongoing support once the site is open for enrollment. Maximizing the sites' contributions enables us to go to fewer sites on many occasions, which has the same impact as reducing the number of countries."

While the trend to reduce the number of sites is evident among top CROs, conducting trials in key global markets remains important for product development and market opportunities. Rick Cimino at Covance said, "In the near term, simplifying clinical trials is a goal; however, the concept of simplification is a complex combination of key site attributes. An overriding trend we see is a reduction of sites; however, this reduction is based on the identification of sites that have a strong history of high quality execution, strong enrollment performance results with timely delivery of those results. With those parameters in mind, fewer sites qualify in this environment and the identification of those sites is of core interest to sponsors. From the cost perspective, sites that deliver high quality and performance keep development costs in line with projections.

"We do not see an overall reduction in number of coun-

tries, rather a trend toward emerging countries outside of the traditional markets. Sponsors are quite clear that it is a combination of site-based quality, performance and global distribution that drives their outsourcing expectations projections," added Mr. Cimino.

A key aspect of site performance lies in enhanced clinical trial designs, data availability, and therefore, the technology employed. "The selection and application of the right technologies is critical to achieving large efficiency gains," noted Mr. Macdonald. "We work with customers from protocol inception to writing the clinical study report and have implemented and deployed processes that help to systematically remove waste from a trial. We aim to optimize the protocol and reduce unnecessary procedures, thereby reducing the burden on the patient and the site coordinator. Building this type of working relationship can create an environment around a trial that helps sites maximize return on a particular trial."

E-clinical Endeavors

According to a recent study by Tufts Center for the Study of Drug Development, contract support and technical service providers are expected to play a growing role in drug development. The value of e-clinical solutions has increased over the years as advances in technology soar. Gaining realtime insight into operational and functional study aspects across an organization continues to expand.

According to Niklas Morton, vice president, Global Biostatistics, Programming and Medical Writing at PPD, "Capturing, sorting, mining and utilizing data across multiple levels of clinical research — in real time — is at the forefront of technology trends. The growing use of realtime data is shaping how the industry moves forward to meet the healthcare needs and challenges of our time. Ongoing access to scientific and operational data helps biopharma companies address issues quickly and efficiently to potentially make faster strategic and tactical decisions about their studies. As the industry trends toward adaptive trial designs, real-time data and analysis capabilities are vital to successful execution of these trials."

Among the latest e-clinical solutions is moving research networks to R&D cloud platforms. While these externalized networks pose security concerns for some, the data efficiencies they create are undisputed. "Cloud is a consistent trend that is making an impact on both on the data collection side of trials and the accompanying ecosystem of tools. Cloud software will become the most prominent software deployment strategy in all enterprises, including life sciences," said Rick Morrison, chief executive officer of Medidata. "There are security concerns with any cloud-based process, but often these are overblown. When moving research networks, the companies that are running the cloud can take advantage of significant economies of scale, including security and redundancy. Cloud networks typically require no upfront capital expense, which allows sponsors and other customers to simply pay for what they use — nothing more, nothing less."

"We are increasingly seeing the implementation of a cloud-based solution in which data can be transferred more rapidly, so that INC and its customers can make better-informed decisions faster and run leaner trials," said Mr. Macdonald at INC Research. "This move has already started to take place as companies realize it's no longer necessary for all of their data to reside inside their firewall. While it's certainly necessary to create a plan and understand the risks before moving data to the cloud, most companies seem to have a greater level of comfort in utilizing a cloud platform today because they're very secure. Knowing how quickly you can recover from data loss used to be a major concern, but the cloud has proven to be very robust over the last few years."

Before reaping all the benefits of the R&D cloud, the challenge of connecting all of the various technology pieces more seamlessly, remains. "Moving to an externalized network is the easy part, but you need to have a data management system in place that enables you to take the information you've created and use it in a meaningful way. This can be done more easily if you take steps to integrate your systems and tools more closely with proven processes," noted Mr. Macdonald.

Additionally, mobile devices play an increasing role in clinical trials. Beyond real-time data collection, they offer a myriad of benefits that can create efficiencies in various aspects of clinical trials and processes. According to Dr. Gareth Milborrow, director of Informatics at ICON, "Mobile is definitely starting to become a feature in clinical trials. We see iPads surfacing as the latest way to gather realtime data from the bedside, eliminating the paper trail, and I expect that they will prove especially useful for eConsent in the coming months and years. Mobile apps are starting to mature into truly useful tools to keep track of your trials (live recruitment data) and as a tool for simple actions, for example, approving documents, tracking study finances and other exciting features to make the life of a CRA simple. Initial forays into this space are likely to be a little over-ambitious with higher than realistic expectations, but as the market settles, we will see the functionalities become more device-appropriate and functional. Looking to the future, I expect to see more connectivity between clinical devices and data capture, possibly via mobile devices or directly through GSM networks."

Technology plays an increasingly important role amidst efforts to identify and address root causes of R&D inefficiency. The latest e-clinical solutions create a new working environment that enables real-time routing of processes and seamless data transfer in the cloud across externalized research networks.

As CROs continue to capture a larger share in R&D spend, sponsors seek the ability to obtain comprehensive services from target identification through to commercialization in their efforts to maximize their portfolios. Creating efficiencies and improving quality through partnerships with experienced CROs continues to lead efforts to overcome the inadequacies of innovation. ■