BY DENISE MYSHKO

GLOBAL DEVELOPMENT

Drug developers are looking to emerging markets and increasing their outsourcing efforts as ways to access expertise and reach.

Pharmaceutical companies will continue to globalize their preclinical and clinical development activities to increase speed-to-market and expand their presence in emerging markets.

Within three years, major sponsors project that up to 65% of FDA-regulated clinical trials will be conducted outside of the United States; Central and Eastern Europe, Latin America, India, and Asia will be the primary new areas, according to the Tufts Center for the Study of Drug Development. This change is due to economic advantages and ready access to well-trained physicians and large numbers of treatment-naive patients.

"This is a paradigm shift for a lot of companies," says Brad Thompson, Ph.D., chairman, president, and CEO of Oncolytics Biotech. "Companies are starting to look at other jurisdictions to generate clinical data for use in their own markets. But they shouldn't miss the greater opportunity, which is the emerging markets themselves. Companies should evaluate these countries independently from the rest of the world."

Emerging markets are expected to account for huge numbers of pharmaceutical products, which may partially offset the tightening markets in traditional payee locations, says Graham Bunn, VP of global partnerships and alliances at Medidata Solutions Worldwide.

"Conducting more trials locally provides additional exposure and assistance to regional salesforces, which can help enhance sales penetration," he says. "Because effective systems now exist for data collection and reporting within emerging markets, the paramount challenges are now ensuring adherence to regulatory requirements and maintaining patient safety. Evidence suggests that major pharma companies are well aware of this and are developing strategies to sell and market more effectively in these locations."

The main challenges, Mr. Bunn says, lie in providing adequate patient and investigator populations, which will allow for the increase in trial numbers that will be required to produce a larger number of approved entities.

"Drug development requires intellectual capital and willing clinical sites and patients, all available at a cost that can be managed within pressured clinical-development budgets," Mr. Bunn says. "Favorable sites will increasingly be located in major population centers with middle-class populations that are demanding increased access to healthcare and to drug trials, as well as those that have adequate infrastructures to support clinical care. India, China, Southeast Asia, and Latin America have significant opportunities to develop clinical-research capabilities."

TOMÁS BOCANEGRA • *Daiichi Sankyo*

CROs can be a lifeline for drug developers, and it's important to view them as an extension of one's own organization, with shared goals and objectives.

OPPORTUNITIES IN EMERGING MARKETS

Industry leaders say the emerging markets offer many opportunities for pharmaceutical developers. According to analysts at PricewaterhouseCoopers, China and India will spearhead growth in the Asian pharmaceutical sector. While the trio of China, India, and Singapore will maintain their positions as the hot spots of the Asian pharmaceutical sector, other territories, notably Korea and Taiwan, will also become more significant players.

Cheaper labor costs and other lower overhead costs, such as property costs, remain key factors. Clinical trials are estimated to be as much as 50% less expensive in India, for example, compared with the United States. Locating clinical trials in lower-cost territories such as China and India can potentially save up to 60% on costs and reduce patient enrollment time by as much as 30%, according to PWC analysts.

Derek Winstanly, MBChB, executive VP, strategic business part-

DR. BRAD THOMPSON ● *Oncolytics Biotech*

Companies are starting to look at other jurisdictions to generate clinical data for use in their own markets.

DR. JEAN-JACQUES GARAUD ● *Roche*

In the early stages of drug development, it's important to consider emerging countries, so they are fully integrated into the global plan. This way, there are no delays in filing dossiers or receiving regulatory approval.

nerships, at Quintiles Transnational, says all developing countries with the resources and interest to improve healthcare for their citizens present opportunities.

"China and India, with a combined population of 2.5 billion, represent enormous opportunities," he says. "Large swaths of Asia, Eastern Europe, and Latin America contain emerging markets with tremendous unmet medical needs and a growing healthcare infrastructure. Ultimately, Africa also will present opportunities."

Dr. Winstanly says these regions pose opportunities, including greater efficiency and faster cycle times; the study and development of treatments and vaccines for diseases of the developing world, including tuberculosis, malaria, and HIV/AIDS. Conducting trials in these countries brings more therapeutic options and a higher standard of healthcare to these countries.

Emerging markets in Asia, including China, Korea, and India, offer great opportunities for translational science as well as clinical studies, says Patrick Keohane, MB BS MRCP, VP, R&D Asia Pacific and Japan, at AstraZeneca.

"Government investment in high-quality research facilities and staff make Korea attractive to innovation-led companies," he says. "India provides many outsourcing and service opportunities and quality delivery of clinical trials. China's expansion of hospital facilities and enthusiastic investigators make clinical trials easier to deliver."

He says the emerging markets offer access to enthusiastic investigators and cost-effective and faster patient recruitment.

"Major opportunities exist to work with world-class Asian KOLs and PIs and to study medical responses to diseases more common in Asia, working with experts in the field," Dr. Keohane says. "Disease expression differs in Asia compared with the west, i.e., liver cancer, and Asian populations may differ in therapeutic response, for example the EGFR inhibitor in lung cancer. Experience levels, infrastructure, and historical quality have been variable and staff turnover can be higher. Regulatory environments can influence the ability to start studies. For example, it is normal to wait one year for clinical trial approval in China."

Dr. Keohane says investing and working directly with local experts is important. For example, in 2007 AstraZeneca established the Innovation Center China (ICC) to build in-house research capabilities, to collaborate with external expert partners in several countries, and to develop medicines for unmet medical needs in Asia earlier.

LOCATING CLINICAL TRIALS IN LOWER-COST TERRITORIES SUCH AS CHINA AND INDIA CAN POTENTIALLY SAVE UP TO 60% ON COSTS AND REDUCE PATIENT ENROLLMENT TIME BY AS MUCH AS 30%.

PRICEWATERHOUSECOOPERS

Vijai Kumar, M.D., president and chief medical officer of Excel Life Sciences, says emerging markets also provide biopharmaceutical companies with access to markets where, in the case of India and China, there are rapidly growing middle and upper classes who are demanding access to the latest and most effective health treatments.

"Companies placing trials in these markets become familiar with the regulatory environment, develop relationships with thought leaders and other potential prescribers of their drugs, and begin to learn the cultural and social intricacies of operating in the environment," he says. "In addition, it is quickly becoming known that these markets have a wealth of highly educated, English-speaking, tech-savvy, and enthusiastic investigators who often studied abroad and who are hungry to grow their credentials through participating in global clinical research studies."

Dr. Kumar says during the past five to six years, India has seen massive growth in its healthcare delivery services.

"A number of world-class hospitals across the country have been established or are expanding rapidly," he says. "They deliver quality healthcare via their experienced physicians, and they are managed by professional managers. These hospitals are amenable to conducting global research projects and are even willing to set up separate clinical-research units."

Companies, however, need to be aware of the challenges of conducting studies in emerging areas.

"Emerging countries, without question, have a role to play in advancing miracles to market," says Larry Meinert, M.D., senior VP, medical and scientific affairs, clinical development services, Covance. "While our investment to leverage emerging countries in a well-balanced manner speaks to our commitment to truly global clinical development, any solution to complex challenges that is touted as a panacea for what ails the clinical research industry is likely to be overstated — and eventually lead to a backlash."

Dr. Kumar says while there is a large number of well-educated

DR. RAYMOND PANAS ● *Sucampo Pharmaceuticals*

As technology creates better systems, this may improve the ability for companies to interact directly with services that have been outsourced, creating new options for the virtual company.

and experienced physicians, their patient loads may prevent them from dedicating the required time for clinical research.

"Such physicians need the help of dedicated clinical research coordinators who understand the rigorous and ethical standards required for GCP-standard clinical research," he says. "Also, large patient pools do not necessary correlate to high patient enrollment numbers for a trial. There has to be a very conscious and well-coordinated effort to research the patient pools and ensure ethical enrollment of patients in the study."

Experts also say some regions may lack trained and experienced clinical-research professionals to support the rapidly growing number of studies.

"By doing some initial background research, these emerging markets can be a valuable place for clinical development," says Raymond Panas, Ph.D., director of international clinical development, Sucampo Pharmaceuticals. "Working with regulatory officials in the planning process can minimize some bureaucratic pitfalls for the conduct of the trial. Using local medical experts during the protocol development can help address variations in healthcare practices. Working with knowledgeable CROs or other technical experts can further improve the conduct of a study when internal expertise is unavailable. Just as one would create a plan for conducting a study in the United States, Europe, or other traditional regions, a similar plan needs to be created for the emerging regions."

Dr. Kumar says operating successfully in emerging markets is as much about planning as it is execution.

TOP CHALLENGES AND OPPORTUNITIES RELATED TO GLOBAL DRUG DEVELOPMENT

DEB BREWER
Senior VP of Global Business Development
Omnicare Clinical Research

Today's sponsors are leveraging a CRO's flexibility to fit their organizations' individual needs. Whether a sponsor's strategy is to outsource all clinical development services, supplement their own in-house expertise, or perhaps even bring a CRO's professionals on-site for a particular assignment, the key is finding a trusted partner that can provide the right balance at the right time.

KATHLEEN DRENNAN
Senior VP, Director Global Business Development
Iris Global Clinical Trial Solutions

As there are more patients who are on lifesaving or chronic-disease therapies, the pool for study volunteers will continuously diminish in size. As genomics take hold in clinical trials, matching potential study volunteers with the needs of given protocol inclusion/exclusion requirements will only increase the difficulty in identifying appropriate volunteers and make patient recruitment more expensive and possibly cost-prohibitive. Until CROs and study sponsors leave behind the one-size-fits-all mentality in their approach to patient recruitment, they will continually end up with rescue studies. As studies become more patient targeted, the approach to trial participation will need to be more strategic.

The clinical-trial industry has to face the reality that good, experienced, and performance-oriented investigative sites are dwindling, and the competition to get their individual studies completed is increasing.

The average experienced site may well have 10 or more competitive studies going on with different study sponsors all looking for the same patient. The ability of the study sponsor to train sites and pay more for their studies will have a direct effect on performance of their clinical studies.

JAN WILLEM ELEVELD
VP, Consulting and Services, Asia Pacific
IMS Health

China and India are the most promising markets for drug development. Not only do these markets have a fast set of treatment-naive patients, they also have a large pool of talented scientists. In addition, the governments are favorable toward stimulating a home-grown drug development industry. Additionally, Korea is a strong candidate that has developed a particular skill in the area of stem-cell research.

Key opportunities are both commercial and scientific and are largely related to the epidemiology and demographics of China and India. Challenges are mainly related to infrastructure development, bureaucracy, and organizational challenges related to the readiness of rapidly growing organizations.

MARK GIANFORCARO
Chief Marketing Officer
i3

Seventy percent of all trials miss their timelines, mainly because of site contracting and selecting sites that do not have the number of optimal patients. Next-generation technology can help sponsors find sites and patients that best match protocol criteria for studies in all phases and for all indications. This technology can also help determine protocol feasibility and the likelihood of successful patient recruitment.

TAMMY ICE
Director, Patient Recruitment and Investigator Services
INC Research

Three best practices that are often overlooked in patient recruitment for

DR. MARK GOLDBERG ●
Parexel

An integrated set of technologies shared by partners across geographies, can provide better information and visibility into how a trial is progressing.

"For example, one of the most important aspects of successful clinical research in India is the study feasibility process," he says. "To understand which studies will enroll well in India, disease prevalence rates need to be understood. Unfortunately, India does not currently produce wide-ranging information via government or industry organizations that will provide an accurate assessment of disease prevalence and incidence. Instead, a more classic feasibility study must be conducted directly through the investigative sites."

He says many factors, including the newness of some sites, cultural customs, and the business and variability of daily life at Indian health centers require the feasibility questionnaire to be distributed in person and information gathered through an interview rather than simply sending a form via fax or e-mail.

"Using an organization with personnel across the country and with good contacts at each of the sites can make the process more efficient and often result in better data," Dr. Kumar says. "Like in the United States, enrollment projections given by Indian investigators typically need to be scaled back considerably, but often the aggregate projections are still much higher than in more mature markets."

Jean-Jacques Garaud, M.D., global head of development and chief medical officer at Roche, says it's important to integrate the needs of the emerging markets into the global plan early in the development phase.

"Historically, we developed global plans based on European and U.S. needs, and then a second plan was developed for Japan," he says. "We did not focus heavily on other countries.

global clinical trials are: creation of a country-specific recruitment and retention plan, allocation of resources to administer proper site recruitment training, and conduction of a true, comprehensive site feasibility.

It is important for companies to note that when it comes to developing a recruitment strategy, one size does not fit all.

CANDACE KENDLE, PHARM.D.
Chairman and CEO
Kendle

Best practices against a large worldwide trial would include using EDC with a balance between remote monitoring and on-site data verification. Instead of sending monitors out every four to six weeks, a combination of EDC, remote monitoring, and telephonic and scan monitoring systems should be used.

The monitoring on-site becomes less about the data and more about patient verification and safety. EDC has been around for years, but it hasn't been used in conjunction with remote monitoring and selective statistical monitoring of source verification for very long.

STEVEN NICHTBERGER, M.D.
President and CEO
Tengion

I believe that the current focus on personalized regenerative medicine will continue to grow globally — as evidenced by Pfizer's significant investment in a new U.K.-based R&D center in this space, as well as a number of important partnerships that have been announced recently in the field. We see the patient need and demand for regenerative medicine products, given their ability to change the standard of care and be economically supported, as undeniably global.

We have made it a priority to build Tengion's global manufacturing, shipping, and quality control capabilities to serve patients' needs through a centralized effort.

Securing EMEA approval for U.S.-based manufacturing translates into a true business advantage, as does a company's ability to consolidate quality control measures.

This approach not only cuts meaningful fixed costs but also allows Tengion to operate as a fully integrated company. We feel that the centralization of discovery to manufacturing provides a tremendous global advantage and creates significant efficiencies.

NIGEL PAGE
Executive VP, Strategic Outsourcing and Corporate Development
i3

Two significant areas of concern in our industry are cost-containment and productivity. By shifting noncore capabilities to a trusted strategic partner, sponsors can take advantage of functional and therapeutic expertise. Joint planning around design and execution has shown itself to be extremely valuable in identifying the right team(s), designing quality from the outset, and developing governance mechanisms to optimize the overall partnership.

DOUG PEDDICORD, PH.D.
Executive Director
Association of Clinical Research Organizations

Drug development is a global endeavor, and because of the key role clinical research organizations play in the process, CROs are increasingly global enterprises. As such, there is a need for the industry to speak with a common voice and to advocate and educate on a global basis.

Our core messages of expertise, efficiency, and patient safety are relevant anywhere in the world.

tries. Quite often, these emerging markets were developed one, two, or three years after the first market. Now, the most important issue is ensuring that emerging countries are taken into account in the early stages of drug development so that they are fully integrated into the global plan. This way there is no delay in filing the dossier and no delay in approval."

Dr. Garaud says Roche has a decentralized process for the execution of the global development plan so that any challenges or issues can be addressed locally.

"The management of this complex environment, being operationally different in all dimensions and with the different countries, cultures, and regulatory authorities in an ever-changing environment, is a pretty tall order," Dr. Garaud says. "The best way to handle these challenges is to give as much freedom and autonomy as possible to local affiliates so that people working in the different markets are empowered."

DEMAND FOR SERVICES FROM CROS IS EXPECTED TO GROW BY MORE THAN 15% ANNUALLY, AS SPONSORS FACE CAPACITY CONSTRAINTS AND A RISING VOLUME OF LARGE, COMPLEX GLOBAL CLINICAL TRIALS.

TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

GLOBAL CRO TRENDS

By 2011, it is estimated that 74% of outsourced drug development will take place outside of the United States, says Mark Goldberg, M.D., chief operating officer at Parexel International.

"As outsourced clinical research accelerates globally, it is important for sponsors to develop partnerships with service providers that offer the broadest geographical capabilities and in-depth local expertise to meet development and commercialization goals for emerging end markets," he says. "Sponsors are working with outsourced partners to access diverse patient populations, navigate regulatory issues, identify investigators, and ensure data quality, which are key challenges in conducting global clinical development programs, particularly in developing regions."

Demand for services from CROs is expected to grow by more than 15% annually, as sponsors face capacity constraints and a rising volume of large, complex global clinical trials, according to Tufts. In fact, a 10% annual growth rate in global spending on investigator grants, coupled with high variability in site performance, will challenge sponsors to establish longer-term partnerships with investigative sites that deliver improvements in efficiency, reliability, and quality.

"There is more pressure now than ever to generate more extensive safety data for regulatory submissions, as well as to reduce R&D costs while at the same time reducing development timelines," says Tomás Bocanegra, senior VP, clinical development, at Daiichi Sankyo. "By establishing collaborations with CROs and outsourcing critical functions, such as site selection, clinical site management, safety surveillance, IT support, compliance training, and even the implementation of electronic clinical trial technology solutions, drug development benefits because expertise is being maximized, internal resources are minimized, and costs are reduced."

Companies have begun to be more selective in deciding what to outsource, says Karla Anderson, a managing director with BearingPoint's life sciences practice.

"During the strategy and design phase of projects, companies are looking at a more hybrid approach that combines offshore resources as well as internal development," she says. "Companies today have become much more sophisticated in determining what their outsourcing models look like."

Bruce Garrett, M.D., president and CEO of Global Research Services, says more sponsors are using CROs with niche specialties in global trials where site selection is drawn from countries outside North America and Western Europe.

"They are also sharing development activities among several CROs on the same trial to maximize the strengths that each group brings to the process," he says. "In addition, many outsourcing partners know the rules and regulations of clinical research in many countries. This skill saves both time and cost in study startup and is being used with increasing frequency by companies interested in faster development timelines."

Dr. Winstanly says sponsors are increasingly seeking to optimize productivity by examining what aspects of their business to retain as core and what can be managed by others with greater efficiency.

"The growth of the CRO industry has been built around resource and process efficiency," he says. "But sponsors have traditionally reaped only a fraction of these rewards as they have tended to manage outsourcing in parallel with the service provider."

Dr. Kumar says smaller well-funded companies are increasingly turning to outsourcing.

"Although there is often a strong focus on the top 50 biopharmaceutical companies, small to mid-sized biopharmaceutical companies are now representing a significant portion of the pipeline and of the outsourcing market," he says. "These companies may only have a few compounds in the pipeline, but they have aggressive timelines that are built on principles of speed and are often looking internationally to newer, high-enrolling markets like India and Eastern Europe to

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DR. PATRICK KEOHANE ● *AstraZeneca*

Emerging markets offer access to enthusiastic investigators as well as cost-effective and faster patient recruitment.

conduct Phase II or proof-of-concept studies. Doing so allows them to establish value with investors and set the stage for future larger Phase II and Phase III studies."

Mr. Bocanegra says CROs can be a lifeline for drug developers.

"Relationships should be viewed as long-term partnerships rather than as one-off transactions," he cautions. "We believe this approach is beneficial because it leads to a better understanding of the goals and accountabilities and better coordination and alignment for functional collaboration and increased productivity."

One company using an outsourcing business model is NPS Pharmaceuticals, which is a 50-person company with two programs in Phase III and a number of partnered programs. The company relies heavily on outsourcing.

"Our development is very much a global development plan, and the way we access the global market is either through a global CRO or through our partners," says Francois Nader, M.D., president and CEO of NPS Pharmaceuticals. "But it is not without challenges. The biggest challenge is to match the strategic value for all parties. In terms of outsourcing, success lies in transforming the vendor relationships into partnership mindsets. The challenge is finding partners that match the entrepreneurial mindset we have here at NPS."

Service providers involved in global development, as well, will need to continue to be very flexible and offer a wide range of services, experts say.

"As suppliers develop new competencies and resources to keep up with the demands of our customers, sponsors have learned how to work with suppliers to customize their interactions in a way that aligns with businesses and delivers the most value," says Patrick Lindsay, executive VP of United BioSource. "Pharmaceutical services providers are customizing their service offerings, leading to new models of supplier/sponsor relationships that focus on delivering and driving portfolio value. These interactions include full business-process outsourcing, alliance-based development, functional outsourcing, and transactional contracts. Based on growing evidence, we expect the approach in the near future to shift from 'which group is performing which task' to 'what we are trying to accomplish together.' In this way, the classic service provider-supplier model will evolve into a truly optimized partnership model."

Dr. Winstanly says he has seen a dramatic change since 2006 in pharma's willingness to form major risk-based strategic partnerships.

"The drivers are patent expirations, higher approval and reimbursement hurdles, underutilized resources, skyrocketing development costs, and lower productivity, to name just a few," he says. "In 2007, it became clear that transformational change was necessary, and more and more companies began making the leap. Companies want partners with a proven track record in driving down costs and increasing productivity and are willing to put skin in the game, sharing the risks and rewards of such partnerships."

Experts say creating true partnerships is key to success.

"Refer to suppliers as partners, partners in the sense their actions deliver," says Neil Patel, director of the pharmaceutical R&D operations group at PricewaterhouseCoopers. "They should be involved in some decision making as well. If you trust giving them work to do on your behalf, then you can trust their opinion as well."

Dr. Goldberg says as the relationships between sponsors and service providers take on a more strategic direction, these partnerships should involve more ownership, accountability, and proactivity in global trial execution.

"Open communication and greater transparency are essential," he says. "Building strong governance models is especially important so that issues can be escalated when necessary and to ensure that the objectives of the partnership are clearly defined. Developing the right metrics provides an important tool in monitoring the progress and success of the partnership."

But, Mr. Lindsay says, total transparency is not easy to achieve.

"It becomes even more difficult when there are concerns that supplier management can prevent complete clarity," he says. "Bilateral accountability is a tool that can help eliminate ambiguity. In this kind of arrangement, both supplier and service provider develop goals and objectives in advance of program implementation and establishing targets that each will achieve. This mutual accountability fosters more candid information sharing, with the potential to reveal aspects of the development program that might otherwise go unannounced. By developing and investing in a transparency of needs, the partnership can set common goals and align strategies and tactics. In this way, suppliers can do a much better job of keeping the focus on speed, cost, and quality measures, which are important for sponsor success."

Warren Levy, Ph.D., president and CEO of Unigene Laboratories, says another challenge is related to team building.

"The issues that we have found in terms of our global relationships — we have a joint venture in China — relate to team building," he says. "There are cultural differences that one must deal with. There are patent-protection issues. There are issues with technical familiarity and expertise, which differ from country to country. There are even differences in goals." ✦

PharmaVOICE welcomes comments about this article.

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