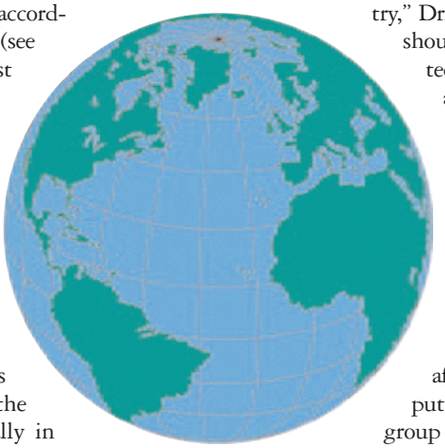
TRIALS AROUND THE WORLD

BY DENISE MYSHKO

MANY PHARMACEUTICAL COMPANIES AND CROS ARE TAPPING EASTERN EUROPE, ASIA, LATIN AMERICA, AND OTHER AREAS TO MEET THEIR CLINICAL-TRIAL NEEDS.

While there are challenges associated with conducting research in nontraditional geographic regions — such as nascent healthcare infrastructures, technology, and connectivity issues — these areas represent tremendous opportunities for pharma and for patients and investigators.

The need for a larger source of patients is great. Delays in clinical-trial enrollment are getting worse, according to CenterWatch data (see chart on page 32). Just 14% of U.S. trials enroll on time, and 57% have more than a one-month delay.



Continued globalization of drug development is moving clinical trials into places not traditionally considered. Many pharma companies and CROs are looking outside the United States — especially in Eastern Europe, Latin America, and Asia — as a way to meet their patient and physician recruitment needs.

But to be successful in conducting research outside the United States, companies first need to identify what their particular challenge or opportunity is and then select the countries that best meet their needs, says Hugo Stephenson, M.D., president of Quintiles Strategic Research Services.

Terri A. Cooper, Ph.D., partner in the global pharmaceutical/life-sciences practice at IBM Business Consulting Services, says companies conducting research outside the United States need to consider several factors before moving forward.

"Companies need to assess the patient population in the target market," she says. "Companies need to determine the epidemiology of the population in those countries and assess the fit in terms of their overall therapeutic areas."

There also are healthcare and technology infrastructure issues to be considered.

"They should fully understand the regulatory requirements that need to be fulfilled to undertake a clinical trial in that country," Dr. Cooper says. "They also should assess the level of technology in the country and how the data are to be collected."

She suggests that sponsors address internal issues to determine how they are going to manage people and processes.

"For example, if a company doesn't have an affiliate in a country, will it put a clinical-operations group in place?" she asks. "Another issue to consider is whether to hire local clinical research associates (CRAs) who the company would deploy on its behalf either on a regional or national basis or whether to leverage the resources of a CRO that already has a presence in a particular country."

According to Lawrence Reiter, M.Sc., general manager, South Africa, Criterium Clinical Research Pty. Ltd., a division of Criterium Inc., if pharma companies use a CRO they should investigate the experience of that potential partner in a particular country, especially that of its staff, organization, and investigator database.

The potential benefits, in terms of patient and investigator recruitment, are many. But to fully reap the rewards, sponsors and their trial partners will have to be adaptable and make the appropriate investments in time, resources, and personnel.

DR. ED HOLDENER
In approaching these emerging areas, it's best not to try everything at the same time. **COMPANIES SHOULD NOT START WITH A LARGE-SCALE STUDY AS A FIRST STEP.** It is wise to start with smaller studies to reduce the risk.

LAWRENCE REITER
IN SOUTH AFRICA, NOT ONLY ARE INTERNATIONAL ICH/GCP STANDARDS ADHERED TO, but there are local SA-GCP guidelines in accordance with policies developed by the Medicines Control Council (MCC) and Ethics Committees.

"In less developed countries, companies have to ensure that there is a reliable regulatory and ethical authority available to oversee the study," he says. "Sponsors and CROs need to know the local customs, communication channels, and adapt to time differences."

Mr. Reiter also advises that just because something is done one way in a country doesn't mean that it is done the same way in another. Likewise, he says companies should not assume that if something is done differently that it is of lesser value.

Mr. Reiter, who is well-versed with conducting trials around the world, says South Africa is among the top research countries outside the United States, and regulatory officials there are committed to promoting high standards of research through an extensive network of professionals.

"From an ICH/GCP point of view, there really are no challenges because most countries adhere strictly to these codes and many, if not all, have their own local GCP guidelines as well," Mr. Reiter says. "Incidences of fraud and scientific misconduct are less frequent, and the quality of research is high because of the competitive environment between these countries.

"In South Africa, for example, not only are international ICH/GCP standards adhered to, but there are local SA-GCP guidelines in accordance with policies developed by the Medicines Control Council (MCC) and Ethics Committees," he continues. "Recruitment statistics are among the highest in the world. English is widely spoken and understood, technology is available, costs are comparable and/or lower, and data collected from trials conducted in South Africa have significantly contributed to FDA approvals."

Alan Wood, Ph.D., general manager of global clinical development services at Covance Inc., says some countries are especially well-suited for trials that address indications for relatively acute conditions or for short-term treatments.

"The additional effort of building a presence and infrastructure in nontraditional areas is paying off because now we are able to recruit the number of patients that we need in the time frames that we have," Dr. Wood says.

For example in May 2003, Covance opened a full-service Phase II to Phase III clinical-development office in Budapest, Hungary, to enhance its existing service offerings in Eastern Europe. Budapest, the administrative center of Hungary, offers quick access to investigators in bordering countries such as Austria, Slovakia, Ukraine, Romania, Yugoslavia, Serbia, Croatia, and Slovenia. The company also has an office in Warsaw, Poland, which began operations in 1998.

In Western European countries that have socialized medicine systems, such as the United Kingdom, patients have greater access to medications and may be less likely to participate in trials.

"But in other areas of the world, treatments may not be available, so participating in a trial may represent a way for patients to receive the medication," says Faiz Kermani, Ph.D., budgets, proposals, and marketing executive, business development, at Chiltern International. "In the United Kingdom, we really have to work hard to recruit patients, whereas in the Ukraine it is a little easier."

DR. TERRI COOPER
COMPANIES HAVE TO BE FULLY CONVERSANT WITH OVERALL REGULATORY ISSUES IN OTHER COUNTRIES, make sure site inspections are adhered to, and ensure that the quality of the trial meets regulatory requirements.

EUROPE: BIG CHANGES

On May 1, 2004, the European Union's membership increased from 15 countries to 25 countries. The 10 new members include: Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia, and Slovenia. When two more countries — Bulgaria and Romania — join in 2007, the EU will have a population of nearly half a billion people.

EU members have set up common institutions to which they delegate some sovereignty so that decisions on issues of joint interest can be made democratically at a European level.

Expansion and change affect all areas of European business, including clinical trials. Beginning May 1, 2004, the European Clinical Trial Directive became effective; it had been adopted in 2001.

Every clinical trial with every medicine on any human subject within any of the 25 member states is required to meet the provisions set forth in the directive. The scope of the EU directive establishes several provisions: it protects trial subjects, improves the quality of clinical research, provides a legal basis for GCP, produces credible data by introducing GMP and GCP verification by inspection, and reduces duplication of paper by harmonizing ethics committee and competent authority requirements and procedures.

The directive is an important guideline whose main purpose is to simplify and harmonize the administrative provisions governing clinical trials. Before the directive, clinical trials were not directly regulated under the European Community code relating to medicinal products but were subject to national legislation.

"The commission established the trials directive and some guidelines at a European level but implementation of those guidelines is a country-level process," says Alan Davies,

Sound Bites From The Field

PHARMAVOICE ASKED EXPERTS INVOLVED IN GLOBAL CLINICAL TRIALS WHAT SOME OF THE BIGGEST CHALLENGES ARE WITH REGARD TO CONDUCTING TRIALS OUTSIDE THE UNITED STATES.

KAREN FALKNER is Senior VP of Parexel International, Waltham, Mass., a biopharmaceutical outsourcing organization that provides a broad range of knowledge-based contract research, medical marketing, and consulting services to the worldwide pharmaceutical, biotechnology, and medical-device industries. For more information, visit parexel.com.

"Optimal country selection is perhaps the greatest challenge in conducting trials outside the United States. Decisions around country selection should be based on objective predictive criteria, which is sometimes difficult to obtain, especially for companies with no physical presence or past experience in the countries under consideration. A number of factors must be weighed carefully, including disease demography, differences in medical practice, investigator training and experience, regulatory environment and time lines, compliance standards, and infrastructure. But if done correctly, trials conducted outside the United States can produce high-quality data, with significant speed and cost advantages that far outweigh the up-front investment."

SERGIO GUERRERO, M.D., is VP and Chief Operating Officer of the Instituto Mexicano de Investigación Clínica, S.A. de C.V. (The Mexican Institute of Clinical Research), Mexico City, which is committed to conducting clinical research of the highest quality standards, in strict observance of international clinical practices guidelines and regulations. For more information, visit imicresearch.com.

"The biggest challenges are mainly the time lines related to regulatory submissions that any sponsor has to deal with, and that usually takes between seven to eight weeks to resolve before initiating any trial. One of the biggest challenges of this is related to drug importation. We usually have delays because of the lack of proper documentation from the sponsors that needs to be submitted to the Ministry of Health agency in Mexico."

LARA KRUPKA is VP of Quality and Process Management at PRA International, McLean, Va., a clinical development organization with more than 2,500 employees working from offices in North America, Europe, South America, Africa, Asia, and Australia.

"One of the biggest challenges of conducting trials outside the United States is the coordination and execution of rapid study start-up, particularly the submission of clinical-trial applications to gain regulatory authority approval within the desired time lines. To meet the challenge of securing timely regulatory authority approval to conduct a clinical trial outside the United States, it is vital to understand the nuances of the concerned regulatory authorities and the current stage of implementation of any new regulations, such as the EU Clinical Trials Directive."

CATHY WHITE is Global CEO of Neeman Medical International, Cary, N.C., a global site management organization, which was founded to bring ethical medical research to the international community. For more information, visit neeman-medical.com.

"Understanding and complying with government and ethical review regulations in each country has to be the baseline from which to begin efforts to conduct clinical trials outside the United States. It is very important to have a local representative who not only knows and works well in this environment, but who has a well-established relationship with local authorities and can thus work through the issues that are not routine. The second biggest challenge is understanding local healthcare systems and how they may affect or interact with GCP/ICH guidelines. For example, in some countries it is common practice to send the patient's records (charts) home with the patient. Therefore the issue of source documentation needs to be carefully addressed."

DR. HUGO STEPHENSON
COMPANIES NEED TO GET AS MUCH ADVICE AND SUPPORT AS POSSIBLE IN EUROPE. To comply with the directive, they will need to draw upon external experts who understand how the rules translate in the gray areas.

SCOTT FREEDMAN
THE FDA OVER THE YEARS HAS BECOME MORE RECEPTIVE AND CONTINUES TO BE RECEPTIVE to studies and accepting data from studies done outside the United States.

DR. ALAN DAVIES
COMPANIES THAT WANT TO DO STUDIES OUTSIDE THE UNITED STATES NEED TO THINK ABOUT THE COMMERCIAL MARKET OPPORTUNITIES. They need a local product champion, and that is typically an investigator who has used the drug.

M.D., European medical director at Kendle International Inc.

According to Dr. Davies the goal may be to streamline and harmonize the processes across all EU 25 member states, but there are still differences in how countries interpret the directive.

"For example, ethical committees have to report in 60 days," Dr. Davies says. "How they do that is up to the local country. The ethics committee process is slightly different in France than it is in Germany, than it is in the United Kingdom. Country and project managers from CROs need to understand the local environment."

The impact of the directive varies between countries, says Claes Jagensjö, M.Sc, Pharm., business development at TFS Trial Form Support International AB.

"The Scandinavian countries, for example, have worked according to the directives for the last few years and do not need to implement new procedures," he says. "But the new procedures impact the pharmaceutical companies and the authorities in Germany and the United Kingdom, for example."

The industry, including CROs, has been cautiously supportive of the directive, Dr. Stephenson says.

"Everybody accepts that in the next few years, there will be many challenges," he says. "The hope is that the legislation will converge toward a single harmonized layer, but there will be some gray areas because of country-specific idiosyncrasies."

In the meantime, he says the directive addresses some of the inconsistencies in the regulatory processes across the European Union.

"Previously, one of the challenges was that there were considerable differences in the way studies were conducted across Europe," Dr. Stephenson says. "For some studies, the regulatory requirements for patient consent and ethics review were very different between countries. The directive has brought this into line."

Another issue, Dr. Davies says, is the changing roles and responsibilities of the sponsor.

"Now the sponsor has legal responsibility for the trial," he says. "In the United Kingdom, liability traditionally had been divided among the academic institutions, the place where the research was being conducted, and the funding bodies, for example, the Medical Research Council. The exact liabilities and responsibilities among those three bodies have not been clearly established under the directive."

"There is no dispute that an initiative was necessary to integrate clinical-trials research and regulatory processes," Dr. Stephenson says. "But now there is another layer of regulatory issues on top of the regulatory requirements within different countries."

According to Dr. Cooper because there isn't a standard approach across the entire European Union, this has made it difficult for individual pharmaceutical companies trying to re-engineer or realign their overall clinical-development program and SOPs to meet the new clinical-trial directive.

"To a large extent, the directive was intended to create conformity across all of the EU countries, but because each country has interpreted the guidance slightly differently, this is generating a lot of confusion," Dr. Cooper says.

For Roche, the directive means more work for everyone involved in the study, says Ed Holdener, M.D., head of the company's global development.

"In dealing with so many countries now, we have to be very careful to validate how we place studies across Europe," he says. "The assumption is that all countries will resource the trials appropriately and will respond to increased demands."

Dr. Kermani notes that during the transition period, companies can't expect immediate returns, but in the future, there will be advantages from the legislation in terms of standardized processes and improved trial data.

"Previously, there was no central data repository for companies to find out whether there were repetitive trials going on for the same drug or to determine which trials had ended and which trials had started," he says. "Now there is a formalized process that will allow companies to better track what's going on, as well as track adverse events."

One of the more important components of the directive is to ensure patient safety and obtain patient consent. Sponsors now must get approval to begin Phase I trials, similar to the U.S. IND

CROs in China: Only the Beginning

WHETHER IT IS PART OF A GLOBALIZATION STRATEGY OR MARKET ENTRY INTO CHINA, CHINA'S CRO INDUSTRY IS POISED TO CLAIM ITS PLACE IN THIS GLOBAL INDUSTRY.


YING LIU


MICHAEL CHU

YING LIU AND MICHAEL CHU OF ASIABIZCO LLC, A CROSS-PACIFIC CONSULTING FIRM FOCUSED ON THE LIFE-SCIENCES INDUSTRY IN THE UNITED STATES AND GREATER CHINA, PROVIDE EXPERT INSIGHT INTO THE CRO INDUSTRY IN CHINA.

According to these two experts, the CRO industry in China as a whole is still young and fragmented, but they anticipate a quick ramp up toward standardization and global competitiveness. Within two to five years, the Chinese CRO industry will offer serious competition to other Asian countries such as India. The Chinese domestic pharmaceutical sector is expected to continue double-digit growth for the next decade and become the fifth-largest pharmaceutical market in the world.

Ms. Liu and Mr. Chu say the current Chinese CRO market can be divided into three groups — foreign CROs, joint-venture companies, and local CROs.

FOREIGN CROS

Although there are only a handful of foreign CROs, their presence in China marked the beginning of a new industry. Leading the way was Quintiles Transnational, which opened its Beijing office in 1997.

"Before Quintiles, no one in China really knew too much about CROs," says Jianguang Ye, CEO of MedSept, a local Chinese CRO.

Multinational CROs have pioneered a new industry in China. Working with pharmaceutical companies, the regulators, and the clinical-trial professionals, they are carving out a place in China and the international marketplace for Chinese CROs.

JOINT-VENTURE COMPANIES

Joint-venture companies, of which there are very few, serve as extensions of their prospective parent companies and, in some cases, take on specific tasks from the parent company much like a subcontractor.

KendleWits was formed by the American company Kendle International and Chinese Acer/Wits. With a team that has a strong medical background, KendleWits offers high-quality, efficient work to its parent company in clinical data entry, coding, and processing.

Ever Progressing Systems (EPS) China was formed between Japan's EPS and a Chinese group. EPS China operates in a similar manner, with almost 90% of its clients coming from its parent Japanese company. Dr. Pihua Jin, a well-known biostatistics professor at Shanghai Medical University who has been involved in CRO work since the 1940s, heads the China-based office.

Medium-sized pharmaceutical companies could do well with this type of CRO for clinical trials or to farm out specific work, such as data processing and analysis. One main advantage is the tight adherence to SOP and attention to quality at a reasonable cost. Also, medium-sized international CROs can consider this method to locate a partner to access the China market and offer lower cost, shorter time, and quality clinical data to their clients.

LOCAL CROS

There are an estimated 100 local CROs in China. This group varies in size, quality of offerings, and management capabilities. Their customers tend to be local Chinese and foreign pharmaceutical companies that are either already set up in China or looking for entry into China.

ExcelChina is perhaps the largest CRO in this category; 70% of its clients are multinational pharmaceutical companies. Mark Engel, an American expatriate, teamed up with a Chinese partner and started ExcelChina in 1999.

A formal partnership arrangement with Covance Inc. earlier this year provides the company with all of Covance's China projects. With offices throughout China, Excel is able to monitor cases for large-scale projects.

Another local CRO company is VenturePharm CRO in Beijing. Sister companies to VenturePharm are focused on drug development, pilot research, and biotechnology.

In Shanghai, a professionally managed local Chinese company, Shanghai NewSummit Biopharma Co. Ltd., was formed in 2001 with strength in preclinical trials.

There also are smaller companies. Beijing MedSept Medical Consulting Co. is one such company, with fewer than 20 people. Started by CEO and President Mr. Ye, MedSept works with mostly smaller Chinese pharmaceutical companies and small- to medium-size companies from Korea, India, and other countries looking to sell their products in China.

An even smaller company, Shanghai Sunline Data Scientific Management Co., specializes in data management and statistical analysis.

For those pharmaceutical companies looking for drug approval from China's SFDA, teaming up with a Chinese CRO could be critical. A local CRO that has a good working relationship with SFDA can speed up approval, monitor the process, and resolve problematic areas without delay or even before they arise.

Whatever the category, China's CROs offer significant opportunities for global clinical R&D through world-class research and laboratory facilities, an abundant supply of internationally trained scientists and medical professionals, and access to large treatment-naïve patient populations.

Ms. Liu and Mr. Chu suggest that when working with Chinese CROs, companies need to consider localized business processes and approaches. China's unique regulatory environment and business culture require foreign companies to adapt.

Source: AsiaBizCo LLC, San Francisco. For more information, visit asiabizco.com.

process. While some EU countries already had similar requirements in place, the directive standardizes this process across the region.

The directive sets out the preconditions under which trials may take place. A trial may only be initiated by the Ethics Committees. The trial subject, or his or her legal representative, must be given certain information about the trial, including the right of withdrawal.

The directive establishes rules on the commencement and conduct of trials, suspension of the trials or infringements, the manufacture and import of investigational medicinal products, labeling, and verification of compliance with good clinical and manufacturing practice.

Dr. Davies notes that the directive also requires standardization of the regulatory approval system across Europe, standardization of the manufacture and labeling of drugs, adverse event reporting in Europe via the Eudravigilance Database, and information exchange between member states by means of the EudraCT database of trial information. All trials, whether commercial or academic, can be audited by the Member State Regulatory Authority, the Medicines and Healthcare Products Regulatory Agency (MHRA), and the European Agency for the Evaluation of Medicinal Products (EMEA) and are subject to mandatory GCP inspections, which will become a legal requirement. Routine inspections are intended to be carried out by MHRA or its delegated representatives every three years.

Another major change is the directive's requirement that noncommercial or academic trials now have to follow the EU GCP guidelines. This will be one of the biggest impacts of the directive, since everyone will have to ensure that documentation is maintained and the studies are monitored and audited in accordance with the directive, Dr. Davies says. These trials also will have to allocate a named sponsor, which may prove difficult if there are many different sponsors, and they will have to register with the European Clinical Trials Database.

Dr. Stephenson says as a result of these increased responsibilities, Quintiles already has experienced about a 70% increase in the number of projects assigned to the company, which in the past would have been investigator-initiated studies.

"Essentially sponsors don't want to take the risk of giving these studies directly to investigators," he says. "Sponsors need to make sure trials are managed from a project compliance perspective."

"Roche is organized for global development," Dr. Holdener says. "Our trials are set up to include patients from all major areas so it would be the exception rather than the rule to have a trial that is only in the United States or a trial that is only in Western Europe."

Another impact of the directive, Dr. Stephenson says, is that it has forced companies to think more about whether they need to do an interventional study or an observational study.

"In many cases, where the objective is data mining, gathering additional data, doing pharmacoepidemiological or safety related studies, or even doing health economics research, there's more interest in conducting observational studies rather than randomized studies by virtue of the directive itself," he says.

Some experts say there could be future modifications to the directive to address uncertainties or gaps. For example, Dr. Stephenson says there is a great deal of regulatory interest with regard to harmonizing postmarketing studies.

"There are many inconsistencies in Phase IV studies country to country, and there is a perception that these studies need to come under

DR. ALAN WOOD IN COUNTRIES SUCH AS POLAND, HUNGARY, AND THE CZECH REPUBLIC, PATIENTS HAVE BECOME RELATIVELY SOPHISTICATED. These countries have made tremendous advances in the past 10 years, and patients now expect to receive high-quality medical treatment.

DR. BRIAN TIPLADY COMPANIES HAVE TO THINK OF DIFFERENT CULTURES AS AN OPPORTUNITY to get data from a richer variety of sources corresponding to the ways in which the treatment will be used.

CLAES JAGENSJÖ
A MAJOR PROBLEM IN EMERGING AREAS could be phone/fax and IT communications. To avoid this, companies have to check and prepare for this early on.

DR. FAIZ KERMANI
THE EU CLINICAL TRIAL DIRECTIVE IS ATTEMPTING TO PROVIDE STANDARDIZATION and a common starting point to clinical trials in terms of format and content to satisfy the regulatory authorities.

DR. JEAN PATY
WHILE IT IS IMPORTANT TO BE SENSITIVE ABOUT LANGUAGE AND CULTURE, we have observed consistency across cultures in how people learn and interact with technology in the context of their day-to-day lives.

more regulatory scrutiny," he says. "For example, in Germany, if a company is conducting an observational study it may have to provide the drug. In France, if a company is providing the drug, it may no longer be considered an observational study."

Because Central Europe and Eastern Europe present tremendous opportunities for recruiting patients and sites, the directive will likely generate a competitive market within Europe, according to Dr. Davies.

"In some ways the directive is a good thing because it increases competition among the different countries particularly in terms of trial start up," he says. "Countries such as The Netherlands won't want to lose their advantage in Phase I studies, for example."

CROs are opening up offices and developing partnerships in these regions. Chiltern, for example, recently opened a new office in Poland that allows the company to build upon the existing foundations they have in place in the Ukraine. The company also has long-term partners in Poland, Hungary, and the Czech Republic. Dr. Kermani says Chiltern is experiencing an average annual growth rate of 30% in trials in Central and Eastern Europe.

"If companies approach the region correctly, they can get phenomenal patient-recruitment rates," he says. "For example, we had a Phase III, multicenter urology study in four sites in the Ukraine. In 30 days, these sites recruited five times more patients than similar sites in another European country, which had a year to complete enrollment."

The Ukraine, he says, has a large untapped patient population, and there are a lot of investigators who are now getting into clinical trials.

"Also, because of the way the hospitals are set up, some centers have huge populations of certain types of patients, so there is one contact point for many patients," Dr. Kermani says.

Recruitment of trial subjects is a key focus for all sponsors. Increasingly, sponsors are asking about retention of subjects and this can be a challenge in long trials, Dr. Davies says.

"In the last five years, there has been more emphasis on retention as well as rapid recruitment," he says. "Sponsors need to tap countries with well-established healthcare systems. Poland and Hungry are excellent examples within EU 25. Outside EU 25, countries such as Romania and Bulgaria also have been excellent locations to do trials. They have large, centralized hospitals as a result of the Soviet era, which makes it easier to keep track of patients."

In June 2004, Kendle announced the opening of new offices in Romania and Bulgaria to expand its presence in the region. The company opened an office in Warsaw in December 2002.

Another opportunity presented by the Eastern European market is a pool of highly qualified monitors, says Scott Freedman, president of Monitorforhire.com.

"Most of the clinical monitors in these countries are physicians, who have made a career decision to move into a pharma company," he says. "Many monitors have advanced degrees, Ph.D.s., M.D.s, or master's degrees."

In contrast, Mr. Freedman says, the majority of monitors in the United States have a scientific background and usually a bachelor's degree.

"There is a certain advantage to having physicians as monitors, particularly when they are communicating with investigators," he says.

While there are advantages in conducting clinical trials in Eastern and Central Europe, Dr. Kermani says companies need to consider the additional costs that may be involved.

"People often make the mistake of thinking that doing research in Central and Eastern Europe is cheap," he says. "There is a difference between cheap and cost effective. In Central and Eastern Europe, the centers may not have the computers or other equipment to do trials. Sponsors can take advantage of fast patient-recruitment rates but may have to spend money in the beginning to get the trial up and running."

According to Brian Tiplady, Ph.D., senior clinical scientist and chair of invivodata Inc.'s European scientific advisory board, IT capabilities in these countries are developing quickly.

"In some ways, Eastern Europe has more advanced systems in place than some of the Western European countries because they built modern systems from the ground up," he says. "The technology infrastructures might be

European Patients Want to Participate in Trials

A RECENT SURVEY OF EUROPEANS FINDS THAT BETTER EDUCATION SURROUNDING CLINICAL TRIALS IS NEEDED.

"Regardless of what country patients live in, if they are sick, they want to get better," says Joan F. Bachenheimer, Founding Principal of BBK Healthcare.

FORTY-TWO PERCENT OF EUROPEANS SURVEYED WOULD BE MORE LIKELY TO PARTICIPATE IN A CLINICAL-RESEARCH STUDY IF THEY WERE AWARE OF THE MEASURES IN PLACE TO PROTECT THEM. These findings come from more than 2,300 men and women who responded to a survey by BBK Healthcare Inc., which was developed to determine Europeans' motivations to participate in clinical-research studies. Respondents from the Czech Republic, France, Germany, Poland, Spain, and the United Kingdom were represented in the survey.

The need for increased education is clear. In fact, 71% of individuals surveyed indicated they were not aware of patient protections such as the Declaration of Helsinki, ethics committees, and the informed-consent process. But after these protection measures were described, 42% said they would be more likely to participate in a clinical-research study.

"In comparing the results from American and European surveys, there were striking similarities," says Joan F. Bachenheimer, founding principal of BBK Healthcare. "These similarities originate from a universal truth about healthcare, which is much different from any other consumer product."

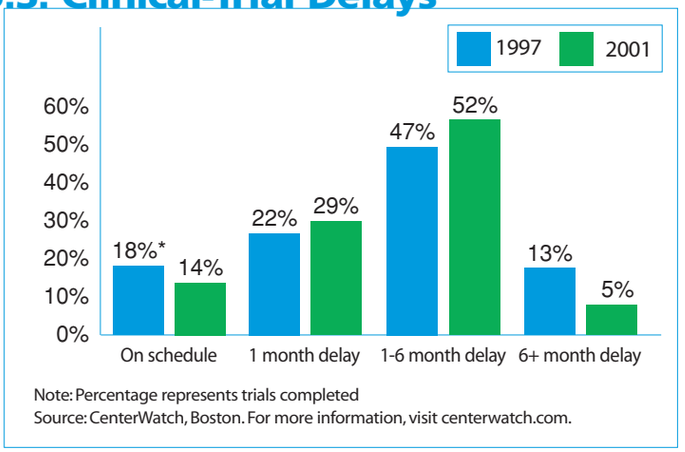
Of the individuals polled, 68% said they would consider participating in a clinical study. When asked to indicate the reasons why, the majority of respondents (69%) said "to advance medicine/science." These findings come from more than 1,490 individuals who said they have not yet participated in a clinical-research study but would consider participating. "Earning extra money" (58%) was the second-most cited reason for participation; "to help others with the condition" was third (57%); "to obtain better treatment for my condition" was fourth (48%); and "to obtain faster access to treatment for my condition" (34%) was fifth.

Despite the rise in clinical studies conducted in Europe, only 6% of respondents indicated they had participated in a clinical study, compared with 8% of Americans who responded to the 2001 survey.

Participation is hindered by low awareness and misconceptions about clinical studies. In Europe, the lack of direct-to-patient communications, such as television, radio, and Internet advertising, which are not permissible or routinely used in all polled countries, presents a barrier not seen in the United States. Furthermore, respondents' considerable concerns "about the health risks of clinical-research studies" and "being treated like a guinea pig," reinforce the need for improved education.

Source: BBK Healthcare Inc., Newton, Mass. For more information, visit bbkhealthcare.com.

U.S. Clinical-Trial Delays



Note: Percentage represents trials completed
Source: CenterWatch, Boston. For more information, visit centerwatch.com.

patchy in the rural areas of Central and Eastern Europe, but there are satellites and satellite phones and a variety of technologies that can bridge those gaps, provided companies are flexible in the way that they use technology."

Dr. Holdener says Roche gives IT support to its sites and investigators.

"We are in a significant expansion mode in terms of introducing electronic data capture to our trials so we provide these institutions with the necessary tools," he says. "For instance, we supply laptops, electronic links to our data centers, and very well-defined processes."

Dr. Wood says another of challenge is the communications infrastructure.

"Most of the study protocols are in English," he says. "But many of the documents need to be translated into the local languages. But the benefit of having access to large numbers of patients and physicians who are concentrated in particular cities outweighs the additional cost."

Dr. Tiplady agrees that language is a hurdle that companies have to overcome.

"In North America, three languages account for about 90% of the population," he says. "In Europe, there are more than 20 languages and several of those have non-Roman scripts such as Greek and Russian. Companies have to have good systems for developing, distributing, and supporting multiple languages, even within individual countries. Up front there has to be support for multiple languages, with processes in place for validating translations."

While this may add some costs to clinical development, it is not a huge expense, says Jean Paty, Ph.D., cofounder and chief quality officer at invivodata.

"Sponsors are accustomed to spending additional funds to obtain valid translations; it's part of the clinical-trial world," he says. "The benefit is in the data collected. We've conducted local-language trials in more than 20 countries throughout Europe, North America, and Australasia and have had consistent compliance with the protocol procedures in these patient-reported outcomes studies, well into the 90% range."

LATIN AMERICA: OPPORTUNITIES

In addition to Eastern and Central Europe, experts say Latin America is an important market with massive opportunity in terms of patient and site recruitment. With more than 500 million people, Latin America is the fourth-largest clinical-trials market behind the United States, Canada, and Western Europe, Dr. Davies says.

"Latin America is quite centralized," he says. "There is a huge concentration of patients in urban areas; there is a tradition of Western medicine; and there are well-established regulations for clinical trials."

Latin America is an important market for Kendle and a growing region for the conduct of clinical research. In October 2003, the company acquired Mexican CRO Estadisticos y Clinicos Asociados SA. Through this acquisition, Kendle is now the largest Phase I to Phase III CRO in Mexico, Central America, and the Caribbean and the fourth largest in Latin America.

"As the European Clinical Trial Directive has become effective, more companies, particularly American companies, are interested in doing Phase IIIb and Phase IV research in Latin America as opposed to Europe," Dr. Stephenson says. "In some cases, the preference is to use a mix of the two. Europe provides a clinical-research environment and access to key opinion leaders who have a more long-term strategic value. At the same time, there are a large number of sites in Latin America, particularly because more and more companies are interested in Hispanic populations. We tend to view Latin America as one unit, but the area also suffers from many of the problems that impact research in Europe. There is a patchwork of different regulatory environments. For example, Brazil has a very different clinical environment from Mexico."

ASIA: ON THE RISE

The Pacific Rim also is gaining a great deal of attention, but companies need to be creative in their approaches. While Japan represents the second-largest consumer market of pharmaceutical products in the world, the rapid growth of its pharmaceutical industry has made it more difficult for pharma companies to enroll clinical-trial volunteers in the island nation.

Pharmaceutical companies conducting research in Asian countries, however, have to be highly sensitive to culture and religion. Dr. Cooper points out that in Japan, there are cultural issues around the overall level of respect that should be afforded to an investigator.

"CRAs working in any other part of the world can book appointments with an investigator and there is an overall partnership during a clinical trial," she says. "In Japan, it is not unusual for a CRA to spend one or two days sitting outside the investigator's office while the investigator determines when it is appropriate to see the CRA. This is slowly starting to change, as investigators adopt a more Westernized attitude."

With the adoption of the International Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data, drug-approval authorities in Japan may now accept data from studies involving ethnic Japanese living outside Japan.

"With the support of the Ministry of Health in Japan, we have set up research centers in Hawaii, Brazil, and Peru where we have access to large Japanese patient populations," Dr. Stephenson says. "The Japanese regulatory authority has indicated that it will accept data from Japanese populations outside the country to satisfy some of its regulatory requirements."

In June 2002, Quintiles signed an agreement with Hawaii Pacific Health, one of Hawaii's largest healthcare providers, to conduct clinical trials with Hawaii's centralized population of ethnic Japanese. In 2003, the company formed an alliance with Newco Trials Pesquisa Cientifica Limitada in Sao Paulo, Brazil, for Phase II to Phase IV clinical trials with adult ethnic Japanese and Phase I trials for ethnic Japanese of all ages.

Elsewhere in the Pacific Rim, the Chinese pharmaceutical market is growing, at a rate of 13% to 17% a year, according to most analysts.

Mark Engel, president of Excel PharmaStudies, a CRO in China, says this growth is primarily driven by an aging population and an increase in disposable income.

He says there are several advantages to doing research in China: quality of the data is high since typically there are fewer queries per CRF; increased acceptance by the FDA, particularly for oncology and hepatitis trials; rapid patient recruitment; lower costs; and motivated investigators capable of performing to ICH/GCP standards.

The healthcare system in China is relatively centralized, with almost all severely ill

patients treated at 10 to 12 large hospitals within a city. This centralization makes recruitment relatively easy, Mr. Engel says.

Since about 60% of the population has no insurance and therefore struggles to afford standard treatments, patients are much more willing to enter into clinical trials. For oncology and hepatitis trials, Mr. Engel says Excel has found little difficulty in recruiting treatment naive patients, adding that recruitment in these therapeutic areas is considerably faster than in the United States or Europe.

"China has invested heavily in its pharmaceutical development infrastructure," Mr. Engel says. "This, coupled with the market potential and lower costs, will make China an increasingly important player in all aspects of pharmaceutical development. As a result, most major international pharmaceutical companies have established, or plan to within the next two years, R&D and clinical-trial centers in China. The opportunity for preclinical and clinical-drug development in China will grow dramatically within the next 10 years."

Several U.S.-based CROs also are tapping the Chinese market (see related box on page 28).

In October 2003, Quintiles signed an agreement with the Peking Union Medical College Hospital (PUMCH) in Beijing to expand its central laboratory services. PUMCH is one of China's premier academic institutions and a leader in clinical research.

Kendle also is conducting trials in Asia from a base of operations in Beijing. Kendle's presence in China originated in February 1998 with the acquisition of ACER/EXCEL Inc. Through this acquisition, Kendle assumed ACER/EXCEL's interests in a 50% joint-venture partnership in Beijing, now known as the Beijing KendleWits Medical Consulting Co. Ltd. Kendle also has a significant presence in Melbourne and Sydney, Australia, and Auckland, New Zealand.

Covance expanded its clinical-trial operations in China in April 2004 through a collaboration with Excel PharmaStudies to support the international biopharmaceutical industry's drug-development needs in China. ✦

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

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