



# Go East!

Clinical trials in Central and Eastern Europe can be faster, cheaper and better. If archaic stereotypes are holding your biopharmaceutical company back, take heed of what those in the know are saying.

**Hugh Gosling**

During the past decade, many multinational biopharmaceutical companies have started to include sites in Central and Eastern Europe (CEE) in their international clinical trials. They have been lured primarily by the twin advantages of lower costs and quicker start-up times when performing clinical trials in countries such as Poland, Romania, Hungary, Bulgaria, Russia and Ukraine.

Despite these and other advantages, many companies have yet to regularly include countries in this region in their clinical trials planning. In fact, many discover the advantages of CEE sites almost by accident, when they are added at the eleventh hour

after trial sites elsewhere in the world fail to recruit sufficient patients. Although this has led to some companies discovering the benefits of CEE countries, most fail to take full advantage of the large number of benefits the region offers. Some are reluctant to use CEE sites because of misplaced fears about data quality. The fear is that sites do not have the equipment or resources to adequately manage the rigours of an international, multisite clinical trial and so are unable to deliver the high-quality data required. Such fears are universally unfounded and the companies that have braved the region have found quite the opposite situation.

The clinical trials community in Poland, for example, has just celebrated its 10th anniversary of its first inspection by the US Food and Drug Administration (FDA). Since 1994, the nine assessments by FDA inspectors have not resulted in any Obligatory Actions and the number of findings per visit have been

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lower than other regions of the world, including many Western European countries (see Table 1). This is during a time when Poland has seen a 15–20% increase, year on year, on the number of trials performed there (see Table 2).

Poland and Romania exemplify what is best about the CEE region, offering the benefits of large populations and knowledge gained through the conduct of international clinical trials during the past decade or more. However, there is an important difference between the two countries, a difference that will, in time, transform the entire region. In May 2004, Poland became one of the ten new member states of the European Union (EU), whereas Romania is not expected to take this step until 2007. This article explores the impact of accession to the EU on clinical trials in Poland and looks at why Romania, although outside the Union, remains a profitable place to conduct clinical trials.

### Speedy start-ups

Few people know these countries better than Dorota Poklonska and Theodora Kloucek, country managers for global CRO Kendle in Poland and Romania, respectively. Both are medical doctors and founding members of their country's Good Clinical Practice (GCP) association, offering firsthand understanding of the impact the changes the EU has brought to their countries in general and to clinical trials specifically.

"In clinical trials, patients are everything, and Poland and Romania share a key advantage — efficient and swift recruitment of patients into clinical trials," says Kloucek. "As western countries continue to find it ever more difficult to recruit patients, it is highly likely companies will turn to countries like Poland and Romania as a remedy."

Patients in the Polish and Romanian healthcare systems have poor access to modern, innovative medicines and diagnostics, certainly when compared with patients in Western European countries. Consequently, they often jump at the chance to become involved in a clinical trial. "In chronic diseases and oncology particularly, where a trial may be the only access a patient has to a new, effective medicine, patient recruitment can be extremely rapid," says Poklonska. "Much of this success in recruitment, however, can be attributed to the investigators themselves. Physicians are often highly motivated to take part in clinical trials, driven not only by their concern to provide their patients the best possible care but also the desire to become part of the wider — regional or international — medical world."

With excellent initial screening of patients, motivated investigators are able to make efficient use of the time between site selection and trial initiation to select patients, improving the speed of trial start-up. "The cost of recruitment and indeed of the trial itself can often be lower than in western countries. Although this does not necessarily mean investigator fees are lower — although they invariably are — the cost per person is less because of the lower costs of treating the patient and the fact that one site may have many patients enrolled, another benefit of easy patient recruitment. It must also be mentioned that gaining regulatory and ethical approval for the trial also comes at a lower cost," says Kloucek.

**Table 1:** FDA inspections for four CEE countries.

Country	Year of first inspection	Number of inspections	NAI	VAI	OAI	Canc.	Wash	FC	DA
Poland	1994	10	7	2	0	1	0	0	10
Romania	1998	1	1	0	0	0	0	0	1
Hungary	1998	10	2	8	0	0	0	0	10
Czech Republic	1998	6	1	5	0	0	0	0	6
UK	1981	157	21	112	21	2	1	0	157
Germany	1985	85	9	61	11	3	1	0	85
France	1987	90	8	76	6	0	0	0	90

(Source: [www.fda.gov/cder/regulatory/investigators/default.htm](http://www.fda.gov/cder/regulatory/investigators/default.htm))

NAI: No action indicated. No objectionable conditions or practices were found during the inspection.

VAI: Voluntary action indicated. Objectionable conditions were found but the problems do not justify further regulatory action.

Any corrective action is left to the investigator to take voluntarily.

OAI: Official action indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.

Canc.: Inspection cancelled. Indicates the inspection assignment was cancelled before the inspection was started.

WASH: (washout) indicates an inspection was initiated but no meaningful information could be obtained.

DA: An investigator-oriented inspection in which the focus is on verification of study data.

FC: A study-oriented inspection in which the focus is on the conduct of the study by the clinical investigator.

Another advantage of performing clinical trials in Poland and Romania is a unique phenomenon — most clinical research associates (CRAs), such as Poklonska and Kloucek, are physicians. "Throughout the past few years, many qualified and experienced doctors have decided to make the switch and start working for the biopharmaceutical industry. This has created a uniquely rich relationship between biopharmaceutical companies and investigators as mediated by CRAs," says Poklonska. "Communications are naturally much easier between two medical professionals and CRAs with this background can have a very high level of influence at the local level to ensure trials follow the protocol as closely as possible."

The pathological profile of patients in Poland and Romania also presents unique opportunities. As a consequence of the current generation's exposure to western culture, these populations experience many of the same medical problems seen in other western countries. In addition, these populations are frequently 'treatment naive' — having little exposure to other treatments — which is often an advantage in clinical trials. "As a result of poor access to modern treatments, many patients are in much later stages of serious diseases than seen elsewhere. This presents a tremendous opportunity for the industry to test the effectiveness of its medicines and to truly make a difference for these patients," says Poklonska.

## THEODORA KLOUCEK

Kendle country manager for Romania, Theodora Kloucek, left medicine in 1990 to work in the growing pharmaceutical industry. She first served as a medical director for Farmitalia Carlo Erba, where she monitored trials in therapeutic areas such as oncology and nephrology. A gynaecologist by training, Kloucek is a member of Renasterea, a non-profit organization promoting education, culture and health in Romania, and a volunteer at the Centre for Patient Information in the Oncological Institute. She is an active member of the advisory board of the *Romanian Journal of Bioethics*.



**Table 2:** Number of studies per CEE country 1995–2003.

	1995	1996	1997	1998	1999	2000	2001	2002	2003
Bulgaria	10	30	59	73	88	103	127	137	116
Czech Republic	123	147	196	267	267	280	266	297	267
Hungary	144	172	224	269	277	290	298	278	NA
Poland	175	210	271	320	287	380	351	339	>400
Romania	NA	NA	NA	NA	NA	NA	168	239	NA
Russia	NA	12	17	50	54	86	112	200	NA
Slovakia	38	47	56	74	87	103	197	179	183
Estonia	13	35	35	49	58	54	59	57	70
Latvia	19	15	18	32	24	28	23	38	38
Lithuania	NA	NA	NA	NA	NA	NA	NA	NA	85
Serbia	NA	NA	NA	NA	NA	NA	NA	17	NA

### Accession boost

Accession to the EU for Poland was described by novelist Nina Witoszek as “the unimaginable coming true,” and that it brought “a spirit of renaissance, of enlightenment in the true sense of the word.” This is not an unsurprising sentiment for a country first dominated by Nazi Germany, then by Stalinist Communism. Despite this it is a uniquely independent nation, the first to break from the Eastern bloc in 1980, a move that precipitated the fall of dictatorships across Europe. Poland also has a larger population than the other nine accession countries combined (38.6 million to a cumulative 26.2 million, including tiny Malta with only 390000) and so its accession will have a profound effect on the EU. The question here, however, is the effect the EU will have on Poland. As with all things there are pros and cons.

“Accession immediately avoids a problem that has blighted Poland in the past — delays in getting supplies and drugs cleared through customs. Now that Poland is part of the freely trading Union, this is no longer the case,” says Poklonska. Sponsors of trials in Poland can also be confident that their trials will be performed under all the rules and regulations, standards and requirements that apply to other member states. “The general principles are the same and investigators have the same way of thinking as their peers in the UK, France, Germany or North America. Sponsors no longer have anything to fear — the data generated will be as good as non-CEE sites and will be collected and managed in exactly the same way,” she says. “The only negative impact of Poland’s entrance into the European Union has been the small number of incidents encountered in the transition to the new Clinical Trials Directive.”

Alan Davies, European medical director at Kendle, has followed the implementation of this Directive across the entire EU. He believes Poland is ahead of the field in terms of implementation. “The EU Clinical Trials Directive was issued to all 25 members states the very day Poland and the other nine countries entered the Union. The Directive aims to harmonize the processes involved in getting clinical trials started, including applications for regulatory approval,” says Davies. “The Directive must be transposed into law in each member state and all have experienced obstacles in getting this done. Poland, however, was able to move over to the new system from the outset so, although there have been some inevitable challenges, it has experienced fewer issues than other member states, including western countries such as France, which has yet to transpose the Directive into law.”

Poklonska is clear that any ‘wrinkles’ caused by the Directive are temporary. “The new paperwork and processes required to get trials up and running have increased the timelines slightly. Everyone within the clinical trials community here expects improvements and we are seeing them already as the new system beds down,” she says. “Even with these challenges, Poland is still unbeatable in terms of quick recruitment, access to patients, quality of data and relationship with the investigators on-site.”

### Members only?

The advantages of membership in the Euro Club are clear but it would be hasty to dismiss other CEE countries from being potential candidates for the conduct of clinical trials. Romania may not yet be a member of the EU but it still offers significant advantages. “In Romania, regulatory and ethics committee approval is very rapid — not just because of the lack of delays caused by bureaucracy but also because the system is quick, centralized and allows for parallel submission,” says Kloucek. “Also, although Romania is not likely to enter the Union until 2007, much of the work has already been done. Inside the research environment, the legislative framework is already aligned with EU requirements. The rules and requirements of GCP are in place as are those recommended by the International Conference for Harmonization (ICH). In addition, the regulatory authorities already comply with the EU Directive on Clinical Trials,” she says.

Companies performing clinical trials in Romania get the best of both worlds — a country untouched by the additional bureaucracy of the EU with the necessary standards already in place. This also means that if Romania waits until 2007 to enter the EU it is unlikely to experience the transitional problems facing Poland. “The cost of conducting clinical trials in Romania is currently lower than other Western European countries. While this cost will increase as EU standards are fully implemented, trials will remain considerably lower for the foreseeable future,” concludes Kloucek.

Accession to the EU has had many advantages and few disadvantages for Poland. Romania, while outside the Union, is advanced in the area of medical research as a result of its long exposure to the requirements of international clinical trials. Both countries and the wider CEE region remain an excellent location for biopharmaceutical companies and their CRO partners to perform high-quality and well-regulated clinical trials. ■

## DOROTA POKLONSKA

Dorota Poklonska has extensive experience in the Polish healthcare system and clinical trials environment, working as a medical doctor and then as a clinical research assistant before joining Kendle in 2002. Her first degree included internal and external medical training (internal diseases, paediatrics, surgery, gynaecology, neurology and radiology). Poklonska was a founding member of the Polish GCP Association ([www.gcppl.org.pl](http://www.gcppl.org.pl)) in which she still plays an active role.

