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Central and Eastern Europe – fertile ground for clinical trials

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INTRODUCTION

Central and Eastern European (CEE) countries are a fertile ground for conducting clinical trials. Last year, there were 346 studies conducted in Poland, 298 in Hungary and over 200 in Russia. The advantages and disadvantages of running studies in this geographical region will be explored and a historical background to developments over the past 20 years will be provided. Other issues, like epidemiology, regulatory affairs, high quality of data obtained and costs involved, will be also discussed.

WHY CEE?

The interest of pharmaceutical research companies in the CEE countries is justified by several factors, including their geographical closeness and large additional patient reservoirs characterised by genetic and cultural similarities. The other important features of this region are epidemiological characteristics, particularly the higher prevalence of certain disorders and the different organisation of health services. The availability of highly specialised investigators, who are interested in conducting clinical research studies and who are also are highly motivated, is another benefit.

Figures 1 and **2** compare the populations traditionally used for research purposes by American and Western European firms with those available in European Emerging Markets. **Table 1** lists the populations of EU members and those of candidates for joining the EU.

HISTORICAL BACKGROUND

Over the past 20 years, the number of clinical trials conducted by pharmaceutical companies, either directly or through CROs, in the CEE countries has increased exponentially.

Figure 3 provides information on the numbers of clinical trials run in Poland, Czech Republic, Hungary, Bulgaria and Estonia over the period of five years until year 2001. **Figure 4** shows the number of clinical trials per million inhabitants in those countries, confirming that some of them still have some spare capacity for clinical research.

In the 1980s, some pharmaceutical companies ventured into countries, such as Poland, Yugoslavia or Hungary, to perform studies other than those necessary for local product registration. However, it was in the 1990s once the "Berlin Wall" disappeared from the map, that several companies added Medical Departments to the existing marketing and sales offices in this region. The

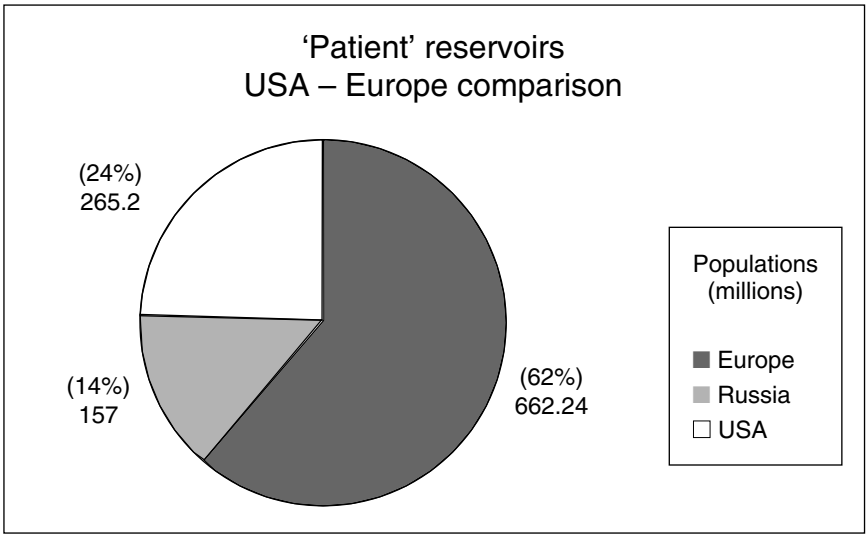

Figure 1.

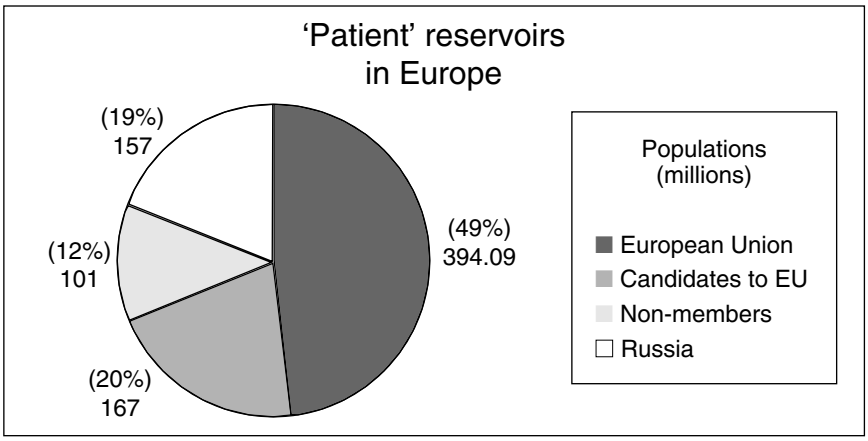

Figure 2.

change to a market economy was of vital importance, allowing the pharmaceutical industry to feel safe while investing in local growth and development. Central Europe; Poland; Czech Republic and Hungary were the main countries chosen initially for conducting Phase II and III clinical trials. Russia, Bulgaria and Baltic States soon followed; a little later other countries,

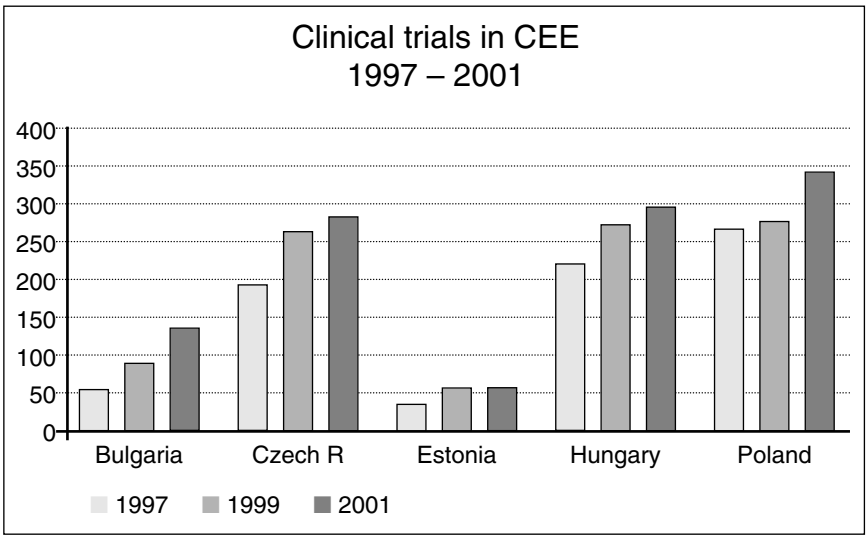

Figure 3

Table 1: Europe (populations; millions)

European Union		Candidates to EU	
Austria	8.00	Poland	38.60
Belgium	10.10	Czech Republic	10.30
Denmark	5.20	Hungary	10.20
Finland	5.10	Estonia	1.60
France	58.14	Slovenia	2.00
Germany	81.10	Bulgaria	8.50
Greece	10.40	Slovakia	5.30
Holland	15.40	Latvia	2.70
Ireland	3.60	Lithuania	2.70
Italy	57.00	Romania	22.80
Luxemburg	0.40	Cyprus	0.70
Portugal	10.40	Turkey	61.70
Spain	39.50		
Sweden	8.75		
UK	81.00		
Total	**394.09**	**Total**	**167.10**

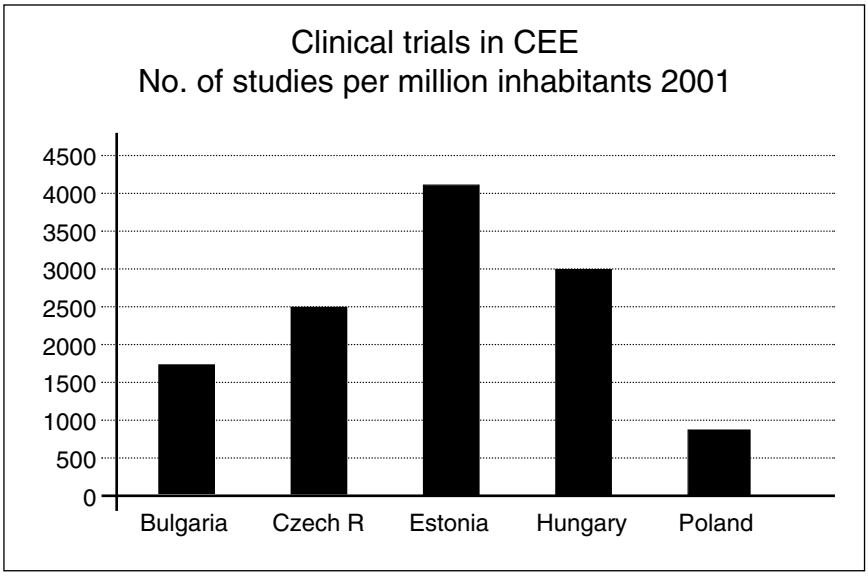

Figure 4.

such as Slovakia, Slovenia, Yugoslavia, Turkey, Belarus, Ukraine and Croatia begun to participate in clinical research.

Table 2: Clinical trials in CEE – GCP legal background

	Basic laws	ICH GCP
Bulgaria	Medicines Act '95& 2000	
Czech Rep	Medicines Act '97	GCP sub law '99
Hungary	Medicines Act '98	GCP since '94
		Health Act '99
Poland	Medicinal Product Act '97	GCP sublaw '99
	Pharmaceutical Act Sept 2001	
Romania	Order of MOH '97	
Slovakia	Medicines Act '98	
Slovenia	Medicines Act '96	GCP sublaw '98

Several CEE countries will accede to the EU in the next two to three years. Their thorough internal preparations and new legislation brought their law and regulations in line with those in the EU. This meant the acceptance and national legislation for principles of Good Clinical, Laboratory and Manufacturing

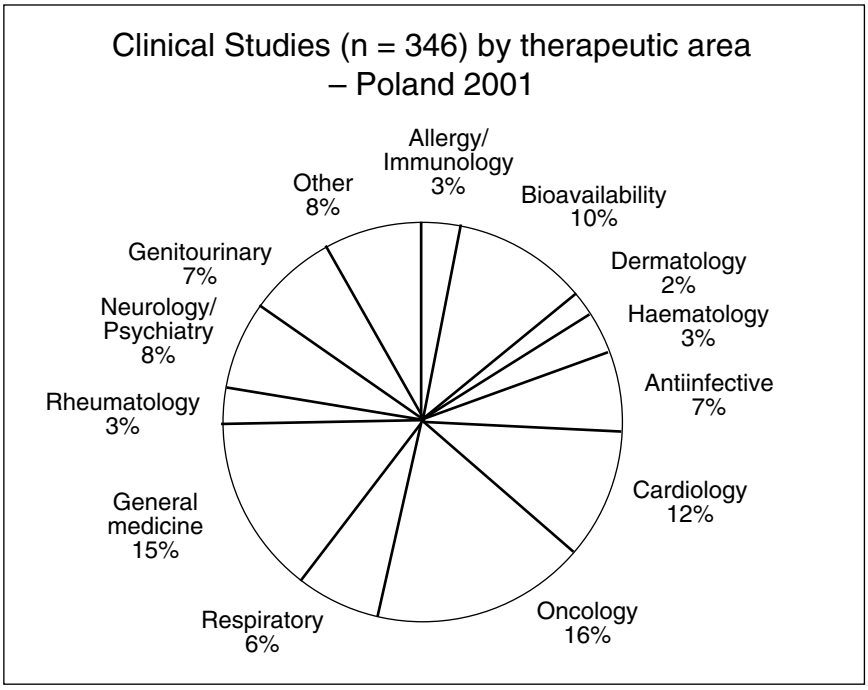

Figure 5.

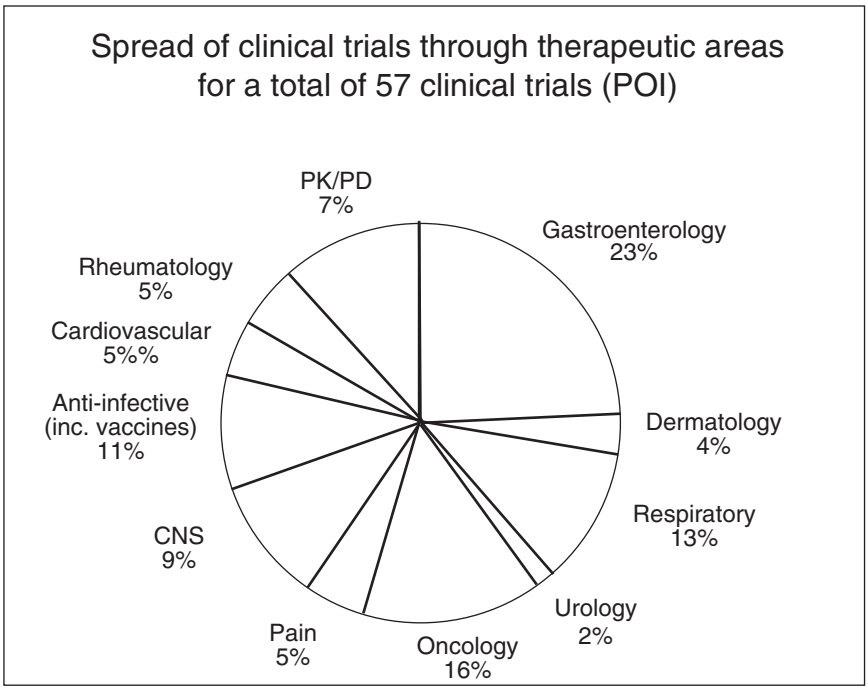

Figure 6.

Practices and their gradual implementation of these practices. This important factor encouraged the industry to explore the possibilities of including many more patients in clinical trials in all therapeutic areas. However, there are differences between the levels of preparation for the accession between CEE countries. Russia, Ukraine, Belarus and Moldova, who are not joining the EU, are far less advanced in their legislation for clinical trials compared with Poland, Hungary, Czech Republic, Slovenia or Estonia, which will be, most likely, the first countries joining the EU.

Table 2 presents the legal background to GCP in some of the CEE countries.

Figure 5 shows the spread of clinical trials through therapeutic areas in Poland in 2001, whilst **Figure 6** shows the spread of clinical trials through therapeutic areas, as conducted in those countries by the CRO, Pharm-Olam International (POI).

ADVANTAGES TO THE PHARMACEUTICAL INDUSTRY

There are several potential advantages to the pharmaceutical industry. The following points will be discussed in more detail: access to patients matching demanding enrolment criteria (as explained by epidemiology), specific characteristics of the population and different, centralised organisation of health services – all these factors contribute to speed of recruitment. Other advantages include availability and motivation of investigators, fast regulatory approvals and high quality of obtained data.

Epidemiology

During the years of the communist regime, the mortality rates from nearly all disorders in both sexes (with exception of malignant cancer of the breast for women) were higher in all the CEE countries than in Western Europe, whilst life expectancy was noticeably shorter. There was a temporary deterioration observed in both these indices during the period of transition to a market economy. The latter has evened out at present in most countries, and the mortality rates and life expectancy are now gradually improving. There are also differences between the CEE countries in the incidence of certain disorders. This fact should be considered when looking for the best country for a clinical trial in a specific therapeutic area. For example the incidence of hepatitis B is much higher in Poland and Bulgaria than in the Czech Republic.

The prevalence of several diseases such as asthma and chronic obstructive pulmonary disease, cardiovascular disorders, diabetes, hepatitis, peptic ulcer, osteoporosis and advanced malignancies, is higher in most CEE countries than in Western Europe. The health of the CEE population is improving as access to several modern medications from Western Europe becomes easier, although often limited by their price. Various preventive actions, such as vaccination against hepatitis, are more common. For instance, the prevalence of osteoporosis is slowly going down as more women have access to hormone replacement therapy.

Organisation of health services

One of the good things that the West brought with the fall of the "iron curtain" was the reorganisation of health services, with the emphasis on creating general practitioner posts and improving preventive services. Previously most of the patients were seen in the big outpatient clinics attached to hospitals. This arrangement was very convenient for conducting clinical trials. In most of the CEE countries the concept of the "family doctor" has become a reality.

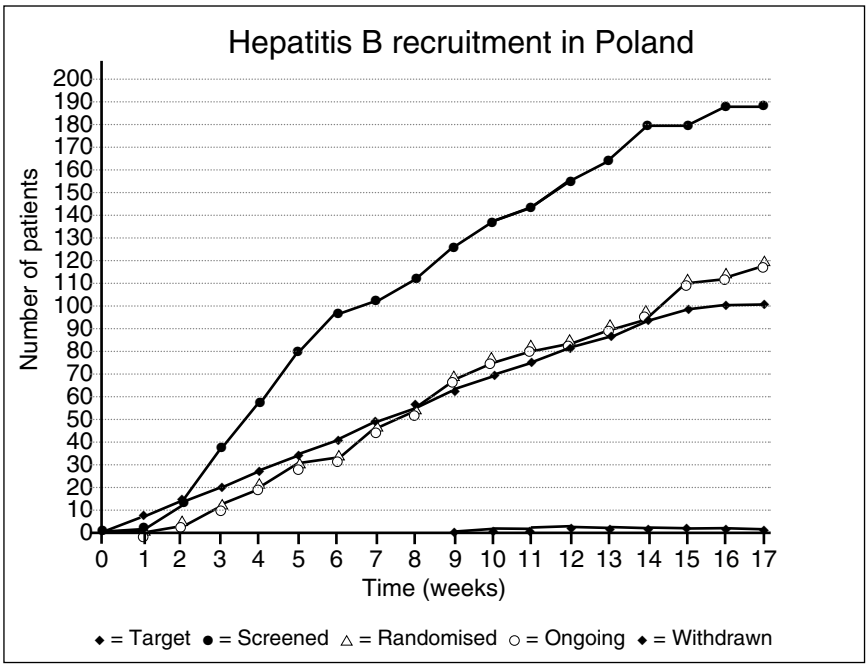

Figure 7.

However, the specialist hospital out-patient clinics are still in existence and continue to be very fast patient enrollers into research studies. Health education was previously inadequate, and consequently it was much easier to find cases of very advanced malignancies. The situation has now improved in the CEE countries, but it will take much longer for it to change in more eastern countries, like Russia, Ukraine or Belarus. In the latter countries, it is easier to find untreated populations, such as those with advanced cancers, or populations not treated according to the guidelines accepted in the EU, such as patients with early asthma not treated with inhaled steroids. As some new medicines are very expensive, only a small proportion of Eastern European populations may have access to them, because they are often not reimbursed by the local social insurance. This fact allows pharmaceutical companies to access populations untreated with some drugs, which may be an inclusion criterion for the clinical trials of certain new medications, such as interferon for the treatment of hepatitis. For these reasons, much faster recruitment of such patients into studies is possible compared with Western Europe.

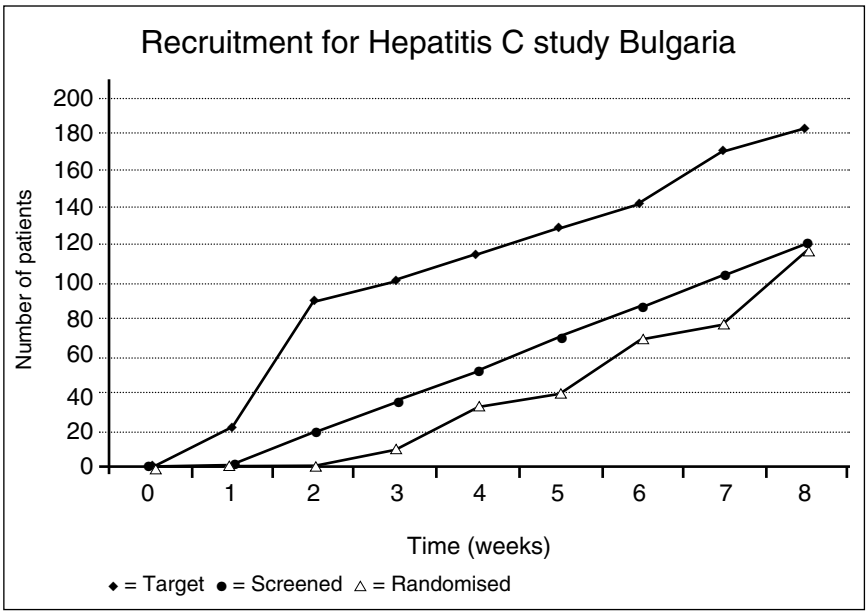

Figure 8.

Figure 7 shows the recruitment and treatment timelines for a Hepatitis B study in Poland. **Figure 8** shows timelines for recruitment in a Hepatitis C study in Bulgaria.

Population characteristics

Another characteristic of the CEE population is good treatment compliance in clinical trials and higher stability of the population than in the West. The former is caused by several factors including high trust in medical practitioners as well as traditional belief that "Western" medications are better than those produced locally. Higher stability is useful particularly where long term patients follow up is needed.

Availability of investigators and their motivation

An indirect influence on the speed of recruitment into clinical trials is the availability of investigators and their motivation. In all the CEE countries there are higher numbers of doctors per capita than in the West. There is also a higher

number of medical schools per million of population. As doctors are "hungry" for the access to Western science, which was very difficult for them for a long time, they find participation in clinical trials is rewarding. They appreciate invitations to scientific meetings and the possibility of publication in Western journals. Although the salaries of doctors in those countries have improved they remain much lower than their Western colleagues, so extra money earned while conducting clinical trials is highly appreciated.

Regulatory approvals

Regulatory approval usually takes from 1–3 months depending on the country. The requirements for documentation in Central Europe are similar to those in the EU, including translations. The rules for reporting study progress and SAEs are also similar. In Poland, Czech Republic and Bulgaria, the approval of local Ethics Committee (EC) is only necessary. In Hungary, approval is needed from a central EC for phase I and II studies, but local ECs have the right to object. The situation in Poland may change soon as the new Pharmaceutical Act has been approved by the Parliament in October 2001 and will be implemented from April 2002. In more eastern countries progress is slower. Local ECs in the Ukraine are in the early stages of organisation, not having as yet Standard Operating Procedures. It is the central EC attached to the Pharmacological Committee which gives approval for all studies in this country. There are differences between countries in obtaining import licences and knowledge of local requirements is necessary. Getting the drug through the customs may be a hurdle unless done by the local staff thoroughly familiar with local procedures.

Contractual aspects

In most of the CEE countries, the contract for the clinical trial has to be signed between the hospital and the sponsor/CRO, as well as between the investigator and the sponsor/CRO. The level of the payment to the hospital varies between hospitals and between countries, just as in the West.

The cost of clinical trials in the CEE countries presently does not differ much from the cost in Western Europe. If some money is saved on the investigator grant, it is spent on providing additional equipment or expensive comparator drug or on staff travelling further for co-monitoring or auditing.

Quality of work

The quality of Case Report Forms (CRFs) obtained from studies conducted in

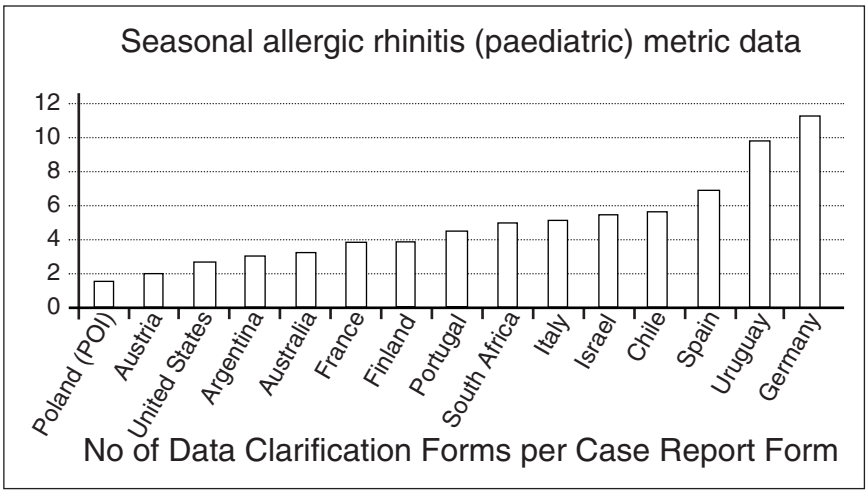

Figure 9.

CEE countries is judged by most pharmaceutical companies as high or very high. This fact has been confirmed by several industry surveys. In the author's experience the indicators of quality in several clinical trials have shown lower numbers of queries per CRF (as shown in **Figure 9**) and lower numbers of protocol violations per study than in data from Western European countries. This has also been the finding of several auditors, whether coming from the sponsor's own Quality Assurance Department or hired as independent auditors. The FDA findings in the audits performed in the CEE countries over many years confirm these findings and are presented on their Freedom of Information website.

Table 3 and **Figure 9** show the comparison of metric indices of quality in a Seasonal Allergic Rhinitis study performed in 1999/2000 in several countries including Poland (the latter monitored by Pharm-Olam International).

Equipment

There are differences between countries and between hospitals in the available equipment. To the surprise of some Western visitors, some teaching hospitals in the CEE countries have modern equipment. It is the support equipment, such as fridges cooling to –70 Celsius or fax machines for the particular ward, which may need to be supplied. An example of between-countries differences may be taken from a real life situation experienced by the author in a cardiovascular study conducted by POI in Poland and Czech Republic. Most of the centres in

Table 3. Seasonal allergic rhinitis metric information on the quality of data

Country	Screened	DCF*	No. of DCFs per CRF**
Argentina	224	652	2.91
Austria	1	2	2
Australia	38	120	3.15
Chile	23	129	5.6
Germany	28	312	11.14
Spain	20	137	6.85
Finland	47	180	3.83
France	29	109	3.75
Israel	11	59	5.36
Italy	32	162	5.06
Poland (POI)	**345**	**506**	**1.47**
Portugal	18	79	4.38
United States	858	2263	2.64
Uruguay	6	58	9.66
South Africa	288	1418	4.92

* DCF = Data Clarification Form

** CRF = Case Report Form

Poland were using treadmills for the exercise test, while all Czech centres were using "exercise bicycles" for the same test. It was necessary to hire the treadmills for the Czech centres in order to achieve the same standards for the whole study.

Laboratories

In most of the CEE countries there is a local, national, centralised system of quality control. One central institution collects all the data from hospital laboratories and conducts periodic quality checks. This institution also issues GLP certificates. There are, however, differences between countries. In the Czech Republic, for example, there are several laboratories that also have a special quality certificate allowing them to be used as central laboratories for that country. Some of the laboratories in those countries can be found on the list of 1000 approved world laboratories. The author has used a laboratory in a Warsaw hospital as a central lab for all centres in Poland. This particular laboratory also had a foreign quality certificate and was working in accordance with GCP principles. It was able to provide results electronically directly to the

sponsor in the West, as well as to the centres, and it had all necessary SOPs in place. It has been satisfactorily audited by representatives of QA departments of several pharmaceutical companies and by independent auditors.

DISADVANTAGES – FACTORS TO CONSIDER

There are several factors which need to be considered before embarking on a clinical trial in the CEE region. One is the status of trials being run in that region by competitors. Some therapeutic areas (for example, CNS and cardiovascular) are as congested as in Western Europe or may be worse. It is important to check whether the assessment instruments, which you are planning to use, are validated (not only translated) in the local languages. The process of validation of some questionnaires may take some time. You should make sure that the comparator drug which is to be used is registered in the CEE country where you are planning your clinical trial and that registration is for the same dosage and formulation you require. The equipment needs to be examined in each country/ centre during the selection visit, looking at what is necessary to fulfil the requirements of a particular study.

You should consider the local, current, medical therapeutic practices. You need to know what medicine is usually given or permitted in each country as a rescue medication in, for example, studies of peptic ulcer or respiratory diseases. This small, but important detail may need to be considered before the study protocol is finalised.

When the use of local laboratories is considered, their methodology and the units used should be checked, as they may differ from those used in the West.

It is also useful to enquire about local courier services. Most of the courier companies are operating in the CEE countries but with differing efficiency. Local staff in each country will give you the best advice about which courier to use in order to avoid your new experimental drug getting stuck at the customs office, instead of being delivered to the investigators.

The poor infrastructure used to be the worst disadvantage in conducting research in the CEE countries. Things have changed a lot with time. The infrastructure has greatly improved in Central Europe. It is still far from the best in Eastern countries, but it is improving.

CONCLUSIONS

Central and Eastern European countries are a fertile ground for clinical trials. Poland, Hungary and the Czech Republic are no longer "Emerging Markets". They are very close to joining the EU and are well prepared for this important

event. Other candidate countries are also making swift progress. There are, however, still some factors remaining which make these countries a good choice for placing clinical trials of some new drugs. Some studies requiring untreated populations or advanced disease states could be placed in countries like Russia with its enormous territory, or the Ukraine or Belarus.

It is the author's belief that quality of data obtained from the clinical trial is as good as the training of the staff monitoring and managing it, and of investigators conducting it, provided that high motivation is also present. This observation definitely applies to clinical trials conducted in the CEE countries. Co-monitoring by project management and Quality Assurance audits conducted early in the study help to produce excellent quality of work.

Local expertise, knowledge of the language, local rules and regulations, as well as customs, help in conducting clinical trials in the region. The author's advice for those who have, as yet, no experience in conducting trials in the CEE countries is either to build your own medical department there using local doctors, who are very willing to be trained, or alternatively to use a CRO that has a lot of experience of working in those countries.