Clinical Trials in Bulgaria

Part Two

In our Summer 2002 issue, Dr Milen Vrabevski, Medical Director at Comac Medical, began an in-depth overview of clinical trials in his native Bulgaria. Here he continues his investigation of the advantages and potential pitfalls for multinational pharmaceuticals operating in emerging scientific markets.

Dr Milen Vrabevski is Medical Director of Comac Medical Ltd., a full service small CRO based in Sofia, Bulgaria. He has over five years of experience in the pharmaceutical industry, mainly in the field of clinical research.

After graduating from the Medical University of Varna in 1995, Milen began his career working as a Junior Doctor in a surgery department, and then as a Medical Representative of a pharmaceutical company before founding Comac Medical Ltd. in 1997, assuming the position of Director.

Being one of the pioneers in the GCP and Quality of Life (QoL) area in his country, Milen has participated in conducting all company clinical studies and QoL projects.

SITE SELECTION AND INVESTIGATOR IDENTIFICATION

Highly critical to the success of any study, these two issues require the utmost care. The decision-making process regarding both site and investigator should make full use of all local expertise:

- Local opinion leaders will be well acquainted with the available professionals in the area, as well as with its hospital structure and facilities
- Local CROs and pharmaceutical companies' affiliate offices (affiliates) will have hands-on experience of potential investigators and sites

This expertise should provide valuable information regarding site potential and suitability for trial requirements, for example available beds, medical/lab equipment, clinical supply, storage facilities and so on. They can also be helpful for assessing a site's desirability, for instance location, physical layout, access to IRB/IEC, quality of clinical trial teams and a suitable patient pool.

Utilising these resources, whilst fundamental, is not without potential problems. For example one should always be aware of the risk of commercial interests affecting advice given by affiliates during site/investigator selection. In an emerging scientific market commercial potential is limited, and therefore sales and marketing opportunities should be carefully balanced with clinical development. In our opinion, the emphasis should be put on clinical development performance. It is much more important to assess a site's real suitability and an investigator's capabilities in new drug trial implementation, rather than future marketing potential.

Bulgaria has several attractions which make it particularly suitable for clinical trials, facilitating easier contact with patients and monitoring control. These include political stability; ethnic and religious tolerance; suitable physical layout; and comparatively good transport infrastructure, the product of recent international programmes. The country also has an extensive hospital network, with a ratio of beds to population that is one of the highest in Europe, providing better access to in-hospital care. However, it must be taken into account that some hospitals might require investment in terms of technical equipment – a site may meet all the selection criteria with the exception of some hi-tech devices. This issue can be solved if the sponsor prepays some enrolment fees enabling such equipment to be purchased. Although still relatively uncommon, this advance payment method has been successful in the majority of cases.

Additionally, in terms of patient pool, Bulgaria's population has a relatively high incidence of certain disorders of particular scientific interest, such as CVD, stroke, COPD, diabetes and malignant diseases. The incidence of the first two is among the highest in the world. Bulgaria's patient population is largely drug-naïve, and for many their only access to advanced treatment is through participating in clinical trials. It would be cynical to interpret patient's interest as subtle coercion, they are happy to assist their doctors and well-motivated to comply with study procedures as they understand the significance of free, new medications of reliable origin and closer medical monitoring of their health. Access to a larger patient population can be achieved by using regional general hospitals, allowing access to patients who can't afford to travel to specialised treatment clinics and university hospitals in the capital or bigger towns.

The increase in multinational clinical trials carried out in Bulgaria has improved the quality of clinical trial teams. Personal economic benefits are important but these aside, local investigators and monitors are also motivated by cultural values. It is considered prestigious and honourable to make a significant, professional contribution to world science, and there is hardly any better acknowledgement for their often underestimated professional skills. Moreover, clinical trials are a very helpful exchange of clinical and scientific experience, not to mention an investment in the local health care system. To supplement the increasing pool of practical experience being gained, May 2000 saw the first National GCP Training programme for investigators and monitors, organised by the Bulgarian Drug Agency (BDA) together with R&D departments from companies represented in Bulgaria. Thus medical reform is already underway, and will continue with the creation of a Chamber of Physicians in the near future. This new organisation will license the implementation of various medical activities, including participation in clinical trials.

Whilst medical reform is certainly aiding Bulgaria's growth as a centre for clinical trials, one must also consider the infrastructure for regulatory and ethics compliance. Many ICH/GCP guidelines-compliant local ethics committees (LEC) are already in place, with their own standard operating procedures approved by the BDA. These LECs are listed on the BDA website. Additionally, in the near future, regional ethics committees (RECs) will be created with national coverage. Individual hospitals will no longer require their own IRBs, improving BDA control.

PRACTICAL CONSIDERATIONS

Patient Protection and Access – Governed by national law and regulatory and monitoring control,

patient protection in Bulgaria is constantly improving. Access to the patient population and the 'Incidence of Medical Condition Under Study' have been thoroughly detailed already, moreover performance metrics show that there is a high level of enrolment and completion and a good record of meeting deadlines.

Regulatory Approval Process – Timely onset of a study is crucial in speeding a new drug's time to market, and the regulatory approval process is key to this. In Bulgaria this process is transparent, relatively simple and fast – based on existing international requirements it is one of the shortest in Europe. Despite potential difficulties with LEC competence, the process from LEC submission to national approval is clear and easily controlled, combining effective feedback between the parties involved with a minimum of bureaucracy.

Market Potential – Sales, and therefore profit, potential within countries such as Bulgaria can be limited given the small market size, generally lower standard of living and as yet incomplete health care reforms. Therefore it is more logical to base site selection on the benefits the infrastructure and professional personnel provide for clinical development.

Investigator Experience – Four or five years ago finding suitable, experienced personnel to conduct clinical trials in Bulgaria was much more difficult than it is today. A progressive and dedicated attitude towards education – particularly GCP qualifications – together with improved training facilities and increasing multinational trial experience mean that professional staff today are much better qualified to conduct trials.

Affiliates and CRO Coverage Capacity – Though the presence of an affiliate is not considered crucial for trial success, both affiliates and CROs are devoted to achieving the study goals within the timeframes and use their local expertise accordingly. Both are competent enough to perform in the field of GCP. In the main, local CROs are well equipped with hi-tech facilities and have considerable multinational trials experience gained during the challenging period of Bulgaria's early involvement in the field. Many of them also function as site management organisations (SMOs), which often influences the sponsor's choice.

Technology and Communications Network – A high grade network is usually available in the specialised offices of affiliates and CROs: LAN, ISDN, non-stop mobile and Internet connections are among the most common facilities. However, clinical institutions have advanced in this area as well, although it is still considered a great achievement to have Internet access at hospitals in some regions. What matters is that there is a stable trend for improving these capabilities.

Language Barriers – Bulgaria is homogenous with regards to its official language. The population is literate to a satisfactory level, facilitating good verbal communication, and all sites have investigators with a good command of foreign languages. Linguistic issues are no more likely than in, say, Spain, Italy or Greece, which are member states.

Lower Costs – As with most emerging scientific markets, costs across the board are lower in Bulgaria than in many more established trial countries.

LOCAL CROs OR AFFILIATES?

This can be a difficult choice in any country and the advantages and disadvantages must be carefully weighed. On the one hand, it is well-known that most marketing representative offices of pharmaceutical companies in Bulgaria opened their medical departments in order to work on their own clinical projects. It is certainly convenient to conduct your own company trial with colleagues from the same company, who are often experts in regional customs, cultural and language nuances, as well as local regulatory requirements. On the other hand, it is no secret that CROs have reached achievements of significant value in conducting clinical trials in this country, revealing their total dedication to scientific projects. Whether sponsors prefer centralised or decentralised decision-making processes when selecting a local CRO or affiliate, there is still no clear consensus on how they should be selected, though it seems key to counterbalance clinical development needs with sales and marketing requirements.

A potential disadvantage of selecting an affiliate rather than a CRO is one of conflicting interests. Affiliates often seek to build good long-term relationships with local experts as they often act as study investigators and they may contribute to a successful new product launch, as well as being the new drug's future prescribers. However a balance must be struck when using prescribing physicians as investigators to ensure that commercial interests do not compromise study performance. Though conducting a clinical trial with an affiliate does ensure that the company is building in-house product knowledge should the drug reach market.

CROs, on the other hand, are not faced with this conflict when selecting a site or identifying investigators, as they are not concerned with the sales and marketing of drugs. A CRO is therefore more likely to exert pressure on investigators to obtain high quality clinical data within the required timeframes (for example more frequent monitoring visits than might be performed by affiliates), as they have no vested interest in them as potential prescribers. Our experience suggests that whilst CROs in Bulgaria often perform as many extra

"Whether sponsors prefer centralised or decentralised decision-making processes when selecting a local CRO or affiliate, there is still no clear consensus on how they should be selected, though it seems key to counterbalance clinical development needs with sales and marketing requirements."

References

1. Paal T L, Recent changes in clinical trial authorization in Eastern Europe, *Drug Information Journal*, 31: pp151-155, 1997
2. Czarnecki A, The central register of clinical trials: Current status of clinical research in Poland, *Drug Information Journal*, 3: pp873-877, 1997
3. Czarnecki A, Development of ADR monitoring activities in Poland subsequent to changes in the pharmaceutical market, *Drug Information Journal*, 32: pp73-77, 1998
4. De Silva J, Site selection for clinical trials, *Drug Information Journal*, 32: pp1,277S-1,258S, 1998
5. HO H-T and Chow S-C, Design and analysis of multinational clinical trials, *Drug Information Journal*, 32: pp1,309S-1,316S, 1998
6. Harrill S M, Boswick J M, Crouch T J, Cahillane G, Watson H and Meloy S M, Incorporating affiliates and Contract Research Organizations into global clinical trials, *Drug Information Journal*, 33: pp1,033-1,052, 1999
7. Frenkel R, Arinos M, Billig H and Katz E, Regulation of clinical trials in Israel: Recent developments, *Drug Information Journal*, 34: pp847-854, 2000
8. Neal H, The Contract Research Organization perspective: audits in central and eastern European countries, *Drug Information Journal*, 35: pp475-480, 2001
9. National program: *Medical standards in Republic of Bulgaria 2001-2007*
10. Annual Report of NHIF for 2000: www.nhif.bg
11. Annual Report of BDA for 2001: www.bda.bg
12. Bulgarian Drug Agency: www.bda.bg
13. National Health Insurance Fund: www.nhif.bg
14. Bulgarian Health Project of the American Agency for International Development: www.health-bg.org

visits as possible (according to their SOPs) to guarantee quality of performance, they too are eager to maintain their relationships with participating investigators/physicians, as they might well require their services for other trials.

Local CROs also have the advantage of acting as SMOs. So, to a certain extent, by choosing a local CRO the sponsor chooses an SMO too.

THE ADVANTAGES AND DISADVANTAGES OF BASING CLINICAL TRIALS IN BULGARIA

We are not alone in observing that auditors visiting Bulgaria have stated that the performance of local investigators is at least equal to that of their colleagues from the West. Naturally there are some points to be made specifically regarding trials in Bulgaria and we shall look at these.

Cultural Characteristics – In Bulgaria physicians are highly regarded as authority figures, which enables good patient trust and closer patient/physician relations, fostering a 'doctor knows best' attitude. Before the onset of reform in the health care system, patient consent was not traditionally sought except for surgical procedures. Naturally the onset of reforms now requires, in accordance with EU standards, written consent from patients involved in trials or indeed any procedure. Initially patients were sceptical as they associated written consent with a significant risk to their health, but this is gradually changing. It is also worth mentioning that when invited for a trial, patients did not feel secure when the explanation of study details included terms like 'test drug' or 'experimental drug'. We would recommend that investigators use terms such as 'new drug under investigation', which does not contravene either local or global regulations.

The reporting of adverse events is another issue that may need further attention, as sometimes lack of experience may lead to either excessive and unnecessary reporting, or no reporting at all. A survey recently performed by Bulgarian SCACCT, called *Assessment of Physicians' ADR Reporting Habits*, showed that most investigators did not know where to send their report, which was given as the main reason for not reporting at all. Other less common reasons were fear of being judged as incompetent, fear of problems with the authorities and so on. Similar problems might occur with missed doses and concomitant medications reporting among patients. However, in an environment of drug-naïve patients this seems less significant. These problems might be solved by the use of local CROs that also function as SMOs, and are able to monitor investigators' work closely; or perhaps through more intensive educational programmes for investigators.

Local Ethics Committees – The last few years have seen positive changes in the local ethics committees (LEC) in Bulgaria. However, the large number of local committees raises questions about their competence, a major concern for regulatory authorities. Recently there were reported cases of approved investigators with no evidence of competence in the CVs they submitted, no information about the reviewed study documentation – versions, dates and so on – and sometimes no data about the EC roster at all, or the data available shows it was not properly formed. In our opinion this problem is often the responsibility of the monitoring organisation and disappears if closely controlled. The situation will also be improved by decreasing the number of LECs and replacing them with a limited number of regional ethics committees (RECs), thus providing a good opportunity to have real GCP expert committees functioning with minimal risk of incompetence. These RECs will not be institutional, improving BDA control – another positive development for the ethics climate in Bulgaria. These changes are to take place in the near future.

Financial Considerations – These can also be problematic if uncontrolled. Currently payment of investigators is based on preliminarily signed contracts with the sponsors and fees go to principal investigators, which does not contradict current legal regulations. For some studies in the past, transferring a certain percentage of investigators' fees to a hospital was accepted practice – 'hospital fees' – and was meant to cover expenses for in-patient treatment of those participating in the trial. Financial issues can lead to misunderstandings and conflicts that are detrimental to the morale of the trial and its personnel. MoH Regulation 14 provides transparency for the whole system, stating that: all principal investigators are obliged to create an 'allotment protocol' for each study they participate in, which provides transparency by documenting all payment details. In this way, those who have objections can apply for changes.

Additionally, it is still rare for Bulgarian investigators to create special study funds for technical equipment, international congress attendance, gaining clinical specialities, subscribing to professional magazines and so on. Should this become possible, accusations of direct personal benefit will be eliminated.

Data/Information Management – It has been stated that patient records in Bulgaria are kept at patients' homes, while hospitals only have files registering patients' visits. This is not the case – hospitals do have archiving departments, though these are currently paper-based as most hospitals do not have computerised facilities. The confusion stems from the fact that all patients used to own a personal ambulatory card (PAC), which contained information about all hospitalisations and so on.

These PACs were abolished in June 2001. There might be study-specific patient files, created as source documents, but this always takes place with the sponsor's permission. In general, all study documentation is acceptable and the data flow is fluent and completed within required timeframes.

Return/Delivery of Study Medication – There have been some problems in this area but they no longer exist – Bulgaria's infrastructure has improved, most of the big courier companies now have offices in Bulgaria and import/export procedures are now in accordance with EU standards. Again these issues are easily solved by selection of a good trial management/monitoring organisation.

A CASE STUDY

In sharing our experiences in Bulgaria, we aim to illustrate that Bulgarian investigators' relative inexperience does not have to be a problem, assuming site staff receive adequate and timely training and support. We have been conducting and monitoring clinical trials in Bulgaria since 1997. Over that period, we have witnessed many favourable changes in regulation and investigators' practice, and a significant improvement as per international standards of performance. The project we will outline here was a mega-trial with 33 participating sites, including most of the big hospitals and specialised clinics throughout the country. This was the first clinical trial of such magnitude to take place in Bulgaria, mainly because of concerns regarding insufficient investigator experience and successful patient enrolment. During the study, we terminated eight out of 33 sites for a variety of reasons. Upon completion of an eight-day sponsor's audit at six sites and our office, we received two certificates: one for successful and timely enrolment and one for quality of performance and data provided. This highlights four issues:

- A proven record has now been established for participation of physicians in large-scale clinical studies in Bulgaria.
- Lack of experience and GCP competence need not exclude Bulgarian investigators, providing they are motivated, dedicated and given good support and adequate training by the study monitors. During this particular trial we financed additional training for investigators and provided study instructions in Bulgarian where appropriate.
- Although we did not have contract site monitoring, we controlled sites' performances closely and supported quality performance. Eight sites were considered inactive or of substandard performance and were terminated, therefore minimising the risk of poor quality study results.
- The opportunity to participate in this trial has motivated some sites to purchase technical equipment and communication devices in preparation for involvement in further trials. This bodes well for future trials in Bulgaria.

As a result of our experience, it is our firm belief (and one supported by numerous other sources) that if the local CRO is competent and dedicated to its business, it can provide the quality and efficiency required to successful complete a clinical trial in Bulgaria.

A further point of interest, in our experience, is dealing with local internal conflicts during trials. For example, during another multi-centre trial we conducted there were considerable misunderstandings among study members, which threatened to compromise the integrity of three sites. By following our standard operating procedures (SOPs) and holding full and open meetings with all the parties involved, most of the problems were solved. Good communication (with both study staff and sponsors) and proactive monitoring to identify problems as early as possible are key to trial success.

As a final point it is also worth remembering that good communication should also include patients. If patients fully understand the benefits of the trial they are participating in – free access to long-term, quality medication and access to medical specialists – they are much more likely to comply with study requirements, facilitating the trial's success.

CONCLUSION

The marked increase in the number of clinical trials carried out in Bulgaria over the last five to seven years is a direct result of the improved conditions for conducting studies in this country. These include:

- Significant improvements in the regulatory environment and investigators' performance on the basis of political stability and ethical integrity
- Faster regulatory approval and patient enrolment, as well as timely data collection to speed up time to market
- A lower cost base, facilitating investment in better GCP training and educational programmes

There are certainly differences between East and West Europe when conducting clinical trials, but as conditions improve in countries such as Bulgaria these differences cease to have negative connotations. By fully utilising local expertise, skilled and diligent local monitors and providing support and training to investigators, sponsors can consider the emerging scientific markets as an excellent option for clinical trials. ◆

The author can be contacted at milenvr@cmbg.bg

Acknowledgement
The author would like to thank Dr Stefan Popov, Senior CRA, Dr Dimiter Enguibarov, CRA and Dr Ivo Tzanev, CRA at Comac Medical Ltd for their help in putting this article together.

Reprinted from European Pharmaceutical Contractor *Autumn 2002 issue.*