Clinical Trials in Bulgaria

Being a typical Eastern European country, Bulgaria has been kept apart from mainstream clinical research for a long time. This isolation was based on the perception that either to work under the conditions of Bulgaria's political regimen was undesirable, or its sequential economic and respectively clinical standards were not reliable enough to meet the high GCP requirements.

By Milen Vrabevski, Medical Director of Comac Medical Ltd., in Sofia, Bulgaria

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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.

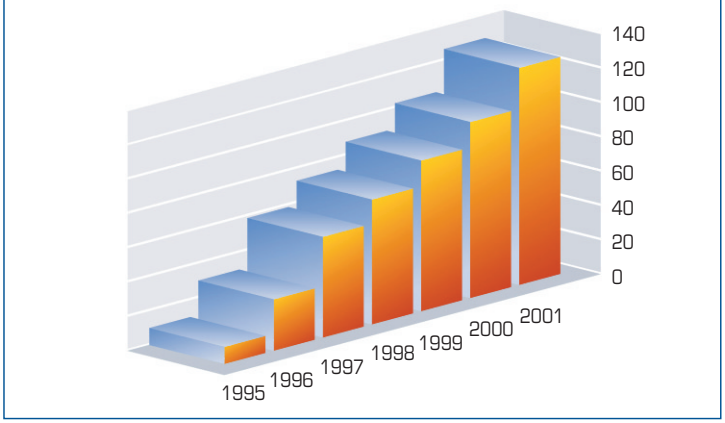
However, this perception is quite likely to be fading away with time, in light of the democratic changes in Central and Eastern Europe. Bulgaria was 'discovered' by the pharmaceutical companies and contract research organisations (CROs) in 1995. Medical departments of most large and mid-sized companies were established, many CROs increased their activity in Bulgaria, and some of them opened local offices there.

Three important prerequisites for conducting clinical research in Bulgaria are:

- The already existing legislation for clinical studies
- The application of The Helsinki Declaration as the basic document for human rights in the country
- The established standards for drug manufacturing

In the last four to five years a considerable increase in the significance of Bulgaria as a partner in multinational clinical trials (CT) has been observed. Practically all large pharmaceutical companies have at least one multi-centre study that includes Bulgarian sites. A good example would be 2001, during which 124 trials run by foreign sponsors obtained national approval, compared with only four to five in 1995. Figures 1-3 show the increased number of clinical trials conducted between 1995 and 2001, as well as their percentage by phase (2001) and origin (1995 to 2001).

Figure 1: Clinical Trials Conducted in Bulgaria for the Period Between 1995-2001



ADMINISTRATION AND MANAGEMENT OF THE MEDICAL SYSTEM IN BULGARIA

Following radical political and social reform, Bulgaria has suffered a dramatic change in the health care system. It started in the early 1990s, but the most important and decisive measures have taken place since 1998. The natural basis of this reformation is the nationwide support it shares and the application of a programme, called 'National Health Strategy', which was created and adopted by the Council of Ministers in 1995.

The initiation of the reforms began in the mid-1990s by returning to some earlier traditions: laws were passed to allow private health services; medical associations were re-established; responsibility for many health care services was devolved to the municipalities; and finally – decentralisation of the omni-power of the Ministry of Health (MoH) to regional administrative structures. The Ministry of Health theoretically has the power to regulate all health care facilities in Bulgaria, by formulating the policy, draft legislation and planning the health programmes of national importance. This structure retained responsibility for the overall supervision of the health care system, administered since 1995 through 28 regional health centres, and thus a flatter management structure was created.

The ministry still owns and administers a number of national research centres including those dealing with oncology, cardiovascular disease, radiobiology, rehabilitation neurology, hygiene, public health and health information. In this way

it is in control of national level institutions. A consultative board is attached to the MoH – the Higher Medical Council – is chaired by the Minister of Health and includes 24 members.

The up-to-date situation in terms of structural organisation of medical care was badly in need of reform. Up to the mid-1990s the Bulgarian health care system was based upon the Soviet so-called 'Semashko' model of public sector provision, with tax-based financing and few incentives for providers to improve the effectiveness and efficiency of health care. Hospital care particularly suffered in this respect. What we had at that time was a health care system with an abundance of skilled physicians but suffering from disastrous management and a total lack of decentralisation.

Some decentralisation took place in 1992 when Municipalities and Mayors under the Local Self-Government Act, became responsible for the greatest part of the health care facilities in the country, with a partial responsibility for financing. These health care facilities were recognised as legally constituted entities under the Amendments to the Peoples' Health Act in 1997.

Figure 2: Ratio of Different Clinical Trial Phases Conducted in Bulgaria in 2001

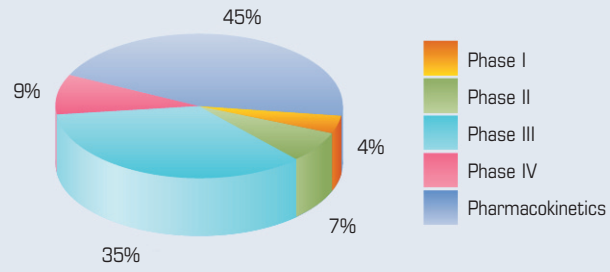
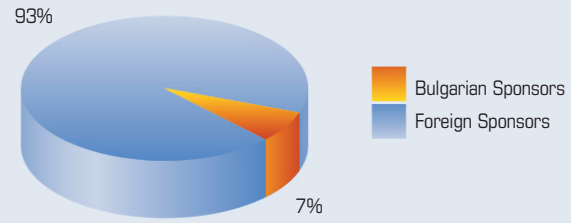


Figure 3: Percentage of Clinical Trials Conducted in Bulgaria by Bulgarian and Foreign Sponsors



However, the most substantial change in the Bulgarian health care system occurred in 1998, as a National Health Insurance Fund was settled by the Health Insurance Act. Article 3 of this act states: "The obligatory health insurance is a system for social health protection of the population guaranteeing a package of health services and shall be carried out by the National Health Insurance Fund (NHIF) and by its territorial divisions – regional health insurance funds (RHIF)". Parliament approved the payroll contribution rate and the collection of the tax has been in place since July 1999, with funding of primary and outpatient care from July 2000 and hospital inpatient care – partially from July 2001.

The fund enabled the reform of primary care, whereby the move towards a family doctor system began in 1999. Patients now choose their own family doctor who acts as a gatekeeper to the rest of the health care system.

Like other former socialist health care systems, Bulgaria had an extensive system of specialised hospital services. Massive resources have been concentrated in hospital care and this level of expensive and inappropriate health care cannot be sustained – Bulgaria still has a much higher ratio of beds/population than most European countries, and the highest in the Central and Eastern European region with 10.5 hospital beds per 1,000 people. In comparison, the European Union average was 7.3 beds in 1996. The positive outcome of this extensive hospital network is that most people in Bulgaria have access to some kind of in-patient care. The negative burden that follows this over-supply is low efficiency, poor maintenance of equipment, and a disproportionate concentration of facilities and qualified staff in urban areas.

To address the major problems in hospital care, a process of hospital accreditation began in 1997. Sub-standard hospitals are now being closed and so far one-third of the regional hospital beds have been removed. This helped to achieve the desired flexibility of management and re-direction of finances towards the improvement of primary and secondary health care. However, the system still does not function properly in terms of re-funding of medications. Moreover, there are still examples of corruption at different levels of the health care system, and most of all for heads of wards, who still need money to hospitalise patients. At some surgery departments, payments for operations are still outstanding. This automatically means that the patients are out-of-pocket.

PRACTICAL ASPECTS OF CONDUCTING CLINICAL TRIALS IN BULGARIA

Permission for conducting clinical trials in Bulgaria (in Phases I, II or III) is firstly granted by the local ethics committee (LEC) of the respective clinical centre (site). Upon receiving the LEC approval, all study documents have to be submitted to the Department of Clinical Trials at the Bulgarian Drug Agency (BDA), covered by a completed clinical trial notification form. The GCP inspectors have to check the study documentation and the compatibility of the study protocol with the local Law for Drugs and Pharmacies in Human Medicine (LDPHM) and Regulation 14 of the Ministry of Health (MoH), and after that to forward the documents to the Specialized Committee for Approval of Conducting Clinical Trials (SCACCT). SCACCT is a structure belonging to the MoH, comprising nine members who have regular sessions twice a month. SCACCT usually announces its decision to allow a trial to be carried out in Bulgaria within nine weeks of the submission of documents.

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When applying to conduct Phase IV clinical trials, the candidates also have to apply for the permission of the LEC. The Director of BDA has one month after the documents are submitted to grant/deny permission. After one month is up, any rejections are void and trials can commence regardless.

The Minister of Health defines the members and the standard procedures of the central ethics committee (CEC), which controls the LECs and appears as an arbitrator in case any discussions arise.

The LECs are established at the medical centres, where clinical trials are conducted. The director of the centre defines their membership. When a member is also an investigator in a trial, he or she cannot participate in the vote. These committees are obliged to create their own standard operating procedures, to be approved by the Director of BDA. The LECs and BDA conduct the overall control of the clinical trials according to their competence. The BDA can also conduct inspections of the trials at any time before, during or after they are conducted.

KEY ETHICS AND REGULATORY REQUIREMENTS

The beginning of drug regulation in Bulgaria dates from 31st October 1904. On that date a decree No.44 was issued, with which – according to article No.169 of the Law for Preventing the Human Health – a chemical laboratory at the Directory of Preventing the Human Health was established. The purpose of this laboratory was to examine the drugs in Bulgaria required for science and forensic medicine. As such, Bulgaria was one of the first countries in the world to establish drug regulation and control as a state policy.

Controlling clinical trials in Bulgaria began back in 1995 with the Law for Drugs and Pharmacies in Human Medicine. This law, together with Regulation No.14, guaranteed for the first time the rights of the patients and the healthy volunteers participating in a trial. In the same year Regulation No.26 appeared, which deals with the activities of the CEC. In 1997 the National Institute for Drugs issued the guidelines of Good Clinical Practice (GCP). All of the above mentioned documents meet the requirements of the European Union.

In order to accomplish specialised control of the quality, effectiveness and safety of the drugs, the Bulgarian Drug Agency at the Ministry of Health was established in 1999. It is the successor of the former State Institute for the Control of Drugs (SICD), founded in 1957 and renamed in 1992 as the National Institute of Drugs.

In February 2000, the new Law for Drugs and Pharmacies in Human Medicine was established. Chapter four of the law, which deals with the clinical trials of drugs in humans, reflects all the novelties of European and world legislation. Regulation No.14, issued on 31st July 2000, introduces the guidelines of Good Clinical Practice as a mandatory standard for conducting

clinical trials in Bulgaria. The new requirements of the regulation act as an insurance, not only for the patients and healthy volunteers, but also for the investigators participating in the trial. A new requirement is also that the sponsor and/or the CRO have a legal representative in the country.

CONCLUSION

The process of radical reformation of the political and social climate facilitated the trend of an increased interest in Bulgaria as a reliable location to base clinical trials. Its legislation in that particular area reflects all the regulatory GCP novelties of the EU and the rest of the world.

Other markers for improved conditions for clinical studies are the already established standards for drug manufacturing, as well as the fact that the Bulgarian authorities apply The Helsinki Declaration as the basic document for human rights in the country.

Last but not least, the rational regulatory base is both time-saving and stringent, which shows that the bureaucratic obstacles for control are minimised.

However, the issues described above can hardly reveal the complete picture of the research environment from a professional point of view. Therefore, we have also tried to analyse all the aspects to consider when selecting a country, site and investigators in the process of conducting clinical trials, on the basis of the local features of an emerging pharma market. All this, combined with examples of our own company experience illustrates the profile of the pros and cons of basing studies in Bulgaria, as well as outlining most of the pitfalls and possible solutions.

This professional review will feature in the next edition of *EPC*. We kindly invite the *EPC* readers to join us again in August. ◆

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