Clinical Trials in the Baltic States – Latvia and Lithuania

Latvia – The Stable Environment for Clinical Research

2010 saw the 20th anniversary since Latvia gained independence and clinical research in medicinal product development had been reestablished. The inevitable milestone in this process was in 2004 when Latvia became an EU member state, and its regulatory and legislative environment was stepwise synchronised with European legislation. In 2011 Latvia passed through tight economic and political times related to the recent global crisis. Recovery after the global economic crisis is slow, and the largest losses in the country are related to the decrease of its population by 13%, returning to the level of 1959 (Figure 1).

The 2011 census results show that today more than half of the Latvian population resides in the capital Riga and its suburbs. Today, 42.5% of the total population are economically inactive (26.6% retired, 7.8% students and pupils, 8.1% others), adversely affecting the economy in the short and the long term. In 2009, taking into account the non-favourable economic situation, the Latvian government issued Cabinet Order No 413, announcing programmes to promote export and attract foreign investment. In 2011, the State Agency of Medicines of Latvia (SAM) promoted clinical trials as the competitive product for export. In the meanwhile, statistics of clinical trials in Latvia reveal some stagnation after 2008 (Figure 2).

In 2011, 77 clinical trial applications were filed and 67 approvals issued (eight of them within the voluntary harmonisation procedure). As usual, the Phase III projects prevailed; 11 pediatric studies were performed in 2011 (10 in 2010); in 19 studies medicines of biological origin were investigated; one authorisation was issued for a Phase I study and one for a Phase IV study. The range of studies according to the therapeutic areas for the most recent two to three years has changed just slightly – studies still prevail in oncology, neurology, pulmonology, dermatology and endocrinology (in descending order). The number of studies in cardiovascular diseases has a tendency to decrease, reflecting the shortage of new medicines in this therapeutic area.

SAM also maintains a list of post-marketing observational studies showing that five observations were introduced and three observations registered in 2011 – the number of observations has decreased since 2006, probably due to the frequently changing state reimbursement system of medicines. From 1st January 2012 a new order for the prescribing of reimbursable medicines and medical devices has entered into force. The new order was developed with the aim of promoting the prescribing of lower-cost state reimbursable medicines having equivalent effectiveness.

A sign that the global tendencies in the clinical research field have reached Latvia is the high number of substantial amendments of study documentation: 218 substantial amendments in 2011 (190 in 2010).

In recent years the mass media have been used more and more in the field of clinical trials. In the websites of the largest university clinics, up-to-date information about ongoing studies can be found. Although advertisements for patient recruitment are not used so widely, it is common to invite healthy volunteers to sign up to a Phase I study register. It is thought that the number of Phase I studies will increase as soon as appropriate infrastructure has been developed.

Modern technologies and highly skilled specialists are concentrated in Latvian university clinics, leading to intensive patient flow. However, the quite difficult and prolonged contracting process frequently hinders a quick site initiation after the receipt of study approval.

There is a clinical research organisation/fund directed by one of the most recognisable vascular surgeons in Latvia, Professor Dainis Krievins. This organisation involves several academic institutions in different Eastern European countries. In the future, the potential of academic research organisations could essentially increase by also growing state grants for the research of new medicines.

Some Latvian pharmaceutical companies (Grindeks; Olainfarm) have long-standing traditions in research into new pharmaceuticals, as well as being clinical research sponsors.
Conclusions
Latvia is a favourable environment for clinical research, with the number of studies performed becoming stable in recent years. Medical care, including pharmaceutical care, is still improving according to European standards. Private practitioners in their private practices, as well as specialists in hospitals (including regional hospitals) willingly participate in clinical research projects, thereby raising their qualifications and economic wellbeing. Availability and know-how of local CROs, and the professionalism of medical persons and state institutions in Latvia, allow the performance of clinical trials according to today’s dynamically changing demands.

Overview of 2011 Clinical Trials in Lithuania
Lithuania is the largest of the three Baltic countries, covering an area of 65,300 km², and it has a population of 3.2 million. Lithuania is an open economy with a small domestic market; the World Bank has placed it in the “above average” group in terms of the level of income.

After joining the European Union (2004), Lithuania has harmonised the legislation on clinical trials with the EU, has implemented Directives 2001/20/EC and 2005/28/EC in local regulations, and also follows the applicable EU guidelines. The function of competent authority was given to the State Medicines Control Agency (SMCA) and the function of single opinion adoption was given to the Lithuanian Bioethics Committee (LBC). Clinical trial documents can be submitted simultaneously to both institutions, which makes the approval process much faster. The examination of the application usually takes no longer than 60 days. The other advantage that makes the setup of the clinical trial faster is that permission to conduct a CT received from the SMCA allows the import of IMP and trial-related material from other EU countries (no separate approval is needed).

The major principles relating to the conduct of clinical trials are covered by the Law on Pharmacy of Lithuania No. X-709 (22-Jun-2006) and the Law on Ethics of Biomedical Research No. VIII-1679 (11-May-2000). These regulatory documents are available on the homepage of Seimas of the Republic of Lithuania11.

Logistics also plays an important role in the performance of clinical trials, as it ensures fast delivery of study-related material and laboratory samples. There is an adequate choice of international courier companies operating in Lithuania, such as DHL, TNT, FedEx, DPD and Venipak, therefore no delays are foreseen. For local shipments, sponsors can choose local courier companies which provide good quality service with lower costs. In Lithuania, sponsors should not face any problems with laboratories, as most of the state hospitals have up-to-date laboratories, and are able to perform high quality and reliable laboratory tests according to the national and EU regulations.

Once the approvals from the SMCA and LBC are received, the agreement between the hospital, principal investigator and sponsor to conduct a clinical trial should be signed, which could be an issue that extends the setup of clinical trial, especially at the state-owned hospitals. The agreement review at the private hospitals and practices can take approximately a week, whereas negotiation with the state hospital can take up to one month.
Statistics of Clinical Trials in Lithuania
The SMCA maintains the list of ongoing clinical trials, which shows that currently there are 447 ongoing clinical trials in Lithuania. The SMCA has also announced yearly reports on its homepage since 2004. 84 applications were submitted in 2004 for approval, and the authority has issued 80 approvals (Figure 3). Since then the number of CT applications has been growing, and in 2008 the SMCA received 123 applications. Due to the global economic crisis, this number decreased in 2009 (only 86 applications were made) but, in 2010, it showed a slow growth, and already 96 applications were submitted in 2011.

Already since 2004 the majority of the studies were Phase III, and the situation has remained the same up to now (Figure 4). SMCA reports show that clinical trials in Lithuania cover a broad range of therapeutic areas: oncology, endocrinology, cardiology, rheumatology, hematology, neurology, psychiatry, pulmonology, surgery, dermatology, gastroenterology, pediatric, ophthalmology, nephrology, infectology and urology. In Lithuania there are a relatively high number of people participating in clinical trials of medicinal products because the access to the National Health System is limited and medications are expensive, so with the offer of better medical care, and free medicines and diagnostic procedures, patient recruitment meets the expectations. Large centralised hospitals also play an important role in meeting the recruitment goals.

Conclusions
Summarising the above mentioned criteria, Lithuania has a very friendly environment for clinical trials. The application approval process is similar to other EU countries. The logistics services are well set in place. Also there is a wide choice of advanced laboratories (including state and private) that provide high quality laboratory tests and meet local and EU requirements. Sponsors will meet investigators who are highly motivated and experienced in clinical trials, with good understanding of local and EU regulations, and a high level of patient enthusiasm. All this together creates excellent conditions for clinical research in Lithuania.

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