

CLINICAL TRIALS IN BELARUS – DESERVING OF A SECOND LOOK

Until very recently Belarus has been considered a country where clinical research was a difficult undertaking. Unlike Russia and Ukraine, where the number of clinical trials has grown over the years, Belarus has remained relatively uninvolved in clinical research. For a country with well developed medical infrastructure and a high quality of patient care this paradox stemmed from unfavorable regulatory environment. Flawed with bureaucratic roadblocks and lack of incentives for participating investigators, Belarus remained behind on the international research front. However, with the latest legislative concessions, the situation has changed dramatically, prompting us to share these new and promising updates along with a brief overview of Belarusian healthcare system and its improved potential for clinical research.

COUNTRY OVERVIEW



The Republic of Belarus is a landlocked country in Eastern Europe bordered by Russia to the northeast, Ukraine to the south, Poland to the west, and Lithuania and Latvia to the northwest. Its capital is Minsk. Its population is around 10 million, with over 70% of it residing in urban areas. Russian is the main language, used by 72% of the population, while Belarusian, the second official language, is only used by 11.9%. The country has a very high educational level with over 99% of Belarusians aged 15 and older being literate. At the time of the dissolution of the Soviet Union in 1991, Belarus was one of the world's most industrially developed states by percentage of GDP as well as the richest CIS member-state.

A quiet neighbor of Russia, Belarus does not receive a lot of press coverage. With its socially oriented financial system and many features of the Soviet administrative-command economy, as well as its having the same contentious leader since 1994, it has been criticized for an overall lack of openness and paucity of reforms. While most of this criticism is well deserved, for a country with almost no natural resources and previous complete economic interdependency with other Soviet republics it has weathered the collapse of the USSR rather well. In fact, one may speculate that the relatively mild economic transformation has resulted in comparatively low rates of unemployment, poverty and inequity, as well as less drastic fluctuations in morbidity and mortality indicators.

HEALTHCARE SYSTEM

Since the collapse of the Soviet Union, Belarus has, for the most part, retained the “Semashko system”¹ of healthcare governance. Its hierarchical administrative arrangements and regulatory framework mean that ultimate management power lies within the central government. While pooling of funds is the responsibility of local authorities, it is essentially a de jure arrangement as Belarus has a single-payer system. Local authorities and national government act as third-party payers for health care services and personnel. The increasing pressure to improve the efficiency of the system and cut unused capacity in the hospital sector has resulted in a modest shift from input-based to output-based funding mechanisms.

The key institution in the Belarusian healthcare system is the Ministry of Health. It plays a cardinal regulatory role at all levels of the highly centralized system, issuing norms for standards of care and service provision. Although regional and district health authorities are deemed to be important stakeholders due to their responsibility for local health care financing, their decision-making capacity is limited at best.

About 50,000 doctors and 122,000 other healthcare personnel provide medical services in hospitals and clinics throughout Belarus. There are around 600 hospitals, with the number of per capita hospital beds remaining much higher than in the West. Doctors' salaries are extremely low, averaging around \$600 a month, while salaries of mid-level providers are in the \$300-400 range.

Even with the existing extensive network of facilities, there are still considerable inequalities in the distribution of personnel and quality of services between urban and rural populations. In rural areas there are still primary care facilities which do not have adequate technical capabilities, and many facilities are severely understaffed. On the other hand, the number of specialized, urban tertiary care hospitals remains high.

Despite these drawbacks, Belarus has recently been ranked 53rd out of 190 countries by the WHO, which gives it the highest standing among all members of the CIS, and some of its recent accomplishments are quite commendable. Over the last 12 years the infant mortality rate has decreased from 13.3 deaths per 1000 newborns (1995) to 4 per 1000 (2011), paralleling Western European countries.

¹ Antoun J, Phillips F, Johnson T. Post-Soviet transition: improving health services delivery and management. Mt Sinai J Med. 2011 May-Jun;78(3):436-48

CLINICAL TRIALS

Given its size and level of healthcare services, the number of international clinical trials that have been conducted in Belarus to date is comparatively low. In the last 5 years less than 200 trials have been carried out. Such scarcity of activity was predicated upon the complex nature of local regulatory approval process, and most importantly, on an inability to adequately reimburse the investigators for their participation in the trials.

Until February of 2011, 2 separate contracts (one with the medical institution and one with the study team) were an accepted custom. Ministry of Health then issued an order (dd 24.02.2011 № 03-3-11/841/125) which mandated Pharmaceutical companies to execute a single contract with the medical institution.

Separate contracts with the investigators were not allowed, and the honorarium for any research team could not exceed 10% of the contract with the medical institution.

On April 24, 2013 the Ministry of Health of the Republic of Belarus issued a new decree (#03-3-11/823/459) that has increased investigator's honorariums to 40% of the contractual amount. Separate contracts with the investigators are still not allowed.

This increase in reimbursement for study activities signifies a substantial shift in state policy towards clinical research and has sparked a renewed interest in clinical trials by both medical centers and investigators. Within the last 4 months a dramatic increase in the number of newly submitted study applications has been noticed.

While this is a very positive development, there still remain challenges to effective clinical trial conduct. These include:

- Lesser investigator experience in comparison to colleagues in the region
- Requirement for import permit for every inbound IMP shipment
- Difficult business climate with hardly any experienced local CROs
- Absence of central laboratories
- Limited number of local depot providers

The issue of business climate is circumvented by a handful of CROs via remote management of clinical trials from Russian/Ukrainian/Baltic offices. In this scenario local trusted partners are used to address legal aspects, such as submissions, patient insurance and payments to institutions.

On another positive note, there are a number of attractive attributes that make Belarus a promising new player in international clinical research. These include:

- All clinical studies are conducted in accordance with GCP
- Large number of study-naïve patients
- There are actually no competitive studies
- More than 50 accredited clinical trial sites
- Developed healthcare system with well-trained healthcare professionals
- Medical standards are close/similar to European medical practice

- Recent and ongoing modernization of medical facilities
- Single specialty tertiary care institutions with immediate access to an extensive patient population
- Social climate that is accepting of clinical trials
- Doctors who are enthusiastic to participate in clinical research
- Clinical trial legislation that is in line with internationally acknowledged requirements
- Russian being a dominant language which allows for easy monitoring from Russia/Ukraine and alleviates the need for document translation into Belarusian

CROMOS PHARMA'S BELARUSIAN OPERATIONS

In 2012 Cromos Pharma opened its second Russian office in the city of Smolensk. Smolensk is located in the Western part of Russia on the border with Belarus. In fact, it takes less than 4 hours to travel by car from Smolensk to the Belarusian capital of Minsk. Since both Russia and Belarus belong to a free trade alliance, travel visas are not required.

The staff of Smolensk office has considerable experience in all stages of clinical trial conduct in Belarus and Cromos Pharma has a strong working relationship with a local partner who has a vast experience in regulatory submissions as well as other aspects of clinical trial logistics.

Cromos Pharma's experts would be happy to answer any questions about clinical trials in Belarus.

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For those readers who want to learn more about regulatory aspects of clinical trials in Belarus, you can find additional information in Addenda 1-4 below.

Addendum 1

REGULATORY AUTHORITIES AND SUBMISSION/APPROVAL PROCESSES

(All documents are submitted to the Regulatory Authorities in Russian)

- The Ministry of Health (MoH) of the Republic of Belarus
- Republican Unitary Enterprise “Center for Examination and Tests in Healthcare” (RUE CETH)
- Pharmacological Committee (monthly meetings)
- Two files (original and copy) are submitted to RUE CETH
- RUE CETH requires the sponsor/representative to sign a standard contract to perform the expert review
- Standard application form, attachment G to the Decree of the Ministry of Health #50 “Good Clinical Practice” (in Russian)
- Single application for a multicentre trial; all sites involved to be listed
- MoH approval is always in writing Initial approval period of new clinical study 2 - 2.5 months, routine approvals take 1 – 1.5months.
- Submission fees for an International study: Initial submission - \$2000 , routine submission - \$400

CURRENT LEGISLATION REGULATING CLINICAL TRIALS IN BELARUS

- Law of Republic of Belarus #161-3 «On Drugs», dd 20.06.2006
- Order of Ministry of Health of Republic of Belarus #254 «On the Approval of Rules of Performance of Clinical Trials of Drugs», dd 13.08.1999
- Decree of the Ministry of Health #52 “Approval of the directions of the order of side reactions presentation and the control of drugs side effects” dd 20.03.2008
- Directions #17 of the medical institutions accreditation and specialists certification for the conducting of clinical trials dd 01.01.2007
- Recommendation of the Ministry of Health for Organization and functioning of the ethics committee #16 dd 01.01.2000
- Order of Ministry of Health of Republic of Belarus #50 «Some questions of Performance of Clinical Trials of Drugs», 07.05.2009
- GCP TPK 184-2009 (02040)
- Order of Ministry of Health of Republic of Belarus # 363-3 reg health care protection dd 20.06.2008
- Letter of Ministry of Health of Republic of Belarus # 01-4-0715 reg contracts for conduction CT dd 14.05.2011
- Letter of Ministry of Health of Republic of Belarus # 03-3-07/823/695 reg contracts for conduction CT dd 20.10.2011
- Letter of Ministry of Health of Republic of Belarus # 03-3-11/823/459 reg contracts for conduction CT dd 26.04.2013

Addendum 2

SUBMISSION DOSSIER FOR CLINICAL TRIAL APPROVAL

(requirements vary for different types of IMP, trials and place of IMP manufacture)

- Application letter (in Russian)
- CT protocol with all valid amendments, if any (in English and Russian)
- Investigator's brochure (in English and Russian)
- Sample CRF (in English and Russian)
- Patient information and consent form (in English and Russian)
- Insurance policy (in Russian or bilingual)
- Investigators' CVs (in Russian)
- Power of Attorney entitling the applicant to act in the name of the sponsor (with apostil and a notarized translation into Russian)
- Results of prior expertise or experts' opinions concerning preclinical and clinical research of IMP, if available (both in English and Russian)
- The list of countries participating in the CT, copies of their decisions, if available (in English and Russian)
- Information about the IMP manufacturer (in English and Russian)
- Certificate of Pharmaceutical Product, if available (with apostil and a notarized translation into Russian)
- GMP Certificate (with apostil and a notarized translation into Russian)
- Draft normative document for quality control for the active and supplementary substances and the IMP (in English and Russian)
- Description of IMP manufacturing process and its control (in English and Russian)
- Qualitative and quantitative composition (active ingredients and reference substances, in English and Russian)
- Results of validation of the quality control methods (the detailed description of procedures and results, in English and Russian)
- Photocopy of quality certificates (certificates of analysis, in English and Russian) for the IMP and all IMP components, placebo and/or comparator
- Documents reg. the primary package material (in English and Russian)
- IMP label (in Russian and English) and IMP samples (if required)
- Results of IMP stability check (at least two series, one of which should be of the batch intended for the CT, in English and Russian)
- If the IMP contains genetically modified organisms – information about potential environmental impact and risks (in English and Russian)

Addendum 3

POWER OF ATTORNEY

- Must be issued by the owner of the rights for the IMP (the sponsor)
- Must authorize the representative (applicant) to act in the name and on behalf of the sponsor
- Must be legalized by apostil Hague Convention of 5 October 1961 Abolishing the Requirement of Legalization for Foreign Public Documents
- All the pages and the apostil (if it is on a separate sheet) should be bound together (laced together with a thread; a piece of paper should be affixed on the thread; this piece of paper should be dated and stamped)
- Both the PoA and apostil should translated into Russian and the translation must be notarized

ETHICS COMMITTEE (EC) APPROVAL

- No Central EC approval required (local ECs only)
- Application to local ECs after receipt of the RA (MoH) approval
- Standard application form
- Attachment to the Recommendation of the MoH for Organization and functioning of the EC #16 from 01.01.2000
- Total time required is about 2-4 weeks
- Local ECs are usually closed in July and August
- An approval always is given in writing
- No timeframe within which the CT must start following the approval
- CT start notification is required
- Fees: free of charge

Addendum 4

IMP / CT MATERIALS IMPORTATION

- Import permit by the MoH required for each shipment of IMP and/or valuable CT materials (no permits are required for importation of lab kits, folders etc.)
- Permit can be obtained by a resident company with a license for distribution of drugs
- Application is only possible after CT approval by RA (MoH)
- Import permit is usually issued within about 10 days and valid for 6 months from the date of issue
- Importation / exportation of all CT-related materials should go via Minsk International Airport (the only international airport in the country)
- Customs services include customs clearance and delivery and have a flat fee of 200 Euros. Application letter with indication of the IMP name, country of origin, manufacturer, dosage form, quantity and the importation purpose (“for clinical trials only”)
- Photocopy of the contract between the importing agent and the sponsor/representative (providing for importation of the appropriate CT materials)
- Two specifications with indication of the IMP name, country of origin, manufacturer, dosage form, quantity and total estimated cost
- Photocopy of RA (MoH) CT approval
- Photocopies of Certificate(s) of Analysis for each lot/batch included in the shipment indicating the country of origin, lot/batch number and expiry date (documents required for import permit application)
- Contract between the importing agent and the sponsor/representative (providing for importation of the appropriate CT materials, photocopy)
- CT protocol synopsis (in Russian)
- RA (MoH) CT approval (photocopy)
- Import permit (original)
- Airway bill (photocopy)
- Proforma-invoice (agreed upon in advance, original and Russian translation)
- Certificate(s) of Analysis for each lot/batch in the shipment indicating country of origin, lot/batch number and expiry date (photocopy)
- Other documents may need to be provided at customs request