Pharm-Olam
Helping Create A Healthier World

Clinical Trials in Belarus

A Primer for Sponsors

- Learn why Belarus has been called "An Undiscovered Gem" for clinical trials
- Gain an understanding of the country profile, the healthcare systems, approval processes, import/export licenses and patient recruitment procedures
- Obtain tips and strategies to capitalize on the advantages of running trials within Belarus

COUNTRY PROFILE

Belarus

- **Population**
  9.6 million in 2013,
  76% in urban centers
- **Land Area**
  Roughly the size of Romania
  or the state of Kansas in the USA
- **Location**
  North-East Europe, bordering
  Poland, Lithuania, and Latvia to
  the west; Ukraine to the south and
  Russia to the east and north.
- **Main Cities**
  Minsk (capital). Brest, Gomel,
  Grodno, Mogilev, and Vitebsk
  are all important regional centers
  representing more than a third of the
  population. Each of these cities has
  a population of 300,000-400,000
  and is served by regional hospitals
  that cover a population of 1 to
  1.4 million.
- **Political Structure**
  Stable, elected government
  similar to EU countries.The last
  presidential election took place in
  2010; the next is slated for 2015.
- **Economic Status**
  Maintains strong economic ties
  with Russia and EU countries and
  receives development funding from
  Russia, Austria, Germany, Turkey,
  and China, supporting general
  economic stability.
- **Health System**
  Government-funded National Health
  Service provides free healthcare
  and drug coverage in hospitals and
  out-patient clinics. Patients with an
  urgent need for consultation or who
  wish to receive a second opinion
  may opt to use private medical
  centers—either at their own
  expense or with coverage from a
  private insurance company.

An Undiscovered Gem

Belarus has much to offer life sciences companies as a location for clinical trials, not the least of which is the fact that it is not generally top of mind among study planners and is not saturated with competing trials. The country has a high percentage of patients who have not been exposed to state-of-the-art treatments, and at the same time it has the clinical infrastructure required to ensure patient safety, quality data, and efficient operations. Its experience with clinical trials dates back to the creation of the Center for Examinations and Tests in Health Service (CETHS) in 1997. Currently, about 40-50 (international, Phase II-IV) clinical trials are conducted in Belarus each year—far below what the population and conditions can support. The country's attractions for sponsor companies include:

- Strong patient enrollment rates, owing to a highly motivated patient population, three-quarters of which reside in urban centers (a ratio similar to that of France and Germany).
- A moderately large, modern-treatment-naïve population.
- A large pool of enthusiastic, English-speaking physicians whose experience in clinical research is continually developing. There are 4.9 physicians per 1,000 patients (double that of U.S., with a ratio of 2.42).
- Highly educated and well trained medical staff who are versed in Good Clinical Practices (GCP) (the regulatory standard) and compliant with requirements of both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).
- An overall cost structure that is favorable compared to other regions.

Understanding & Navigating Requirements

The Legislative & Regulatory Environment

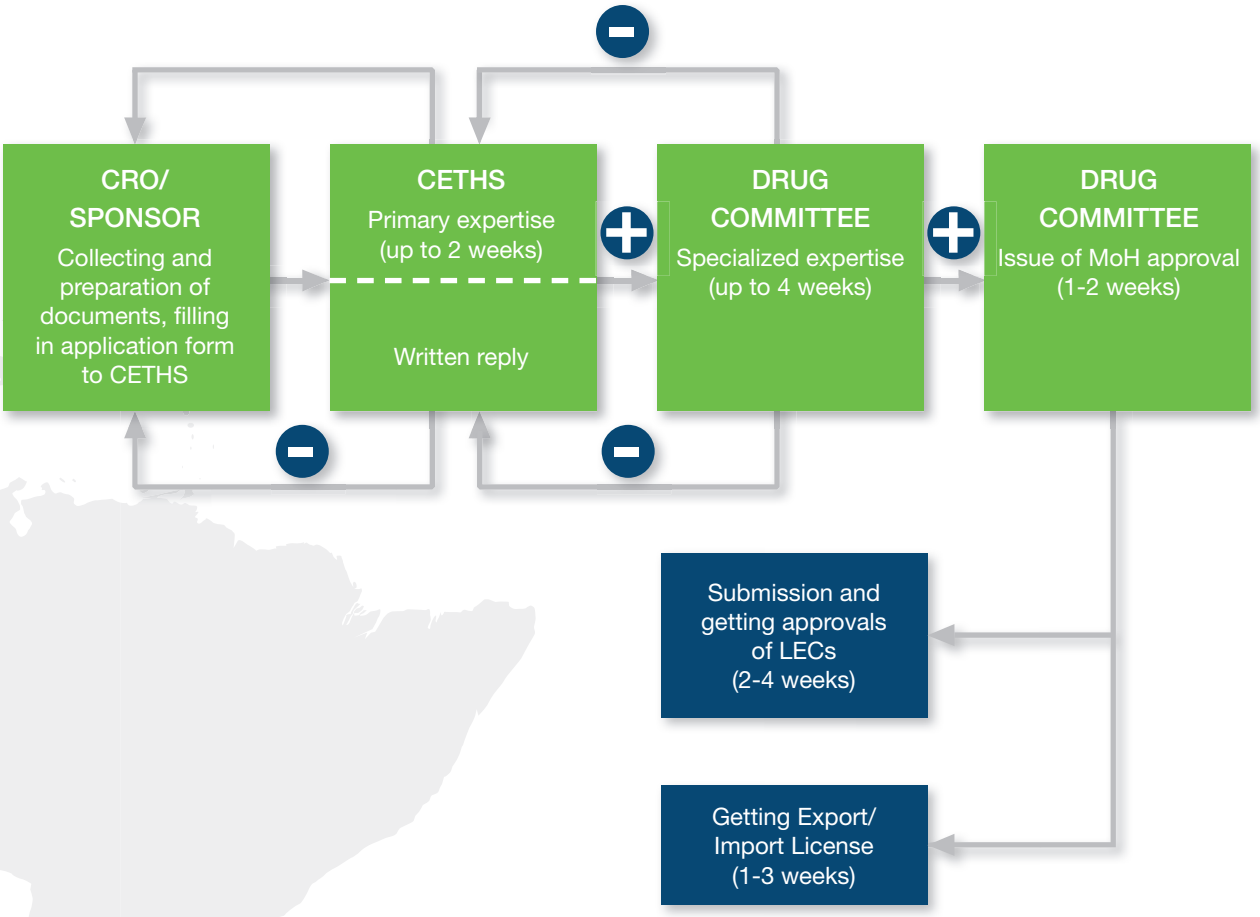
Within the Ministry of Health (MoH), the Center for Expertise and Trials in Health Services (CETHS) regulates pharmaceutical products, medical devices, and medical equipment in Belarus, ensuring their safety, efficiency, and quality. A division within CETHS, the Clinical and Pharmacological Laboratory (CPL), oversees clinical trials, evaluating applications and protocol amendments, supervising trials in progress, monitoring Serious Adverse Events (SAE) reporting, and approving drug import licenses.

The country's trial regulations follow the principles of the Declaration of Helsinki and the guidelines of the International Conference on Harmonization (ICH).

Approval Process for Conducting a Clinical Trial

The submission process for clinical trial approval is Belarus involves multiple handoffs between several different entities. *(See figure below)*. In general, approvals are managed by the MoH, through CETHS. Initial submissions are sent to CETHS and agreement for the conduct of expertise is issued on the day of submission. The fee ($2,400) is to be paid before expertise starts as the timelines commence after the fee is received on the RA account. CETHS forwards the hard copy files of the submission package to CPL for *primary expertise* and if CPL's feedback is positive – to the two independent experts for *specialized expertise*. These parties have eight weeks to complete their review. The files examined by experts are then discussed during the meetings of the Drug Committee, which are held monthly. Drug Committee issues an order with a list of approved studies. Based on this list, approval letters are then prepared and sent to the Deputy Minister of Health for review and signature. It may take approximately 1 to 3 weeks to be signed.

Approval of these additional submissions takes between 5 and 8 weeks.



Some steps can be completed in parallel (such as obtaining the MoH import/export license and seeking EC approval). In our experience over the past few years, the entire process, when planned properly, can normally be completed in 14-18 weeks.

The application documents, including nearly all sections of the Investigational Medicinal Product Dossier (IMPD) and certificates of quality for all intellectual property and concomitant medications, must be translated into Russian. It's worth noting that when studies are also being conducted in Russia, the documents prepared for that country can simply be replicated for Belarus, avoiding the need for a fresh translation.

Should changes in any number of specifications (such as the number of trial sites, the number of patients, or the names of the parties involved) be made, additional submissions are required. Approval of these additional submissions takes between three and ten weeks.

Import/Export Licenses

A separate import license (IL) is required to import pharmaceutical products into Belarus; it can be sought only after the above trial approvals are secured. Import licenses are only required for IMP and only Belarusian residential legal entities holding special permit (license) for the conduction of pharmaceutical or medical activities may apply for import licenses. This limits the applicants for import licenses to the warehouse/depot companies. This application for IL typically takes approximately two weeks and a fee of not more than $10 per license. Lab kits and study materials may be imported without an import license and can be delivered via broker companies or shipping depots.

Export licenses are required for biosamples, are free of charge and may be obtained by a CRO on behalf of Healthcare Institutions (sites). Export licenses can be obtained in approximately 2 weeks (~ 7 - 20 days). New guidelines released in November 2013 require that export licenses will not be issued prior to at least one shipment with IMP was imported to the country.

The Customs Union of Belarus, Kazakhstan, and Russia allows registered or marketed drug products and lab kits to be transported between these three states without having to go through customs procedures. This "open border" can be advantageous in provisioning and distributing intellectual property within the region.

The Healthcare System

Patients' medical expenses are covered by the government-funded National Health Service; although coverage for pharmaceuticals generally extends only to the lowest cost products—typically local generics. Patients opting for imported, branded products must pay out of pocket. This situation contributes to the high percentage of patients who have not been exposed to the latest pharmaceutical advances and who are eager to have access to groundbreaking treatments.

Care is provided in regional clinics and republic centers in urban areas and through out-patient clinics in rural areas. Rural patients are directed to urban centers for further consultation and treatment as necessary. In most cases, patients must be referred to specialists by a general practitioner following an examination and any necessary diagnostic tests.

The country has a high number of private medical centers which are licensed by the MoH and provide specialist consultations and laboratory testing, although these services are not covered by the government-funded healthcare program.

Belarus is particularly well suited to trials in oncology, cardiology, rheumatology, and transplants as Minsk is home to large, Republic Scientific Centers specializing in these areas. These centers are well equipped, staffed with clinicians who are experienced in conducting clinical trials, and maintain a rich patient database of potential trial participants. Regional treatment facilities are located within a 300 km radius of Minsk, so travel costs for Clinical Research Associates to and from Minsk are not exorbitant.

The country is not, however, conducive to running Phase I clinical studies sponsored by Multi-National Companies; there is little experience within the medical community, and the MoH and ECs impose many restrictions.

Physicians within Belarus are both highly educated and motivated to serve as Principle Investigators (PIs). They speak English at an intermediate or advanced level, are trained in GCP, and have experience in working with the local ECs.

In Belarus, sponsors may contract solely with the medical institution or with the hospital and PI together. Hospital administrators, of course, prefer that the contracts be made with the institution alone so that the facility can receive up to 90% of the grant. However, PIs are naturally more motivated to conduct trials in which they have a

contracted stake. A best practice approach is to give sites and PIs the opportunity to select the best variant for them.

Contracting with sites can be a lengthy process that requires review by the site's accounting, legal, and clinical teams as well as by the MoH calculation and legal departments. It is advisable to begin consultation with hospitals on the trial agreement three weeks before receiving MoH approval and to plan on another couple of weeks post approval to formalize the site contracts.

The Healthcare Profile

Cardiovascular diseases and cancer are the leading causes of mortality in Belarus. As of 2011, cardiovascular disease accounted for 52% of the country's mortality and oncology, 13.4%.

Patients' willingness to participate in clinical trials is generally very strong. They recognize that through the process they receive more intense medical attention than might otherwise be available. Trial participants have access to the latest treatment advances (rather than local generics) and benefit from additional examinations and tests under the constant supervision of the PI. Typically, in routine care, such experienced staff are not available to patients until after several consultations with specialists.

Study Implementation

Patient Recruitment

Clinical trial sites in Belarus (the large, Republic Scientific Centers) maintain rich patient databases from which potential trial participants can be recruited. PI's within these facilities also have extensive referral networks with local outpatient clinics and other consulting physicians, adding to their ability to identify potential study candidates. This, combined with patients' eagerness to receive the latest treatments means that conditions are conducive for rapid enrollment. In fact, efforts in Belarus can often make up for enrollment issues in other countries when one general target is used across multiple countries.

Data Quality

The technical code governing trials, as issued by the MoH, is in accord with GCP, and all Principle Investigators and site staff are trained in GCP as required by law and follow FDA and EMA requirements. In addition, CETHS inspects sites annually, and the MoH requests regular reports on trial progress, results, and safety findings. These steps have helped to ensure consistently high standards in how trials are conducted.

Strategies for Capitalizing on Advantages of Trials Within Belarus

To ensure the success of a clinical research study within Belarus, an organization should:

- Tap the knowledge of local experts in guiding trial applications through the approval process. It can be very beneficial to work with resources "on the ground" in Belarus to ensure that timelines are met.
- Seek support from local staff who have experience in working with regulators in order to facilitate progress in gaining customs clearance for imported products.
- Rely on highly qualified staff, with MDs serving as CRAs, Lead CRAs, and PMs whenever possible.
- Train sites during investigator meetings and site evaluation visits.
- Monitor sites, minimize travel costs, and increase quality via local offices.
- Develop relationships (or work with partners who have them) with local pharmacy depots to help furnish sites with the investigational drug in the most efficient way.
- Plan shipments of trial supplies carefully, given the absence of umbrella import licenses.

A Pro-Trial Environment

In summary, Belarus is a very rewarding clinical trial environment for sponsors, offering a trifecta of benefits:

- **Relatively expeditious trial approvals**, thanks to an efficient regulatory structure that conforms to the Declaration of Helsinki and ICH guidelines.
- **Rapid patient enrollment**, aided by rich patient databases of modern-treatment-naïve patients and extensive referral networks emanating from large, scientific centers.
- **High quality results**, owing to well-equipped facilities and sophisticated, English speaking clinician who are trained in GCP and FDA and EMA requirements.

About Pharm-Olam International

Pharm-Olam International is a global contract research company with a presence in over 40 countries, offering a wide range of comprehensive clinical research services to the pharmaceutical, biotechnology, and medical device industries. Since 2004, Pharm-Olam has conducted 20 trials in Belarus through our dedicated office in the capital city of Minsk.

For more information on planning successful trials within Belarus, contact **info@pharm-olam.com**.

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