

# **Clinical Studies in Eastern Europe: critical assessment of the regulatory requirements**

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## **List of Abbreviations:**

CIS	Commonwealth of Independent States
CRO	Contract Research Organization
CTA	Clinical Trial Application
CTP	Clinical Trial Protocol
EC	Ethics Committee
FDA	Food and Drug Administration
FECCIS	Forum for Ethics Committees in the Confederation of Independent States
EMA	European Medicines Agency
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
SOP	Standard Operating Procedure
US	United States
WHO	World Health Organization

## **CHAPTER 1: INTRODUCTION**

### **1.1 Eastern Europe as emerging market in clinical research**

Eastern Europe along with Latin America and Asia is viewed as an emerging market in clinical research. In the beginning of 1990es this region has attracted the attention of large pharmaceutical companies and contract research organizations (CROs) by offering lower operational costs and high recruitment rates of patients when compared to the well-established markets<sup>1</sup>. The definition of Eastern Europe depends a lot on the context, namely on whether political, geographical or socio-economical characteristics of the region are taken as a reference point. For the purpose of this work the term Eastern Europe refers to the countries that used to be the part of the Soviet Union and now form the Commonwealth of Independent States (CIS): Russia, Belarus, Ukraine, Moldova, Kazakhstan, Armenia, Azerbaijan, Kyrgyzstan, Tajikistan and Uzbekistan.

In addition to significant cost reductions and high recruitment rates, the market drivers for clinical research in Eastern Europe include centralized healthcare systems, broad disease spectrum, large pools of treatment naïve populations and low number of drop-outs<sup>1,2</sup>. According to some analysts, pharmaceutical industry currently utilizes only 15% of the clinical study enrollment potential in Eastern Europe<sup>1,3,4</sup>. Reports of the CROs and industry organizations confirm the growth of clinical activity in this region for the last fifteen years and predict that this tendency will continue<sup>4,5,6</sup>.

Along with the market attractiveness Eastern Europe brings in a number of limitations that cause concerns for many companies. Key barriers common for Eastern European countries and in fact for all emerging markets include poor infrastructure, lack of experienced researchers, erratic regulatory systems, ethical challenges and cultural perceptions about clinical research<sup>7,8</sup>. The level of manifestation of these limitations differs from country to country and has to be considered carefully when planning clinical studies in the region.

Although each Eastern European country has its own legislation, a number of steps have been done to harmonize the regulatory framework and principles for clinical research on the territory of the CIS. Growing attention to the ethical issues and the necessity to consider national perceptions and realities have led to the creation of the regional Forum for Ethics Committees in the Confederation of Independent States (FECCIS) under the umbrella of the World Health Organization (WHO) project on Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). This forum unites most of the countries that previously formed the Soviet Union, including those discussed here. Main goal of FECCIS is to contribute to the development of national ethics committees (ECs),



improve quality and transparency of the ethical review, ensure capacity building and promote policy development in clinical research<sup>9,10</sup>.

### **1.1.1 Eastern European countries chosen for the study**

Despite of the recognized geographical, cultural and economical similarities, Eastern Europe is far from being homogenous. For the purpose of this study we have chosen four countries in order to take a detailed look at the region and discuss the countries' regulatory and national particularities relevant for clinical research. Brief description of the chosen countries is given below.

#### *Russia*

Russia is a country in the northern Eurasia with a population of 141 million and a territory of 17 098 242 sq km. It is a multinational country with 79.8% of ethnic Russians, 3.8% of Tatars, 2% of Ukrainians and other nationalities<sup>11</sup>. 73% of the population lives in urban areas and is densest in European part up to the Ural Mountains and in southwest Siberia. Official language is Russian, the capital is Moscow. Other large cities, attractive for clinical research, include Saint Petersburg, Novosibirsk, Kazan, Yekaterinburg, Nizhniy Novgorod, Samara, Ufa and Rostov.

Russia was one of the first Eastern European countries that became involved in international clinical research in 1990es. From that time the national clinical research industry has entered the period of significant growth. For the last ten years the number of studies conducted in Russia by foreign companies has nearly tripled<sup>2</sup>, which is an affirmative sign for an emerging market. According to the report of the Synergy Research Group, a large CRO active in Eastern Europe, in the first quarter of 2010 Russian competent authority has approved 134 new clinical studies of all types, which corresponds to the 18% increase over the same period of last year. The main contribution into the total number of studies is made by multinational multi-center clinical studies.

Currently there are about 55 international and local CROs operating in Russia. Data obtained from the Russian sites is accepted by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)<sup>1,5</sup>. The high quality of Russian investigators is confirmed by FDA inspections, with the lowest deficiency rate among emerging markets including India, China and Latin America<sup>1,2</sup>. The investment power of global companies has created a well-developed study infrastructure in Russia during the past 15 years, and established a favorable environment for the second wave of middle-size sponsors to come into play.

#### *Belarus*

Belarus is a landlocked country with the total territory of 207 600 sq km. The capital of Belarus is Minsk, other major cities include Brest, Gomel and Mogilev. Most of Belarus's population of 9.67 million reside in the urban areas surrounding Minsk and other regional capitals<sup>12</sup>. More than 80% of the population are native Belarusians, with sizable minorities of Russians 13%, Poles 4% and Ukrainians 3%<sup>13</sup>. Belarus has had two official languages: Belarussian and Russian.

Although not known by many sponsors, Belarus is an attractive place to carry out clinical studies. For the last couple of years there were conducted about 60 international multicenter studies mainly in oncology, cardiology and diabetes<sup>6</sup>. One of the main advantages of the country are short approval times (1-3 months) and positive attitude of patients towards clinical research<sup>6</sup>.

#### *Kazakhstan*

Kazakhstan is located in Eurasia, northwest of China and is ranked as the ninth largest country in the world with the territory of 2 724 900 sq km and population of 20 million<sup>14</sup>. Kazakhstan has 131 nationalities including Kazakh 63%, Russian 30%, Ukrainian 3.7%, Uzbek 2.5% and Tatar 1.7%<sup>14</sup>. The capital is Astana, other major cities include Almaty, Karagandy and Oskemen. Official languages are Kazakh and Russian. Kazakhstan is a relatively new participant in the arena of clinical trials, however, continued growth is expected because the area offers opportunities for multiethnic studies – over half the population is composed of a variety of Asian ethnic groups.

#### *Moldova*

In comparison to the other three East European countries discussed here, Moldova is a small landlocked country in area and population. The territory of Moldova equals to 33 843 square km. Its population numbers nearly 4 million people including Moldovan 78.2%, Ukrainian 8.4%, Russian 5.8%, Bulgarian 1.9% and other 1.3%<sup>15</sup>. The country's main cities are the capital Chişinău, Tiraspol and Tighina. Official language is Moldovan. The current clinical research activity is very low, to the large extent due to the low healthcare standards<sup>8,15</sup>.

Due to the shared history of the Soviet Union Era the countries have common features in the structure of healthcare systems that include centralization, well-developed referral system and compulsory state insurance with basic healthcare package<sup>11,14,15,16</sup>. Main types of medical facilities are general hospitals and specialized clinics (located in all major towns and cities), polyclinics (serving residents in administrative districts) and first-aid stations offering medical care to the people in the rural areas. The quality of the healthcare has declined in the post-Soviet times due to the lack of adequate government funding and

loss of qualified experts through emigration<sup>11,14,15,16</sup>. Private medical sector is present only in the large cities and is accessible to the very narrow section of the population. The current conditions in the state hospitals are not always favorable: lack of hot water or absence of waste disposal system is identified in about 30% of the medical facilities<sup>14,15,16</sup>. Tables 1 and 2 provide data on the countries' healthcare workforce and infrastructure.

**Table 1. Healthcare workforce in the study countries<sup>17</sup>**

Country	No of physicians	Physicians density*	No of nursing personnel	Nursing personnel density*	No of pharmaceutical personnel	Density of pharmaceutical personnel
Russia	614183	43.1	1214292	85.2	11521	0.8
Belarus	46965	48.7	121114	125.6	2994	3.1
Kazakhstan	57387	38.8	115944	78.3	12651	8.6
Moldova	11167	26.7	27815	66.5	2993	7.2

\* per 10 000 population

For comparison, physicians' density in Germany is 34.8; density of nursing and pharmaceutical personnel is 79.9 and 6.0 respectively<sup>17</sup>.

**Table 2. Healthcare infrastructure in the study countries<sup>11,14,15,16,17</sup>**

Country	Number of hospitals	Number of outpatient clinics	Hospital beds*
Russia	11 100	21 100	96.6
Belarus	649	796	112.3
Kazakhstan	1054	3720	77.2
Moldova	65	254	61.2

\* per 10 000 population

For comparison, there are 82.9 hospital beds per 10 000 population in Germany with about 2221 hospitals<sup>17,18</sup>.

## 1.2 Study Objectives

The purpose of this study is to analyze the regulatory requirements for clinical research in four East European countries: Russia, Belarus, Moldova and Kazakhstan. The analysis is done from the position of the foreign company, rather than the competent authority or national manufacturer. Special attention is given to the differences in the regulatory systems between the countries and cultural particularities that may impact clinical research. Eastern European countries still remain unknown territory for many sponsors due to the language barrier, legal and cultural differences. We believe that this work will help companies to understand advantages and disadvantages of each particular country as

potential study site and improve their strategic planning. Apart of evaluation of legislative documents this study provides the outcome of the survey carried out with the representatives of competent authorities and research industry, where they share their opinions in conducting clinical studies in these countries. Their experience is of a great value, because it helps to appreciate the current state of affairs in clinical research market from practical point of view and show how indeed regulatory requirements and procedures get implemented in real life.

The study objectives are the following:

1. To describe main regulatory procedures in clinical research
2. To compare regulatory requirements and procedures between the countries
3. To describe opinions of regulators and research companies on existing regulatory systems in the region

### **1.3 Methods of data collection**

To attain the desired objectives of the study, the following methods of data collection were used:

1. Review of the national legislative documents

Since the format of this work does not allow covering all regulatory aspects relevant for conduct of the clinical study, the focus is put on the following procedures:

- Approval of a clinical trial application (CTA)
- Notification of amendments
- Declaration of the end of the trial
- ECs structure and procedures
- Requirements to clinical studies in vulnerable populations
- Customs regulations on the investigational medicinal product (IMP) and human biological material

2. Questionnaire survey of the representatives of the competent authorities and research companies

The questionnaire survey was carried out to collect the data from representatives of the competent authorities and research companies active in the study countries. The questionnaire was developed with the help of the European Forum for Good Clinical Practice. The questionnaire was accompanied by the open letter, which explained the purpose of the study, survey procedure and confidentiality aspects (Annex 7). Both documents were provided to the respondents either in English or Russian language. The surveys was carried out either per email or per telephone depending on the choice of the

participant. The initial contact to the representatives of the competent authorities was established with the support of Prof. Dr. O. Kubar, Education Officer and Ex-Chair of the FECCIS.

To ensure the confidentiality of the survey, no personal names or names of the companies are mentioned in this study. When presenting the results of the survey, reference to the country (e.g. Moldova) and to the professional area of respondents (defined either as “representative of the competent authority” or “industry representative”) is made.

## **CHAPTER 2: CLINICAL RESEARCH IN RUSSIA**

### **2.1 Overview of major national legislation in clinical research**

Clinical research in Russia is regulated by the following legislative documents:

1. Federal Drug Law No. 61 of 24 Mar 2010 – enters into force on 1 Sep 2010;

After series of discussions the Russian legislative authority – State Duma – has adopted the new federal Drug Law No. 61 in March 2009. This law amends a number of legislative documents, among them the federal Drug Law No. 86 that currently regulates clinical research in Russia. Although the new Drug Law enters into force in Sep 2010, principles and procedures described here refer to this new regulation. The Drug Law No. 61 introduces significant procedural changes in the pharmaceutical regulation, including changes in marketing authorization procedure, new requirements to the state regulation of prices on essential medicines and pre-clinical and clinical studies. With respect to the latter it changes the clinical trial authorization procedure, strengthens requirements to the sponsor and investigator, lays down new conditions for compulsory health insurance for study subjects. It introduces new terms: international multicenter clinical study, post-marketing study, drug formulation and bioequivalence study.

The Drug Law No. 61 requires conducting local clinical studies in Russia for the purpose of marketing authorization, except of the following cases:

1. Medicinal product has been on the market for the last 20 years and does not allow conduct of bioequivalence studies;
2. Clinical development program of medicinal product include Russia as a study site;
3. There is a bilateral agreement between the countries on the recognition of the results of clinical studies.

The Drug Law No. 61 for the first time lays down separate approval procedure for local clinical studies and international multicenter and post-marketing studies. For authorization

of generic medicinal products bioequivalence and/or therapeutic equivalence studies are required.

2. Federal Drug Law No. 86 of 22 Jun 1998 – to be amended by the Drug Law No. 61;
3. The National Standard on Good Clinical Practice adopted by the Order No. 232 of 27 Sep 2005 –a comprehensive and exact translation of ICH GCP;
4. The Guideline on monitoring of adverse drug events during clinical studies of 5 Oct 2009;
5. The Order of the Ministry of Health No. 2314-Пp/07 on the National Ethics Committee of 17 Aug 2007;
6. The Order of the Ministry of Health No. 235 on organization of departments for conduct of clinical studies in healthy volunteers of 25 Aug 1992;
7. The Regulation No. 291-22/101 on national ethics committees of 23 Aug 2001 – lays down the responsibilities of local committees and their role in clinical research.
8. The Guideline on conduct of bioequivalence studies of 10 Aug 2004;
9. The industry standard on clinical-economical studies 91500.14.0001-2002.

## **2.2 Main regulatory procedures**

### **2.2.1 Clinical trial authorization**

Clinical studies in Russia can be conducted for the following purposes:

1. To ensure safety and/or tolerability of the IMP in healthy volunteers except of the IMP manufactured outside of Russia;
2. To develop optimal dosage and course of treatment of the IMP in patients and dosage and vaccination schemes for immunological products in healthy volunteers;
3. To ensure safety and efficacy of the IMP in patients and safety and efficacy of immunological products in healthy volunteers;
4. To develop a new indication and/or to identify adverse drug reactions of authorized products.

Under the Drug Law No. 86 the competent authority responsible for approval and supervision of clinical studies is Federal Service on Surveillance in Healthcare and Social Development (hereinafter referred as Roszdravnadzor). It has in its structure the Scientific Center for Expertise and State Control of Medicinal Products that performs scientific evaluation of the CTA. The Roszdravnadzor is also responsible for accreditation of health facilities wishing to become research sites and for issuing import permissions for the IMP.

The Drug Law No. 61 transfers functions of study approval and supervision to a new federal state authority (FSA). The FSA does not perform any evaluation, but issues study

approvals based on the opinion of the federal state-financed agency responsible for scientific evaluation of medicinal products (hereinafter referred as the Expert Commission).

The study approval procedure consists of the following steps:

1. Pre-assessment phase: the applicant submits an application to the FSA that evaluates its accuracy within 5 days and decides on the start of the assessment procedure or rejects the application due to its incompleteness. When the application is submitted during the evaluation of the registration dossier to conduct local clinical trials, the required CTA documents include:

- Results of pre-clinical studies
- Clinical trial protocol (CTP)
- Investigator's Brochure (IB)
- Informed consent form
- Patient information
- Information on compensation to study participants
- Results of clinical studies conducted worldwide (optional)
- Certificate of Pharmaceutical Product if product is not registered in Russia
- Mock ups for primary and secondary package
- Copy of manufacturing authorization translated into Russian
- Description of the manufacturing process
- IMP storage and transport conditions
- Payment of administrative fee

The CTA to conduct international multicenter or post-marketing studies includes:

- Application form
- Reports on pre-clinical studies
- Reports on already conducted clinical studies (if applicable)
- CTP
- IB
- Patient information
- Payment of administrative fee
- Information on the IMP composition (only for international multicenter trials)
- Copies of compulsory health insurance contracts for study subjects
- Documents confirming qualification of investigators

2. The FSA sends submitted documents to the National EC and to the Expert Commission with the request to conduct ethical and scientific evaluation of the CTA.

3. Opinions of the National EC and the Expert Commission are sent to the FSA within 30 days.
4. The FSA communicates results of conducted expertise to the applicant within 5 days and informs him whether he can proceed with application.
5. When the applicant is allowed to proceed with the application, he submits a request for study authorization to the FSA together with documents confirming qualification of investigators and copies of health insurance contracts for study subjects.
6. The FSA evaluates submitted documents within 5 days and issues a study approval. For international and post-marketing studies the last two steps seem to be omitted, since the applicant is required to submit all the documents at once; however, there is no direct indication to it in the law.

Post-marketing study is defined as a study conducted by the manufacturer of the medicinal product after its registration in order to gather information on its safety and efficacy, adverse events and for development of new indication.

International multicenter study is defined as a clinical study of the medicinal product conducted by the sponsor in different countries according to the single clinical trial protocol.

After receiving a study approval, the sponsor submits clinical trial documentation to the local EC, although its approval is not required for study initiation.

### **2.2.2 Notification of amendments**

Every amendment to the CTP should be submitted to the FSA for approval. Procedure for amendments is not described in the reviewed legislation, it is only stated that the FSA opinion is issued within 30 days. The Drug Law No. 61 does not specify procedure for urgent amendments and does not distinguish between substantial and non-substantial amendments. However, the standard operation procedure (SOP) No. 4 of the National EC describes accelerated procedure for ethical evaluation of certain types of amendments. It is used for example, in the following cases:

1. Change of the principle investigator;
2. Introduction of additional patient materials: booklets, diaries etc.;
3. Inclusion of new study site or change in the number of patients;
4. Extension of study duration;

A decision on whether the accelerated procedure can be applied is made by the National EC on case by case basis. During the accelerated procedure evaluation is performed by the Working Group of the EC, which consists of a chairman or its deputy and 5 EC members.



Opinion is adopted by the unanimous vote. When at least one member of the Working Group does not agree with the proposed amendment, the evaluation is carried out through the regular review procedure.

### **2.2.3 Declaration of the end of the trial**

The sponsor should notify the FSA about the end of the trial, its temporary halt or premature termination within 5 days. Decision to halt the trial can be made by the sponsor or by the head of medical facility concerned. Decision to prematurely terminate the trial can be made by the FSA or by the sponsor after the written notification from the head of medical facility is obtained. Documents submitted to the FSA, regardless of the nature of study end, include a list of participated centers, study description, information on the principle investigator (name, qualification, experience in clinical research), status of the study (ended, prematurely terminated, temporary halted) with justification and overall risk-benefit assessment for the IMP with proposed actions. Information about study status is posted on the website of the FSA within 5 days after the notification is obtained.

## **2.3 Ethical principles in clinical research**

### **2.3.1 Structure of the Ethics Committees and review procedure**

There are two types of ECs in Russia:

1. National EC– is organized within the Ministry of Health and is responsible for carrying out ethical expertise during the clinical trial approval procedure;
2. Local ECs – are organized at the medical facilities, higher educational institutions or research centers accredited to conduct clinical studies. After the FSA study approval the applicant submits clinical trial documentation to the local EC. Approval of the local EC is not required for the study initiation but is usually carried out.

The review procedure at the National EC is the following:

1. The National EC receives a request from the FAS to conduct ethical evaluation together with the study documentation: CTP, IB, Patient information and information on payments and compensation to study participants.
2. An assessment report is prepared by one of the EC members and is discussed during the next committee meeting. Based on the received comments, the member who has prepared the report formulates the final opinion.

In case of raised questions or unsolved issues a decision is postponed until the applicant provides the response. Re-examination of the documents is done by one EC member (preferably the same as during the first assessment) and the final opinion is issued during

the next meeting. Re-examination can be conducted through accelerated procedure designed for the review of certain types of amendments. A mandatory requirement in this case is participation of expert(s) who raised question(s) during the initial assessment. A decision on whether the documents for re-examination are eligible for accelerated procedure is made by the Working Group of the National EC. The National EC has to submit its opinion to the FSA within 30 days after receiving a request.

National EC meeting is considered valid when at least a half of the members is present. When necessary, the sponsor or investigator can be invited to the ethical review procedure in order to provide additional information on any aspect of the study. However, they do not participate in the discussion or voting. The National EC may request participation of external experts when additional expertise to assess the CTA is needed. A list of national EC members, meeting schedule and current activities are published on the website of the Ministry of Health.

Local ECs assist the applicant in the development of the CTP and monitor the study conduct in the respective medical facility. In particular, local ECs ensure compliance to the CTP, timely notification of amendments and adverse events and protection of study subjects. Local ECs closely cooperate with the National EC and inform the latter about infringements or violations of regulatory and ethical principles at the study sites.

### **2.3.2 Clinical research in vulnerable populations**

Clinical trials in Russia can not be conducted on:

1. Orphans and children left without parental care;
2. Pregnant or breast-feeding women, except when the following conditions are met:
  - The IMP is being developed for use in pregnant and/or breastfeeding women;
  - There is no other way to obtain the necessary information except clinical study;
  - All necessary measures are taken to eliminate the risk for woman, fetus or child;
3. Armed forces personnel, except of the IMP being developed for use in hostilities, emergency situations, prophylaxis or treatment of diseases emerged due to the chemical, biological factors and radiation.
4. Personnel of law enforcement agencies;
5. Persons in detention;
6. Adults incapable to give informed consent;

Incapacitated adults with mental diseases can be included in the clinical study when the IMP is developed for treatment of mental diseases. The agreement of the legal representative is mandatory.

## **2.4 Customs regulations on IMP and human biological material**

Russia, Belarus and Kazakhstan have established a single customs union regulated by single legislation. According to the Position on the import of the medicinal products and pharmaceutical substances on the territory of the customs union of 1 Dec 2009, unauthorized medicinal products and pharmaceutical substances can be imported on the territory of the customs union for the purpose of clinical research. Permission from the competent authority of the concerned country is required.

In January 2010 a Resolution No. 132 on a single nontariff regulation of customs union of Belarus, Kazakhstan and Russia has entered into force. It states that medicinal products, pharmaceutical substances, human organs and tissues, blood and its components can be imported and exported on/from the territory of the customs union only under the license from the competent authority. This resolution however does not hold true for human biological material obtained during the clinical studies. According to the Article 3 of the Position on the import and export of the human organs and/or tissues, blood and its components in the territory of the customs union of 1 Dec 2009, export and import of the human biological materials intended for diagnostic and scientific purposes or obtained during the biomedical studies requires a permission of the competent authority of the country concerned and not a license.

In Russia customs requirements to the IMP and human biological material are reflected in the Articles 40 and 47 of the Drug Law No. 61. Sampling of human biological material (e.g. body fluids, tissue, waste products, etc) during clinical study can be done for the purpose of its examination in or outside of Russia. The competent authority issuing import and export permissions for unauthorized medicinal products and human biological material for the purposes of clinical research is Roszdravnadzor. Requirements to the import and export of unauthorized medicinal products are described in the Regulation No. 438 of 16 Jul 2005. Import permission is issued for every new product batch; required documentation includes application form with the calculation of the amount needed with the reference to the CTP. Import permission is issued within 3-5 working days. Article 64 of the Drug Law No. 61 lays down the labeling requirements for medicinal products including those to be used in clinical studies. A statement "For use in clinical trials" should be put on both primary and secondary package. Organizations that can import unauthorized medicinal products include: foreign manufacturers of the IMP or other authorized juridical bodies, national research organizations, higher educational institutions and national manufacturers of the IMP. Documents to be provided to the customs at the entry point include copy of clinical study approval from the competent authority, copies of

the IMP quality documentation from the manufacturer including the manufacturing authorization and import permission from the Roszdravnadzor issued for each batch of the imported IMP. Export of the medicinal products is done without regulatory restrictions.

To obtain export permission for human biological material the applicant submits to the Roszdravnadzor an application form, description of intended tests with the references to the CTP and to the laboratory reports.

In Kazakhstan import and export requirements for the IMP are stated in the Articles 80 and 81 of the Code and in the Order No. 710 on regulation of import and export of medicinal products and medical devices of 16 Nov 2009. The competent authority responsible for issuing permissions is the Committee on Supervision of Medical and Pharmaceutical Practice within the Ministry of Health. Documents required to issue permission include application form, copy of state registration as a physical or juridical body, copy of invoice in Russian and in national language, copy of clinical study approval and the IMP quality documentation. Importation can be done by manufacturers registered in Kazakhstan, research organizations and laboratories, by foreign manufacturers, their subsidiaries or their authorized physical or corporate body for the purposes of clinical study. Requirements to the documentation necessary to obtain export permission for human biological material in Kazakhstan have not been found in the reviewed legislation.

In Belarus competent authority responsible for issuing import permissions for unauthorized medicinal products and human biological material to be used in clinical research is the Center of Expertise and Examination in Healthcare within the Ministry of Health. Requirements to import and export of the IMP are laid down in the Regulation No. 1397 on movement of the specific types of the goods through the customs of Belarus of 23 Sep 2008. Documents required for import permission include application form (with trade name and INN, manufacturer, manufacturing country, pharmaceutical form, importing amounts and purpose of import stated), copy of invoice or import agreement with specifications, copy of clinical study approval, the IMP quality documentation. Documents submitted in foreign languages have to be translated either in Russian or Byelorussian and translation has to be notarized. Permission is issued within 20 days.

Customs requirements to human biological material are laid down in the Resolution of the Council of Ministers of Belarus No. 1397 of 23 Sept 2008. Documents required for export permission are application form, import permission from the competent authority of importing country (except of international multicenter clinical studies), copy of the contract (except of human blood and its components used in international multicenter clinical studies) and copy of contract specification. Permission is issued within one day

and is valid 6 months for human organs and/or tissues, blood and its components; for international multicenter clinical studies export permission for blood and its components is valid during the complete study duration.

## **CHAPTER 3: CLINICAL RESEARCH IN BELARUS**

### **3.1 Overview of major national legislation in clinical research**

Clinical Research in Belarus is regulated by the following legislative documents:

1. Public Health Law No. 2435-XII of 18 Jun 1993 with amendments;
2. Drug Law No. 161-3 of 20 Jul 2006 with amendments – described procedures on pre-clinical and clinical studies, import and export of medicinal products, lays down rights and responsibilities of study subjects.
3. The Resolution of Council of Ministers No. 1677 on quality control of medicinal products of 22 Dec 2009;
4. Good Clinical Practice of Belarus approved by resolution of the Ministry of Health No. 50 of 7 May 2009;
5. The Guideline on Ethics Committee No. 57-0004 of 24 Apr 2000 – provides description of principles and procedures of ECs including clinical trial authorization, review of amendments, inspections. The guideline lays down content of the Informed consent form, application form and clinical trial report.
6. The Order of the Ministry of Health No. 88 on Pharmacological and Pharmacopoeia Committees of 18 Mar 1998;
7. The Instruction of the Ministry of Health No. 50-0504 on accreditation of health facilities and health specialists to conduct clinical studies of medicinal products and medical devices of 7 May 2005;
8. The Order of the Ministry of Health No. 274 on the National Bioethics Committee of 17 Apr 2006.

### **3.2 Main regulatory procedures**

#### **3.2.1 Clinical trial authorization**

Clinical studies in Belarus can be conducted for the following purposes:

- To discover or verify clinical effects of the IMP;
- To identify adverse events;
- To study absorption, distribution and excretion;

The competent authority responsible for approval and supervision of clinical studies is the Center of Expertise and Examination in Healthcare within Ministry of Health

(hereinafter referred to as the State Center). There are two expert agencies responsible for scientific assessment of the CTA within the State Center: Pharmacological Committee and Pharmacopoeia Committee. Responsibilities of Pharmacological Committee relevant for clinical research include:

- To review pre-clinical data when deciding on reasonability of a clinical study;
- To submit proposals to the State Center to conduct clinical trials for new pharmacological substances, new indications for already authorized medicines and medicines, authorized abroad.
- To review and approve guidelines on clinical studies of new pharmacological substances, new indications for already authorized medicines and medicines authorized abroad;.
- To conduct expert review of national guidelines on pre- and clinical studies;

Responsibilities of the Pharmacopoeia Committee relevant for clinical research include:

- To review regulatory documentation on quality of medicinal products intended for use in clinical studies and for registration;
- To conduct expert appraisal of dossier documentation of foreign medicinal products submitted for registration;

The study approval procedure consists of the following steps:

1. The applicant submits the following documents to the State Center:

- Application form
- CTP
- IB
- Informed consent form
- Patients information
- Certificate of Analysis of the IMP
- GMP certificate
- List of the study sites
- Draft contract with health facility
- Health insurance contracts of study subjects
- Payment of administrative fee

2. The State Center forwards submitted documents to the Pharmacologic and Pharmacopoeia Committees for scientific evaluation

3. In parallel the principle investigator submits the following documents to the local EC:

- Application form
- CTP

- IB
- Informed consent form
- Patient information
- Advertisements for subjects' recruitment
- Diaries, questionnaires for study subjects, if applicable
- Compensation to study subjects, if applicable
- Resumes of investigators (only after explicit request from the EC)
- Copies of previous EC opinions, if applicable
- Additional documents that may facilitate review procedure

Submitted documents go through either standard (30 days) or accelerated (one week) ethical review procedure.

4. Opinion of the local EC is sent to the applicant within 5 days for standard procedure or within two weeks for accelerated procedure.
5. The applicant submits result of ethical evaluation to the State Center.
6. When scientific and ethical evaluations are positive, the Chairmen of Pharmacological committee approves the CTA and study can be initiated.

### **3.2.2 Notification of amendments**

Requirements to the submission and review procedure by the competent authority have not been identified in the reviewed legislation. The Guideline on Ethics Committee No. 57-0004 of 24 Apr 2000 states that ethical review of minor amendments to the study protocol can be done through accelerated procedure. Minor amendments are defined as those that do not increase risk for study subjects, do not infringe upon subjects' rights and upon the principle of confidentiality.

### **3.2.3 Declaration of the end of the trial**

Notification of the study end of is submitted by the investigator to the State Center, the EC concerned and to the administration of the health facility only in case of premature termination or temporary halt of the study.

## **3.3 Ethical principles in clinical research**

### **3.3.1 Structure of Ethics Committees and review procedure**

Ethical evaluation of every CTA in Belarus is done by the local EC at the health facility concerned. The National Bioethics Committee established in 2006 has a status of advisory body. Its responsibilities include providing training in bioethics, developing legislative

initiatives, facilitating international cooperation. Since the National Bioethics Committee is not directly involved in clinical study authorization and monitoring, we will focus on the structure and procedures of the local committees in Belarus.

Main purposes of ethical evaluation of the CTA are:

1. To assess risk-benefit ratio for study subjects and society;
2. To ensure that study subjects fully understand nature of a study and are able to make informed decision regarding their participation;
3. To ensure confidentiality and sanctity of the study subjects' private life;
4. To ascertain that selection of study subjects is unbiased;
5. To confirm that safety of study subjects has been considered during the development of the CTP;
6. To evaluate financial aspects of the study, namely compensations to study subjects (if applicable) to avoid financial incentive in participation;

According to the procedural guidance on Ethics Committees, informed consent of the study subjects is not required when:

1. A person is in the life-threatening condition, all conventional therapeutic methods have no effect or their efficacy is not proven and an overall amount of available information, including data from randomized placebo-controlled trials, is sufficient to estimate safety and efficacy of planning intervention.
2. It is impossible to obtain an informed consent because:
  - Study subject is not able to give an informed consent due to their clinical condition, or
  - Clinical study intervention must be assigned before it is possible to obtain an agreement of subject's close relative/legal representative, or
  - It is not possible to determine in advance whether a study subject meets inclusion criteria of the study.
3. A participation in the study will possibly provide direct health benefit, because:
  - Study subject has a life-threatening condition that requires medical intervention, and
  - All necessary pre-clinical studies have been conducted and obtained information and other supporting data confirm that planning intervention will bring direct benefit to study subject, and
  - Risk attributed to the participation in a study is justified, considering clinical condition of study subject, risk and benefit of conventional therapeutic methods (if they exist) for the well-being of study subject as well as risk and benefit of planning intervention.

The EC may abolish informed consent procedure for some or all study subjects, if it decides that:



1. Informed consent form is the only documentary confirmation of participation in the study and the main risk for study subject lies in the breach of anonymity. In this case every participant should be asked whether he/she wants to have a documentary confirmation of participation in the study and his/her reply should serve as a guide for action.

2. Clinical study includes minimum risk for participants and does not contain any procedure that usually requires informed consent.

If informed consent procedure is abolished, the EC may still request the investigator to provide information about clinical study to the participants in the written form.

There are two ethical review procedures in place: standard and accelerated procedure. Decision on which procedure applies is made by the chairman on the case by case basis after the CTA submission. When the CTA goes through standard procedure, the chairman determines the date of the meeting, which should be not later than 30 days after the receipt of the application. The EC provides its opinion to the investigator within 5 days after the meeting; EC opinion can be one of the following:

- approval of the CTA;
- request to introduce amendments to the CTP;
- rejection of the CTA;

In case of a positive decision the EC determines the duration of issued approval, frequency of study documents revision, date of the next inspection and specifies investigator's responsibilities (e.g. notification of amendments, notification of the end of the study, submission of study results or decisions of other EC). By minor amendments or when document(s) of minor importance are requested, the EC may delegate a final approval of the CTA to the chairman. In this case approval is issued after amendments are introduced or required documents are submitted by the investigator; the EC not allowed to issue preliminary approvals. If the investigator does not agree with the EC decision or required amendments, he can appeal to the State Center or request the EC to appoint independent adjudicators or submit such request to the competent authorities.

Accelerated procedure is designed to spare time and resources of the EC and to facilitate the beginning of the clinical study. This procedure can be applied to a limited number of studies and its unjustified implementation is a violation of ethical principles. The purpose of accelerated review is to make sure that study subjects undergo a minimum risk and that the study does not exceed limits set by accelerated procedure.

Examples of the studies that impose a minimal risk on the health of study subjects and therefore eligible for accelerated procedure are given in the guideline on Ethics Committee and include the following:

- Hair and nails sampling if it does not impair appearance of study subjects;
- Collection of primary teeth and temporary teeth, extracted according to the medical indication;
- Sampling of physiological discharges of human body including sweat, saliva, placenta obtained during delivery; amniotic fluid obtained by rupture of amniotic fluid sac before or during delivery;
- Collection of data from the subjects not younger than 18 years old with the help of noninvasive methods used in clinical practice, such as weighing, electrocardiography, electroencephalography, thermography, diagnostic echoscopy, electroretinography and physical sensors, applied on the body surface or operating on the distance. X-ray methods and ultra short wave radiation exposure are not eligible for accelerated procedure.
- Venous blood sampling (not more than 450 ml) from healthy volunteers not younger than 18 years old, except pregnant women. Blood sampling should be done with the maximum frequency of twice a week and no longer than for 8 weeks.
- Collection of dental deposit und dental tartar, which is in line with generally used methods of prophylaxis;
- Medium physical activity for healthy volunteers;
- Secondary data analysis (medical documentation, postmortem specimen, diagnostic specimen);
- Study of human behavior, both individual and in the social medium, or study of personality features such as perception, cognitive ability, tests, and games – provided that investigator does not influence the study subjects in any way and participation in the study is not stressful.
- Non experimental studies of pharmaceutical products or medical devices;
- Voice recording for research purposes, e.g. study of speech defects;

Accelerated procedure is carried out within one week either by the chairman or by one of the experienced members of the EC. Positive decision is communicated to the investigator in the written form within two weeks. In case of negative decision or when amendments to submitted documentation are required, the CTA goes through the standard procedure.

Local EC usually consists of 5 to 12 members including medical specialists experienced in clinical research and members with the expertise outside of medicine and natural sciences. Decision on the CTA can be made only in the presence of minimum two thirds of the EC members with constituent including at least one non-scientist. Decision is adopted either unanimously or by majority of the votes. In the latter case opinion of the

minority voters is documented and communicated to sponsor and investigator together with the adopted decision.

Belarus legislation implies close communication between sponsor and the EC during study conduct. In Procedural Guideline on Ethics Committee No. 57-0004 it is stated that review of clinical study documentation and constant assessment of risk-benefit ratio during the study conduct is as important as the initial study approval. Into consideration are taken not only intermediate results from one particular study, but also data obtained from other clinical studies on the same IMP.

Methods of ethical supervision of the study include the following:

1. Review of investigators' reports. Frequency of reporting is determined by the EC and stated in the initial study approval. Investigators' reports should include the following information:

- Recruitment rate;
- Information on adverse drug events and adverse drug reactions;
- Exclusion of the subjects from the study and the reasons for it;
- Protocol amendments;
- New data on the IMP safety profile;
- Detected or anticipated problems with regard to the study conduct;

Investigator shall immediately submit reports to the EC regarding any changes or incidents, which may influence study performance and increase risk for study subjects, such as:

- Protocol amendments;
- Urgent measures taken to eliminate immediate danger for study subjects;
- Adverse and unexpected drug reactions identified during the trial;
- New data that may affect safety of trial subjects or study performance;

2. Inspection: the EC reviews clinical study documentation annually or more often, depending on the risk level for study subjects. The EC review procedure is the following: The EC members or third party experts, appointed by the EC chairman, inform the investigator about date and time of inspection and type of the documents for review. During inspection the investigator provides all requested documents and allows access to primary medical documentation on study subjects.

Reviewers evaluate the following aspects:

1. whether current risk-benefit ratio corresponds to risk-benefit ratio estimated in the CTA;

2. whether any adverse or unexpected drug events have been registered during the study and whether they have been reported to the EC;
3. whether protocol amendments have been introduced and if yes, whether they have been approved by the EC and properly documented;
4. whether serious accidents have been registered during the study;
5. whether new data on the IMP safety are available and whether it were reported to the EC;
6. whether Informed consent form has been amended, and if yes, whether it was approved by the EC;
7. whether informed consent procedure is carried out with compliance to regulatory requirements; to control this, reviewers should attend the informed consent procedure.

Reviewers provide written report to the EC chairman together with recommendations on prolongation, suspension or termination of the study. Within one week after report is submitted EC issues one of the following opinions:

- to prolong the study approval;
- to suspend the study approval;
- to withdraw the approval;

If during the EC meeting minor critical comments are made, investigator should resolve them within the certain period determined by the EC; after that study approval can be prolonged. The EC determines effective period of the new approval and date of the next inspection. When study approval is suspended or withdrawn, the EC informs the investigator and competent authorities about its decision. In case the EC does not come to the decision and the period of initial study approval is expired, the investigator should stop the study until the decision is made. When report is reviewed through the accelerated procedure, the EC chairman can prolong study approval himself.

### **3.3.2 Clinical research in vulnerable populations**

Clinical studies in Belarus can not be performed on:

1. Pregnant women, unless the IMP is developed only for use in pregnant women or the study purpose is to optimize dosing or treatment regimen in pregnant women, and when required information can be obtained only through a clinical study and there is no risk for woman and fetus.
2. Children, unless the IMP is developed to be used in paediatric population or when the purpose of the study is to optimize dosing or treatment regimen in paediatric population.
3. Orphans and children left without parental care;

4. Armed forces personnel;
5. Persons kept in detention;
6. Adults incapable to give informed consent;
7. Persons suffering from mental derangement and being on compulsory treatment in psychiatric facilities;

When clinical study is to be performed on vulnerable populations, the EC invites to the review procedure one or more specialists who are familiar with this population group and have experience of working with them. They become temporary members of the EC and possess constituent power.

### **3.4 Customs regulations of IMP and human biological material**

See Chapter 2, section 2.4

## **CHAPTER 4: CLINICAL RESEARCH IN MOLDOVA**

### **4.1 Overview of major national legislation in clinical research**

Clinical research in Moldova is regulated by the following legislative documents:

1. The Drug Law No. 1409 -XIII of 17 Dec 1997 with amendments – determines main principles of the CTA approval procedure, protection of study subjects and role of expert commissions in clinical research. The Drug Law also includes provisions on drug registration, manufacture, quality assurance, labeling and promotion.
2. The Law No. 1456-XII on pharmaceutical practice of 25 May 1993 with amendments – provides definition of pharmaceutical practice, approval and registration procedure, registration dossier, medicinal product and drug quality; describes principles of pharmacovigilance, lays down requirements to the import and export of pharmaceutical products.
3. The Law No. 552-XV on accreditation in healthcare system of 18 Oct 2001 – provides definition and main principles of accreditation procedure for healthcare facilities carrying out clinical research, lays down requirements to the material and technical basis, personnel and documentation management. It defines competent authorities carrying out accreditation: National Council and Expert commissions – and describes their responsibilities.
4. The Law No. 263-XVI on the rights and responsibilities of the patient of 27 Oct 2005 – gives definitions of medical intervention, patient, legal representative, close relative, informed consent, clinical study, medical information and medical error. It describes rights and responsibilities of the patient, such as a right to free medical care, health insurance,

respectful and humane attitude of health personnel etc. It also describes cases when the rights of the patient can be restricted, e.g. by mentally sick patients, or mandatory hospitalization and quarantine of patients with contagious infectious diseases. Finally the law stipulates procedures to ensure confidentiality of medical information, informed consent and voluntary refusal of medical treatment, protection of the patients' rights judicially and extra judicially (through healthcare institutions, patient organizations, and insurance companies).

5. The Law No. 264-XVI on medical profession of 27 Oct 2005 – defines scope of medical practice in Moldova, namely medical treatment, promotion of healthy lifestyle, carrying out of preventive activities, teaching in medical institutions, constant improvement of medical skills and knowledge. It also describes rights and responsibilities of physician, conditions and professions incompatible with medical profession (e.g. pharmaceutical practice), stipulates principle of humanity, respect to every individual and principle of confidentiality. Finally the law defines roles of professional organizations and procedures protecting rights of physician.

6. Resolution of the Parliament No. 1352 on public policy on medicines of 03 Oct 2002;

7. The Order of the Ministry of Health No. 10 on conduct of clinical studies in Moldova of 14 Jan 2001 with amendments - lays down clinical trial approval procedure and procedures for study supervision. The order specifies the following types of clinical studies:

- Study on investigation of safety and pharmacokinetic/pharmacodynamic profile of an active substance – phases I, II and III;
- Study on investigation of efficacy, safety and bioequivalence of medicinal products not registered in Moldova (originals and generics) – phases I, II, III and IV;
- Bioequivalence studies of generic products – phase IV;
- Clinical studies on registered medicinal products investigating new indications, dosage regimen, new drug combinations, route of administration, new patient populations – phases II and III;
- Multicenter clinical studies;

8. Good Clinical Practice of Moldova;

9. The Order of the Ministry of Health No. 54-p §12 on National Ethics Committee of 9 Jul 2002;

10. The Order of the Parliament No. 10 on State Surveillance in Public Health of 3 Feb 2009;

11. The Law No. 185-XV on reproductive health and family planning of 24 May 2001 with amendments – defines reproductive health, in vitro insemination and family planning.

It stipulates the reproductive rights of the people:

- right to reproductive health services and family planning services;
- right to in vitro insemination, etc.

It also describes national strategy and public health activities in reproductive health, such as support of scientific research in reproductive health, development of national legislation etc.

## **4.2 Main regulatory procedures**

### **4.2.1 Clinical trial authorization**

Purposes of clinical research in Moldova are reflected in the classification of clinical studies. The competent authority responsible for approval and supervision of clinical studies is the Drug Agency within the Ministry of Health and Social Protection (hereinafter referred to as the Drug Agency). The study approval procedure consists of the following steps:

1. Applicant submits the CTA to the Drug Agency. Reference to the documents required for the competent authority has not been found in the reviewed legislation.
2. In parallel the applicant submits the following documents to the National EC:
  - Application form
  - CTP and its synopsis
  - IB
  - Informed consent form
  - Patient information
  - Resume of investigator(s)
  - Description of recruitment methods
  - Information on compensations for study subjects (if applicable)
  - Insurance of study subjects
  - Case Report form, diaries, and questionnaires
  - Decisions from other EC, if applicable
  - Statement on absence of personal interests of investigators in the outcome of the study
3. The EC submits the outcome of ethical evaluation to the Drug Agency.
4. Drug Agency approves the CTA when the following conditions are fulfilled:
  - Positive safety and efficacy profile based on the results of pre-clinical studies
  - Positive risk-benefit ratio

- Positive opinion of the EC

5. Drug Agency submits its decision on the CTA to the Ministry of Health for authorization

#### **4.2.2 Notification of amendments**

During the study conduct the investigator submits amendments to the study protocol and to the patient information to the National EC for approval. After review of submitted documents the EC decides on adoption or rejection of proposed amendments and measures to be taken to ensure safety of study participants.

#### **4.2.3 Declaration of the end of the trial**

There is no stipulated procedure on how the end of the trial is declared in the Moldavian legislation. However, the order No. 10 of 14 Jan 2001 states that Ministry of Health or another competent authority should stop a clinical study when:

1. There is a danger for life or well-being of study subject;
2. Ethical norms are violated;
3. Positive effect of the IMP is absent or insufficient;

### **4.3 Ethical principles in clinical research**

#### **4.3.1 Structure of Ethics Committees and review procedure**

Establishment of the ECs in Moldova began in 2002 with foundation of the National EC within the Ministry of Health. From 2006 health and educational facilities active in clinical research began to organize their own ECs. Currently there are the following types of ECs in Moldova:

1. National EC within the Ministry of Health – responsible for ethical evaluation of all clinical trial applications
2. Regional ECs
3. Local ECs within health facilities and higher educational institutions – participate in the development of study protocols and study supervision. Local and regional ECs provide consultations to pharmaceutical companies and perform appraisal of ethical questions in clinical research. They are responsible for ensuring compliance of study sites to the GCP principles.

Ethical evaluation of the CTA by the National EC is based on the review of the following aspects:



- Compliance of the CTP to study aims and objectives, justification of the risk level for study participants
- Investigators qualification; requirements to the investigator are the following: higher education, sufficient professional experience in clinical research, sufficient research experience confirmed by publications and other documents.
- Suitability of chosen study site, notably technical and personnel resources, capacity to recruit necessary amount of patients and provide adequate medical care in case of adverse drug effects and other complications;
- Recruitment procedure;
- Insurance provisions;
- Content of Patient information;
- Informed consent procedure;

After evaluation of submitted application the EC opinion can be one of the following:

- approval of the CTA;
- request to introduce amendments to the submitted documentation;
- rejection of the CTA;
- cancellation of the earlier adopted decisions.

#### **4.3.2 Clinical research in vulnerable populations**

Moldavian legislation provides very general recommendations on conduct of clinical studies in vulnerable populations. The Drug Law No. 1409-XIII states that research in children and people incapable to consent can be done when informed consent of their legal representatives or close relatives is obtained. The law No. 263-XVI on the rights and responsibilities of the patient stipulates that clinical study on people unable to consent can be carried out only if it pursues the interests of the patient and informed consent of their close relatives or legal representatives is obtained.

Close relative is defined as a person being in cognate relations with patient (parents, brother or sister, grandfather and grandmother) or his spouse and who kept the closest contact with the patient for the last years or was appointed by the patient, when he/she was still legally capable, to speak on his behalf.

Legal representative is defined as a person who is empowered by law to speak on behalf of the patient when the latter is considered fully incapable or his/her capacity is limited. However even when only an agreement of legal representatives is required, patients still get involved in the decision making process to the possible extend depending on their

level of capacity. It was not possible to identify requirements to the clinical research on other vulnerable groups e.g. on children or pregnant women in Moldavian legislation.

#### **4.4 Customs regulations of IMP and human biological material**

Import permission for non-authorized medicinal products for the purpose of clinical research is issued by the Drug Agency. Documents required for submission include study approval, information on the IMP (quality documentation, manufacturer), and CTP synopsis.

Export requirements for human biological material for the purpose of clinical research have not been identified in the reviewed legislation. The law No. 1456-XII states that written agreement from the patient is required for sampling, storage and use of all types of biological material. Written agreement is also required when the biological material is used for diagnosis or treatment of disease.

### **CHAPTER 5: CLINICAL RESEARCH IN KAZAKHSTAN**

#### **5.1 Overview of major national legislation in clinical research**

1. In the last three years healthcare legislation in Kazakhstan underwent substantial changes. In November 2009 a comprehensive Code on Public Health and Healthcare system of Kazakhstan (hereinafter referred to as the Code) has entered into force and amended 11 legislative documents including 7 relevant for clinical research. The Code harmonizes national regulations in public health and reduces subordinate legislative documents. It lays down definition and purposes of pre-clinical and clinical studies, determines rights and responsibilities of the patient, regulates principles of importation and exportation of the IMP and human biological material and introduces a concept of orphans drugs and diseases.

2. The Order of the Ministry of Health No. 442 on conduct of medico-biological experiments, pre-clinical and clinical studies in Kazakhstan of 25 Jul 2007 – lays down main ethical principles of pre-clinical and clinical research. It strengthens the role of the ECs and brings national legislation in line with the international standards. The order gives special attention to the protection of study participants by stipulating the content of the Informed consent form, recruiting procedure, responsibilities of the investigator. It defines population groups that can not be included into the clinical study.

3. Instruction on conduct of clinical studies and/or trials on pharmacologic substances and pharmaceuticals adopted by the Order of the Ministry of Health No. 53 of 14 Feb 2005

(hereinafter referred to as the Instruction) – gives definitions of the study phases (I-IV) and sets up the following classification of the studies:

- Full-scale clinical studies (phase I-IV);
- Pilot studies (on the limited number of patients);
- Bioavailability/bioequivalence studies;
- Multicenter clinical studies;
- International multicenter clinical studies;

The Instruction describes regulatory procedures for clinical trials: approval procedure, notification of amendments, reporting of adverse events and declaration of the end of the trial. Structure and content of the CTA, CTP, IB, Informed consent form, adverse event notification form, and clinical trial report are provided in the annexes to the Instruction.

Finally, the Instruction lays down responsibilities of the sponsor:

- Timely delivery of the IMP to the investigator(s);
- Maintenance of documents on delivery, receipt, distribution, return and utilization of the IMP;
- Development of procedures on withdrawal of the IMP from the study (e.g. by defective batch, expiry of shelf-life);
- Insurance of stability of the IMP during the study conduct.

In addition for multicenter clinical studies the sponsor must ensure that:

- All investigators refer to the single CTP, signed by the sponsor and approved by the competent authority;
- Format of the Case Report form allows entrance of necessary data at all study sites by multicenter studies;
- Responsibilities of the investigator are defined and stipulated in the clinical study documentation before the study initiation;
- All investigators receive instructions on single evaluation parameters of clinical and laboratory data, on adherence to the CTP and completion of case report forms.

4. Instruction on monitoring of adverse drug events adopted by the Order of the Ministry of Health No. 52 of 14 Feb 2005 – defines procedures on reporting and monitoring of adverse event of already approved medicinal products (pharmacovigilance system). It includes the following definitions:

- Additional pre-/clinical study – is a study conducted to identify or confirm any hazardous characteristics of medicinal product during its medical use.
- Monitoring of adverse events – activities aiming to detect, evaluate, analyze and handle adverse events of medicinal products.

5. The Order No. 425 on Central EC of 30 Jul 2008 – lays down goals, rights and responsibilities of the Central EC, its structure and procedures.
6. The Order No. 304 on establishment of orphan drugs list of 10 Jun 2009 – defines criteria on inclusion of medicinal products in the orphan drugs list, documents required for application, and review procedure.

## **5.2 Main regulatory procedures**

### **5.2.1 Clinical trial authorization**

Clinical studies in Kazakhstan can be conducted for the following purposes:

1. Upon decision of the competent authority to obtain information on safety and efficacy of the medicinal product. For example, during registration of a new medicinal product competent authority may request additional clinical studies when provided evidence on safety and efficacy is not solid.
2. Development of innovative medicinal products by domestic manufacturers;
3. Development of a new indication, pharmaceutical form, dosage regimen or route of administration for already authorized product;
4. Development of medicinal product within international multicenter clinical studies.

The competent authority responsible for approval and supervision of clinical studies is the National Center on Expertise of Medicinal Products, Medical Devices (hereinafter referred to as the National Center). The study approval procedure consists of the following steps:

1. Pre-assessment phase: the applicant submits the following documents to the National Center:
  - Application form
  - Certificate of Product Origin
  - Documents on quality, manufacture and control of the IMP
  - Certificate of Analysis of the IMP from the Pharmacopoeia Center, except the following cases:
    - a. IMP is an innovative product developed by domestic manufacturer
    - b. Clinical study under review is a part of international multicenter study
  - CTP signed by the sponsor and investigator
  - IB and IMP Information leaflet for specialists
  - Informed consent form
  - Patient information
  - Case Report form (when applicable)

- Resume of the investigator (most current version) and/or other documents, confirming his/her qualification

- Payment of administrative fee

The National Center evaluates completeness and accuracy of documentation within 30 days and informs the applicant whether he can proceed with ethical review. During pre-assessment phase the National Center may request additional information on the clinical study. The applicant has 90 days to submit requested documents or may ask for extension of this period. Time required for the preparation of the documents is not included in 30-days pre-assessment phase. If the applicant fails to provide requested documents within the given timeframe, the CTA is considered invalid and is withdrawn from the review.

2. After positive outcome of pre-assessment phase, the applicant submits the CTA to the Ethics Committee; ethical evaluation is conducted either by the Central EC (for international multicenter clinical trials) or by the local EC at the health facility concerned.

Application submitted to the EC includes:

- Application form

- Positive decision of the National Center

- CTP

- IB

- Informed consent form

- Patient information leaflet

- Advertisements to be used for recruitment of study participants (if applicable)

- Available safety information on the IMP

- Health insurance of the study participants. If the study is performed based on the international contract, international insurance requirements apply.

- Resume of investigator (most current version) and/or other documents, confirming his/her qualification and knowledge in clinical research

- Other documents that may be requested by the EC

The Central EC reviews clinical trial documentation within 90 days and informs the applicant about its decision in written form.

3. The applicant submits results of ethical evaluation to the National Center. The latter decides on the scientific rationale of the study within 90 days and provides its recommendations to the Ministry of Health.

5. The Ministry of Health adopts a final decision on the CTA within 10 days.

6. After receipt of positive decision from the Ministry of Health, the National Center approves the CTP and informs the applicant that the CTA has been approved.

## **5.2.2 Notification of amendments**

Procedure for notification of amendments is described in the chapter 3 of the Instruction. It refers to the changes in the CTP and does not differentiate between substantial and non-substantial amendments. The applicant submits every CTP change to the National Center and the EC concerned for the review before it can be implemented. Approved amendment is signed by both the sponsor and investigator and added as annex to the CTP. When urgent measures have to be taken to eliminate the immediate hazard for study participants, the investigator may deviate from the CTP without prior notification of the sponsor, the EC and the National Center. However, taken measures have to be later documented and proper justification provided. Study participants should be informed about changes to the CTP; if changes lead to the amendment of the Informed Consent form, it should be provided them for signature.

## **5.2.3 Declaration of the end of the trial**

Declaration of the end of the trial is required only for the temporally halt and premature end of the study or some of its stages and is submitted in parallel to the National Center and to the EC concerned.

## **5.3 Ethical principles in clinical research**

### **5.3.1 Structure of Ethics Committees and review procedure**

There are two types of the ECs in Kazakhstan:

1. Central EC - is organized within the Ministry of Health;
2. Local ECs - are organized within medical facilities accredited to conduct clinical studies;

The Central EC is responsible for ethical evaluation and supervision of international multicenter studies; other types of the studies are approved and supervised by the local ECs. The Central EC has controlling function over the local ECs: it evaluates their performance, provides counseling and training and serves as arbitrary in the questions at issue. The Central EC may request any information on the clinical study from the local EC to ensure safety and rights protection of study participants.

During authorization procedure for international multinational trials the Central EC evaluates submitted application within 90 days. The exact procedure is not described in the reviewed legislation. However, the order No. 425 stipulates that meetings of the Central EC take place at least once in three months and are considered valid in the presence of at least a half of the EC members. Decision is adopted by the open vote. Vote

of the chairman is considered as decisive in case of equal number of positive and negative votes. The outcome of ethical evaluation can be:

- approval of the CTA;
- request to introduce amendments to the submitted documentation; final decision is issued after amended documents are submitted to the EC;
- rejection of the CTA;
- postponement of the issue of opinion until the next meeting in case there are questions to submitted documentation;

Approval procedure of the local ECs is stipulated by the regulations of respective health facility. Apart of ethical evaluation of the CTA, the National and local ECs are responsible for assessment of adverse events reports, review of CTP amendments, new versions of study documents (e.g. Informed consent form, IB) and may request changes to submitted documents. After study initiation frequency of the documents review depends on the risk level for study subjects but can not be less than two times per year and for pilot studies at least once during the study conduct. The local EC issues recommendations to the National Center on temporary halt or prematurely termination of the study or one of its stages when there is a direct hazard to life and well-being of study subjects, absent or insufficient efficacy of the IMP or when ethical principles are violated.

### **5.3.2 Clinical research in vulnerable populations**

According to the Order No. 442 clinical studies in Kazakhstan can not be conducted on:

1. Children, except of studies when IMP is developed for use only in paediatric population. In this case informed consent of parents or legal representatives is required; children who do not have a legal representative can not be included into the study.
2. Pregnant women except the situations when:
  - The IMP is developed for use only in pregnant women;
  - There is no other method to obtain required information other than a clinical study;
  - There is no risk for woman and fetus;
3. Armed forces personnel;
4. Persons in detention;
5. Adults incapable to give an informed consent, except of the cases when the IMP is developed for treatment of mental disorders in mentally sick patients.

### **5.4 Customs regulations of IMP and human biological material**

See Chapter 2, section 2.4

## CHAPTER 6: SURVEY RESULTS

### *Feedback from the competent authorities:*

Altogether 4 interviews have been conducted with the representatives of the competent authorities (one per country). None of the respondents was able to provide statistical data on the number of approved studies per year. Below we will summarize the responses obtained during the survey:

*Question: In cases when sponsor and investigator are two different organizations, who shall submit an application?*

Sponsor (in all four countries)

*Question: Based on your experience please identify the most common reasons why CTA have been rejected.*

1. Safety and health insurance provisions for study participants do not meet regulatory requirements (Belarus).
2. Clinical study does not meet GCP standards or requirements of the national legislation (Kazakhstan).
3. Poor quality of the informed consent form that lacks proper communication of risks and benefits, use of terms and vocabulary understandable for local communities, consideration of cultural perceptions of nature, cause and treatment of certain diseases (in all four countries).

*Question: What regulatory aspects may serve as an attractive point for the industry to conduct clinical research in your country?*

1. Clear regulatory requirements to the sponsor and investigator (Kazakhstan, Russia, Belarus);
2. Quick approval process (Moldova, Belarus);
3. Emerging clinical research market, highly qualified medical specialists, low financial expenditures on study conduct, health facilities and laboratories are well-equipped (Kazakhstan);

*Question: According to your experience are there any areas of improvement in the regulatory system for clinical research (compare maybe to other countries)?*

1. Requirements to the study sites (Belarus, Kazakhstan);
2. Requirements to provision of health insurance for study participants (Moldova, Belarus)
3. There are no uniform standards on training of GCP experts, their accreditation and accreditation of Ethics Committees (Kazakhstan, Moldova);
4. Quality of inspections of study sites and their frequency is not adequate (Kazakhstan);



5. Lack of cooperation between local ECs and their formal role in clinical research (for all countries);

Although national systems stipulate active participation of the ethics committees in the ongoing monitoring of a study, they often focus only on the initial study review and do not give enough attention to the monitoring of unexpected adverse events or study subjects protection in general. More guidance is needed to empower the ethical committees on the local and regional level and ensure their decision-making capacity.

6. All respondents share the opinion that although national legislations include clear regulatory provisions and procedures, many of them do not work in practice and therefore a strong law enforcement mechanism is needed.

*Question: Are there any cultural specialties that you consider to be important for an international company, wishing to perform a clinical study in your country?*

1. Pharmaceutical companies have to consider national and religious diversity of the countries. In Kazakhstan, for example, there are more than 100 nationalities and more than half of the population practices Islam.

2. It is important that the international pharmaceutical companies coming to the emerging markets acknowledge the limited resources especially in the health sector of the hosting country and design the studies avoiding exploitation of the local communities but rather bringing benefits (Belarus, Kazakhstan).

3. Vulnerability of the certain populations has to be considered by the companies. Since for some people participation in a clinical study is the only way to get an access to medical treatment, researchers have to avoid overstating the benefits of the study. Due to the paternal doctor-patient relations and high authority of the physician in these countries, it is important to ensure that the patient is empowered to make his own decision about participation in the study (Moldova, Kazakhstan).

***Feedback from the industry representatives:***

Overall responses from 6 pharmaceutical companies and 3 CROs operating in the reviewed countries have been obtained during the survey. Their responses are summarized below.

*Question: Every year, more trials are placed in Eastern Europe. How do you see the recent development of the clinical research market in above chosen countries, and what does the future hold?*

1. Industry representative acknowledge that Russia is a big and therefore important clinical research market. However, in the light of the new requirements introduced by the federal drug law 61, they express their concerns about the future of the clinical research in Russia

and question the reasonability of certain requirements. Adoption of this law demonstrates how quickly the regulatory environment may deviate from the chosen direction, which does not allow long-term planning.

2. More efforts from the officials to control corruption in Kazakhstan are needed.
3. Due to demographical and other particularities Moldova is not suitable for large phase multicenter studies, but offers perfect conditions for small mono-center studies with limited number of patients. Partly due to the low number of clinical studies performed per year, the approval times are very short compared to other East European countries. This is optimal for early development studies that also do not last long.

*Question: Based on your experience, what are the most common reasons for rejection of a clinical trials application?*

1. In Russia and Belarus the most common reasons of the CTA rejection are related to the study design, e.g. placebo controlled studies are difficult to approve. In general, rejections in Russia are very rare.

*Question: Where industry can find information/advice on regulatory requirements and procedure when they want to submit a trial in one of these countries?*

Information comes from the contract partners (CROs) or companies own medical offices in the countries (Russia, Kazakhstan, Belarus).

*Question: Based on your experience, are there any requirements for CTA and conduct of a trial that are laid down in the regulations but are not working smoothly in the practice in any of these countries?*

1. This is usually not the case for Russia and Kazakhstan; sometimes, new laws are unclear in the interpretation or are differently interpreted.
2. Customs regulations in Moldova and Kazakhstan are not always working as defined.

*Question: What changes in regulatory system, if any, would you like to see in these countries in the coming years?*

Common desire shared by all the respondents is that these countries could “come closer” to EU legislation and have a bit more reasonable approach for customs clearance.

*Question: Are there any cultural specialties that you consider to be important for an international company, wishing to perform a clinical study in your country?*

Main challenge determined to the large extend by the cultural perceptions in the study countries is the collection of human biological samples and ethical issues associated with it. Companies operating in Moldova and Kazakhstan have come across cultural beliefs that hampered the sampling of biological materials, such as:

- Samples are collected for the wrong or hidden purposes;

- Collecting samples from healthy people attracts a disease;
- If health condition under investigation has no cure, biological samples should not be collected;

To address the issues specific for a particular nation, cultural sensitivity and cultural competence become crucial qualities for researchers. Experience has shown that the participation of local researchers having close liaison with the community is an essential factor for the successful study and the best way to ensure that cultural particularities are taken into consideration during the whole process of study conduct. Ways to overcome cultural aversion include detailed description of the tests to be performed with the samples, sampling procedure and discomfort associated with it, confidentiality of the test results and whether samples will be taken outside of the country and how they will be stored.

*During the survey industry representatives shared the following experience and recommendations:*

Common difficulty for all four countries is logistic aspects associated with delivery and storage of the study medication in the study site. It is determined first by the import requirements, since in all four countries customs regulations are complex and are strictly adhered to by customs staff. Any issues with the shipment itself or the accompanying documentation can result material being held in customs. With the current growth in temperature-sensitive products and time-sensitive shipments, a strategy to avoid these issues is essential.

In addition to the complicated customs regulations the countries have poor infrastructure in comparison with their western counterparts, especially true for small or remote towns. A solution to this can be a assistance from local CROs and international organizations with a strong local presence. As the clinical trial markets in these countries grow, the number of CROs with local knowledge is also increasing. For multicenter studies it may be helpful to also identify a local logistics company with appropriate pharmaceutical and clinical trial experience to support the activities of the CRO.

## **CHAPTER 7: DISCUSSION**

### *Structure of the competent authorities*

Belarus, Moldova and Kazakhstan have one competent authority within the Ministry of Health responsible for scientific evaluation and approval of the CTA. The new legislation in Russia abolishes the role of current national competent authority in the CTA approval

and divides scientific evaluation and issue of approval between two new authorities: the Expert Commission and the FSA. The latter will issue the study approval when the submitted documentation is complete, and will rely on the scientific assessment of the Expert Commission. This might turn the issue of a study approval into a technical procedure, since the FSA itself does not perform the CTA evaluation. It is also unclear, who finally bears the responsibility for approving the study: federal officials, issuing an approval or subordinates, carrying out the scientific expertise. The status and position of the new competent authorities – the FSA and the Expert Commission – is not specified in the legislation.

*Procedural aspects:*

The study approval procedure in all four countries consists of the ethical evaluation by the EC and scientific evaluation by the competent authority. Submission to the competent authority and EC is done either in parallel (Belarus, Moldova) or sequentially (Russia, Kazakhstan). The list of the documents required for submission is quite similar with the largest set of documents focused on the IMP related information. Russia and Kazakhstan have different document requirements and procedural steps for the local and international/post-marketing clinical studies applications. Both countries have included pre-assessment of the submitted application in the approval procedures.

Duration of the study approval is laid down in the legislation of Russia and Kazakhstan. From September 2010 the CTA approval in Russia will be conducted within 7 weeks which is twice as quick as the current procedure (15 weeks on average)<sup>3</sup>. Defined procedural timelines is a favorable regulatory provision; it increases transparency of the procedure and allows better planning for companies as well as for the competent authorities. In Kazakhstan, however, stipulated duration of each procedural step is very long and sums up in 33 weeks for a standard procedure or maximum 46 weeks in case the applicant has to answer questions raised by the competent authority. Currently Kazakh legislation has the longest approval procedure among the reviewed countries.

In Moldova and Belarus duration of the approval procedure is not specified in the legislation. Based on the reports of pharmaceutical companies, the study approval takes about 4 weeks in Moldova<sup>4,8</sup> and 4-12 weeks in Belarus<sup>3</sup>.

From September 2010 foreign companies will have to conduct local clinical studies except phase I in order to register their products in Russia, unless there is a bilateral agreement on recognition of clinical studies. This provision is from many points of view will most likely become a substantial barrier for registration of foreign medicinal products in Russia, at least for the next several years. The officials, however, comment this

provision as necessary to ensure the competitiveness of the national medicinal products over the foreign ones and to consider demographical and other peculiarities of the population in Russia<sup>46</sup>. To avoid carrying out local studies when the dossier is submitted for authorization, they recommend pharmaceutical companies to conduct phase II and III studies in Russia as a part of international multicenter study.

The ECs in all four countries have a similar organizational structure and include a central (national) EC within the Ministry of Health and local/regional ECs organized at the health facilities and higher educational institutions. Their composition and operations are in line with the ICH GCP standards. However, the ECs have different scope of responsibilities with respect to clinical research. The Central ECs in Russia and Moldova approve all clinical studies, in Kazakhstan – only international multicenter studies, in Belarus the Central EC has legislative and advisory functions and all CTAs are approved by the local ECs. There are advantages and disadvantages in both centralized and decentralized system of ethical approval. Centralized system allows better control over clinical research, uniformity of procedures, consistency in adopted decisions, and ability to deal with complicated issues due to the large application flow and therefore accumulated experience of assessors. Shift of the responsibilities on the local ECs, on the other hand, ensures closer monitoring of the study, allows identifying and resolving ethical issues much quicker, and facilitates direct and active communication with the investigators and the sponsor. Combination both approaches, when the initial study approval is done centrally but the responsibility to ensure compliance to the ethical principles during the study conduct lies on the local EC seems to be optimal. This combined approach in ethics review is clearly defined in Moldavian legislation. According to Russian legislation local committees are also involved in study approval and supervision together with the central EC, however, in practice they are not duly empowered to influence the adopted decisions and communication between the local and central levels requires improvement<sup>10</sup>.

Belarus is the only country where the EC has two ethical review procedures in place – standard and accelerated – depending on the type of the study. On the one hand it is definitely an advantage to have an accelerated procedure for certain types of the clinical studies that require minimum intervention for the study subjects. Examples of the studies eligible for the accelerated ethical review are listed in the Belarus legislation; however, the list is not exhaustive. Moreover, there are no defined criteria for the use of accelerated procedure except of general formulation that the study subjects should undergo a minimum risk. The legislation entrust the chairman of EC to make a decision on the use of accelerated procedure, and this provision can potentially become a subject of abuse. From

the regulatory prospective it is preferable to either define strict criteria for application of the accelerated procedure or make an adoption of this decision a collegiate process. Ethical review in Russia also has an accelerated procedure in place, but it applies only to minor amendments and not to the initial CTA.

Reviewed legislation of all four countries lacks proper description of the regulatory procedures carried out after the study approval, such as notification of amendments, submission of progress and final reports, notification of the end of the study. For these procedures it is not clear to which organization documents have to be submitted, who carries the responsibility (e.g. sponsor, investigator, head of health facility), what are the timelines and requirements to the documentation. With respect to amendments, reviewed legislations of all countries referred only to the CTP amendments and did not include any requirement or definition of CMC or administrative amendments as well as distinction between substantial and non-substantial.

#### *Requirements to the investigator*

The reviewed countries legislation stipulates different requirements to the investigator. The toughest one is the Russian legislation: after adoption of the Drug Law No. 61 the investigator should possess 5 years of experience in clinical research plus specialization in the area of the study. For many health facilities it will be difficult to fulfil increased requirements, especially for the rare conditions, because there are simply not so many specialists with 5 years experience (previous regulation required 2 years). By excluding general practitioners from clinical research the new federal law constrains opening of new study sites in the regions, where there are not so many specialists. It is not clear what has induced strengthening of the requirements to the investigator, since the quality of data and study conduct has not been an issue for national and international (FDA, EMA) authorities<sup>1,2</sup>. Possible consequences of this provision are consolidation of studies within a narrow circle of investigators, loose of competition and increase of study costs. Other countries formulate the requirements to the investigator in a general way: sufficient knowledge and working experience in clinical research. In practice it means presence of GCP training certificate issued by the national competent authority or international organization.

#### *Requirements to the health facility*

In all four countries clinical study can be carried out only in accredited medical facilities. When compared to the international practice, accreditation seems to be an excessive barrier for the clinical research; however, it is necessary considering the current state of the healthcare systems in the region. There are still a number of medical facilities

especially in the remote areas that require substantial renovation, do not meet international standards and therefore can not be used as study sites. Accreditation therefore confirms compliance to the GCP standards and adequate resources availability of the health facility. Currently there are 946 accredited health facilities in Russia, about 50 in Belarus, 26 in Kazakhstan and their number increases annually<sup>3,5</sup>.

#### *Studies in vulnerable populations*

In the assessed countries clinical studies on orphans, people in detention, adults incapable to give informed consent is prohibited without exceptions. In addition Belarus requires proper justification for inclusion of patients with incurable diseases, persons in retirement homes, unemployed or low-income population groups and many more. Ethical principles on clinical research are compliant to the ICH GCP and Helsinki Declaration in all four legislations.

However, there are substantial differences in the conditions to clinical studies in pregnant women between the countries. From the regulatory prospective it seems impossible to obtain an approval for a clinical study on pregnant women in Kazakhstan and Belarus. Although in theory they allow clinical studies of the IMP indicated in pregnant women when clinical study is the only way to obtain necessary information, but they also require a study not to pose any risk on fetus and woman. This last provision is not feasible to be fulfilled in practice because due to the nature of clinical research it is not possible to completely exclude any risk for study subjects. With this respect the Russian legislation does not require a study not to have any risk but requires conducting all necessary measures to exclude it and therefore is more realistic to follow. In Moldova no recommendation on clinical research in pregnant women in the reviewed legislation has been identified. In general, provisions on clinical research invulnerable populations and are the toughest in Belarus and softest in Russia where mentally sick people and armed forces personnel can be included in the clinical study under certain conditions.

#### *Types of clinical studies*

When comparing study types and classifications given in the legislation of the reviewed countries, substantial differences can be found and should be considered by the international sponsor. Russian legislation distinguishes between clinical study, bioequivalence study, post-marketing study and international multicenter study. Moldova and Kazakhstan go further and provide classifications of clinical studies by phases (I-IV) and types (pilot, bioequivalence study, full-scale study) that are not always consistent with the international definitions. It should be noted that although clinical trials do differ by

phases, it is not fixed in the law in the international practice due to the relativity of classification.

None of the countries provides definition and regulatory procedures for non-interventional (observational) studies. The only reference was found in the procedural guideline on EC No. 57-0004 of Belarus that states that non-experimental studies on pharmaceutical products and medical devices are eligible for accelerated ethical review procedure. With respect to other countries it is not clear what regulatory procedures apply to non-observational studies.

## **CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS**

Based on the outcome of the survey and analysis of national legislations the following conclusions and recommendations to research companies wishing to perform clinical studies in the reviewed countries can be made:

1. All four countries offer enormous growth potential in clinical research. This is true not only for Russia but also for the countries that are currently not widely known and explored by international companies, such as Moldova and Kazakhstan.
2. The assessed countries differ on the regulatory requirements and definitions, as well as on the level of detailed elaboration on certain regulatory procedures in the national legislations. Generalized regulatory approach on clinical research is inefficient.
2. The company should consider demographic and regulatory particularities when choosing a country for a particular type of the clinical study (Russia and Kazakhstan phases I-IV multicenter, large, long-term; Moldova – phase I, mono-central studies, Belarus – phase II mono-central, post-marketing).
3. The company should seek to design studies that are responsive to the health priorities of the host country when possible. This certainly increases the community participation.
4. The company should consider cultural particularities when setting up a procedure for informed consent, collection of biospecimen, ensuring privacy and confidentiality of the subjects.
5. The value of local knowledge in these countries cannot be understated. If it is likely that a country in which the sponsor has limited experience is to be included in the clinical study, it is important that planning and identification of potential issues starts as early as possible.
6. Complexity of study logistics is manageable, and will become less of an issue as the industry becomes more familiar with operating in these geographies. In the meantime, assistance is available from a range of local and international service providers who have



already experienced the highs and lows of managing the clinical supply chain in emerging markets.

7. It is important to consider the requirement to conduct local clinical studies in Russia introduced by the new legislation in clinical development strategy. If the company is going to seek registration of its product in Russia in the future, it should include Russia in the clinical development program, when possible.

8. Since a number of procedures are not clearly described in the law (amendments, reporting), liaison with the competent authorities is the best possibility to clarify the regulatory requirements.

9. In Russia, Belarus and Kazakhstan demonstrate close cooperation on different levels (Russian as an official language, single customs regulations) that can be beneficial for a multicenter clinical study.

## **CHAPTER 9: SUMMARY**

For the last fifteen years Eastern Europe has become one of the dynamic and attractive markets in clinical research. This region offers a perfect solution to the shortage in patient recruitment and high study costs in the established markets such as the US and Western Europe, which is especially relevant for the phase III multi-center studies. Despite of political, geographical and socio-economical similarities this region is far from being homogenous. The purpose of this study is to take a closer look at Eastern Europe and to analyze the regulatory requirements for clinical research in four countries: Russia, Belarus, Moldova and Kazakhstan. The focus of the assessment is put on the clinical study approval procedure, notification of amendments, structure and procedures of the ethics committees, requirements to clinical research in vulnerable populations and customs regulations on human biological material and medicinal products. In addition, this study provides the outcome of the survey carried out with the representatives of competent authorities and research industry, where they share opinions on the regulatory frameworks and experience in these countries.

The study approval procedure in the reviewed countries consists of the ethical evaluation by the ethics committee and scientific evaluation by the competent authority. Submission of the application is done either in parallel (Belarus, Moldova) or sequentially (Russia, Kazakhstan). Duration of the study approval is laid down in the legislation of Russia and Kazakhstan and corresponds to 7 weeks and 33 weeks respectively. In Moldova and Belarus duration of the approval procedure is not fixed by the legislation, however

according to the industry reports Moldova has the shortest approval times (4 weeks on average), and in Belarus it takes from 4 to 12 weeks to approve the study.

Ethics Committees (EC) in the reviewed countries are organized in the similar way and include central EC within the Ministry of Health and local ECs at the health facilities and higher educational institutions. Establishment of the ECs has been supported by the international organizations (WHO, UNESCO). Structure and operations of the ECs are in line with the ICH GCP standards. Ethical evaluation of the study is carried out by the central EC in Russia and Moldova; in Belarus it is always done by the local EC; in Kazakhstan the central EC reviews applications only for the international multicenter studies. Centralized ethical review system in Russia, Moldova and partly in Kazakhstan allows better control over clinical research, uniformity of procedures, consistency in adopted decisions, and ability to deal with complicated issues due to the large application flow and therefore accumulated experience of assessors. Shift of the responsibilities on the local committees, on the other hand, ensures closer monitoring of the study, allows identifying and resolving ethical issues much quicker, and facilitates direct and active communication with the investigators and the sponsor.

The reviewed legislations differ remarkably in their requirements to the investigator, studies in vulnerable populations and classifications or definitions of the study types. The common provision between the countries is the requirement to carry out the clinical study in accredited medical facilities. This regulatory restriction is necessary considering the current state of the healthcare systems in the whole region. There are a lot of medical facilities, especially in the remote areas, that require substantial renovation, do not meet international standards and therefore can not be used as study sites. Accreditation, therefore, confirms compliance of the health facility to the GCP standards and adequate resources availability. Currently there are 946 accredited health facilities in Russia, about 50 in Belarus, 26 in Kazakhstan and their number increases annually.

The reviewed legislations of all four countries lacks proper description of the procedures carried out after the study approval, such as notification of amendments, submission of progress and final study reports, notification of adverse events and the end of the study. A number of regulatory concepts are not defined in the legislation: orphan drug (absent in Moldova, Belarus), observational study (absent all countries), post-marketing study (absent in Belarus, Kazakhstan, Moldova), substantial and non-substantial amendment (absent in all countries), etc.

In the survey the industry representatives have identified two main challenges for clinical research true for all countries: customs regulations and cultural perceptions to

clinical research. The best strategy to overcome these hurdles is to seek assistance from local and international service providers and to empower local investigators in order to gain trust of the communities and overcome cultural issues. Areas of improvements in the national regulatory systems, identified by the representatives of the competent authorities, included poor requirements to health insurance for study subjects (Moldova, Belarus), non-harmonized standards on training of investigators and accreditation of the ECs (Kazakhstan, Moldova) and poor quality of the study site inspections (Kazakhstan). All respondents share the opinion that although national legislations include clear regulatory provisions and procedures, many of them do not work in practice and therefore a strong law enforcement mechanism is needed.

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28. Ministry of Health (Belarus): Resolution on Good Clinical Practice No. 50 (May 7, 2009).
29. Ministry of Health (Belarus): Procedural Guideline on Ethics Committee No. 57-0004 (April 24, 2000).
30. Ministry of Health (Belarus): Order on Pharmacological and Pharmacopoeia Committees within the Ministry of Health No. 88 (March 18, 1998).
31. Ministry of Health (Belarus): Order on National Bioethics Committee No. 274 (April 17, 2006).
31. Ministry of Health (Moldova): Drug Law No. 1409 -XIII (December 17, 1997) with amendments.
32. Ministry of Health (Moldova): Law on Pharmaceutical Practice No. 1456-XII (May 25, 1993) with amendments.
33. Ministry of Health (Moldova): Law on accreditation in healthcare system No. 552-XV (October 18, 2001).
34. Ministry of Health (Moldova): Law on the rights and responsibilities of the patient No 263-XVI (October 27, 2005).
35. Ministry of Health (Moldova): Law on medical profession No 264-XVI (October 27, 2005).
36. Ministry of Health (Moldova): Order on conduct of clinical studies in the Republic of Moldova No. 10 (January 14, 2001) with amendments.
37. Ministry of Health (Moldova): Good Clinical Practice of the Republic of Moldova.
38. Ministry of Health (Moldova): Order on National Ethics Committee No. 54 (July 9, 2002).
39. Code on Public Health and Healthcare system of Kazakhstan (September 18, 2009)
40. Ministry of Health (Kazakhstan): Order on conduct of pre-clinical, medico-biological experiments and clinical studies No. 442 (July 25, 2007)
41. Ministry of Health (Kazakhstan): Instruction on conduct of the clinical studies and/or trials of pharmacologic substances and pharmaceuticals approved by the Order No. 53 (February 14, 2005)
42. Committee on technical regulation and metrology (Kazakhstan): National Standard of the Republic on Kazakhstan on Good Clinical Practice CT RK 1616-2006 (January 1, 2008).

43. Ministry of Health (Kazakhstan): Instruction on monitoring of adverse drug events adopted by the Order No. 52 (February 14, 2005).
44. Ministry of Health (Kazakhstan): Order on Central Ethics Committee No. 425 (July 30, 2008).
45. Ministry of Health (Kazakhstan): Order on establishment of orphan drugs list No. 304 (June 10, 2009).
46. Minzdravsoc.ru [Internet]. Ministry of Health and Social Development in Russian Federation; c2008-2010 [cited 2010 Jun 3]. Available from:  
<http://www.minzdravsoc.ru/health/remedy/40>
47. Position on the import and export of the human organs and/or tissues, blood and its components in the territory of the customs union of 1 Dec 2009

**Annex 1. Information required by the Competent Authorities for clinical study approval**

	Country specific information	Russia		Belarus	Kazakhstan
		Local	International/ Post-marketing		
<b>1.</b>	<b>General</b>				
1.1	Application form		Yes	Yes	Yes
1.2	Confirmation of fee payment	Yes	Yes	Yes	Yes
<b>2.</b>	<b>Subject related</b>				
2.1.	Informed Consent form	Yes		Yes	Yes
2.2	Patient information	Yes	Yes	Yes	Yes
2.3	Case report form				Yes
<b>3.</b>	<b>Protocol related</b>				
3.1	Clinical trial protocol	Yes	Yes	Yes	Yes
<b>4.</b>	<b>IMP related</b>				
4.1	Results of pre-clinical studies	Yes	Yes		
4.2	Information on clinical studies conducted before	Optional	Study reports (if applicable)		
4.3	Samples of the IMP				
4.4	Investigators' Brochure	Yes	Yes	Yes	Yes
4.5	Description of manufacturing process	Yes			
4.6	Copy of manufacturing authorization	Yes			
4.7	Certificate of Pharmaceutical Product	Yes			
4.8	Mock ups for primary and secondary package	Yes			
4.9	Information on IMP composition		Yes (only for international)		



			trial)		
4.10	Certificate of Product Origin				Yes
4.11	IMP quality, manufacture and control			Yes	Yes
4.12	Certificate of Analysis			Yes	A
4.13	IMP Storage and transport conditions	Yes			
<b>5.</b>	<b>Facilities and staff related</b>				
5.1	CV of investigators	Yes	Yes		Yes
5.2	List of study sites			Yes	
5.3	Draft contract with health facility			Yes	
<b>6.</b>	<b>Finance related</b>				
6.1	Compensations to study subjects, if applicable	Yes			
6.2	Compulsory health insurance contracts for study subjects	Yes	Yes	Yes	

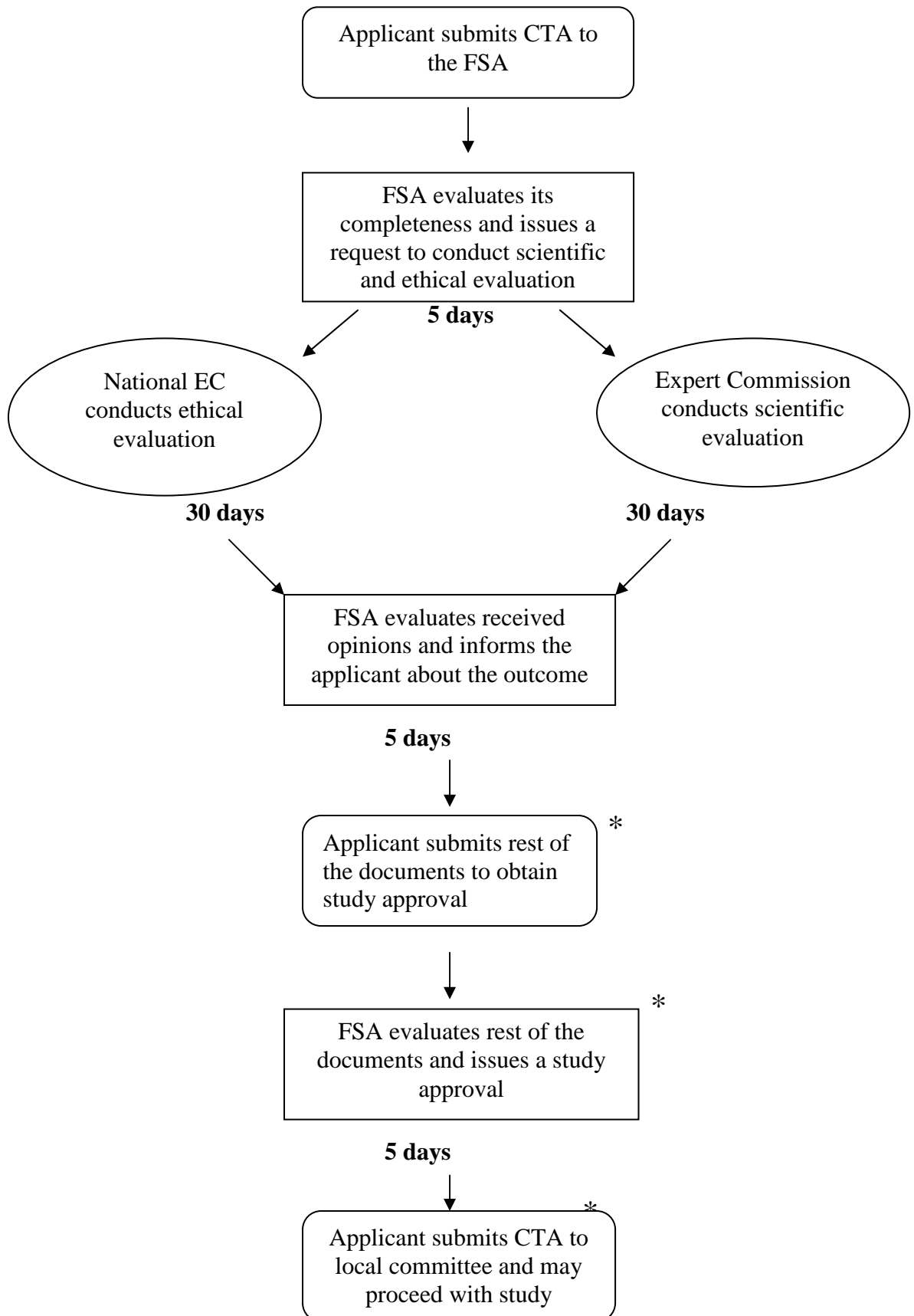
**Kazakhstan:**

**A:** Certificate of Analysis is required except of international multicenter trials and when IMP is an innovative product developed by domestic manufacturer

## Annex 2. Information required by the Ethics Committees for clinical study approval

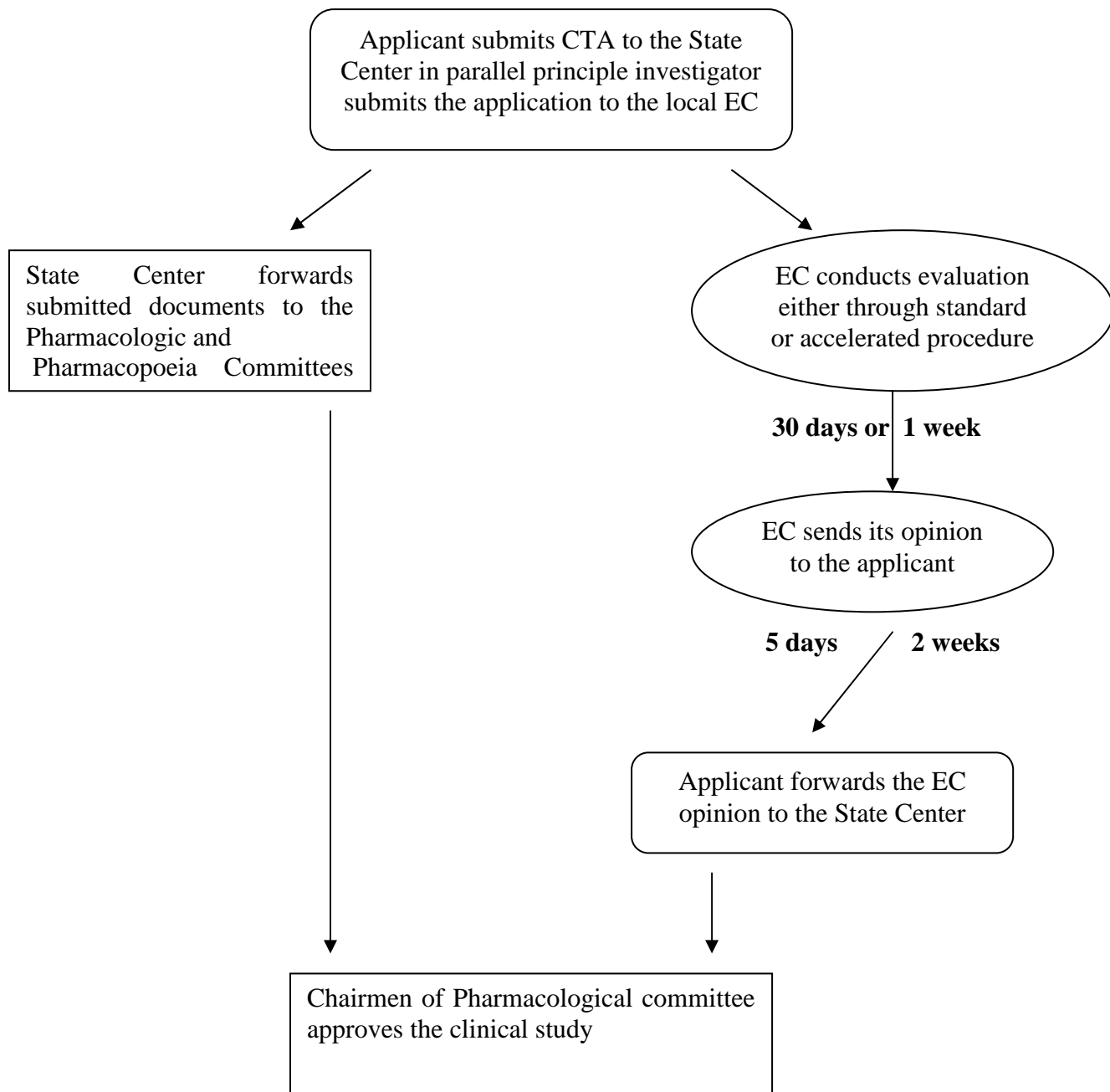
	Country specific information for the Ethics Committees	Russia	Belarus	Moldova	Kazakhstan
<b>1.</b>	<b>General</b>				
1.1	Copy of the previous national Ethics Committee opinions		Yes	Yes	
1.2	Application Form		Yes	Yes	Yes
1.3	Positive outcome of pre-assessment phase				Yes
<b>2.</b>	<b>Subject related</b>				
2.1.	Informed consent form		Yes	Yes	Yes
2.2	Patient information	Yes	Yes	Yes	Yes
2.3	Questionnaires, diaries if applicable		Yes	Yes	
2.4	Advertisement information for subject recruitment		Yes	Yes	Yes
2.5	Case report form			Yes	
<b>3.</b>	<b>Protocol related</b>				
3.1	Clinical trial protocol	Yes	Yes	Yes	Yes
<b>4.</b>	<b>IMP related</b>				
4.1.	Investigator's Brochure	Yes	Yes	Yes	Yes
4.2	Safety information on IMP				Yes
<b>5.</b>	<b>Facilities and staff related</b>				
5.1.	Facilities for the trial				
5.2.	CV of investigator			Yes	Yes
6.6	Statement on absence of personal interest from investigator			Yes	
5.3	Application form of a principle investigator				
<b>6.</b>	<b>Finance related</b>				
6.1	Compensations to study subjects	Yes	Yes	Yes	
6.2	Health insurance for study subjects	Yes		Yes	Yes

**Annex 3: Flowchart on Clinical trial approval procedure in Russia**

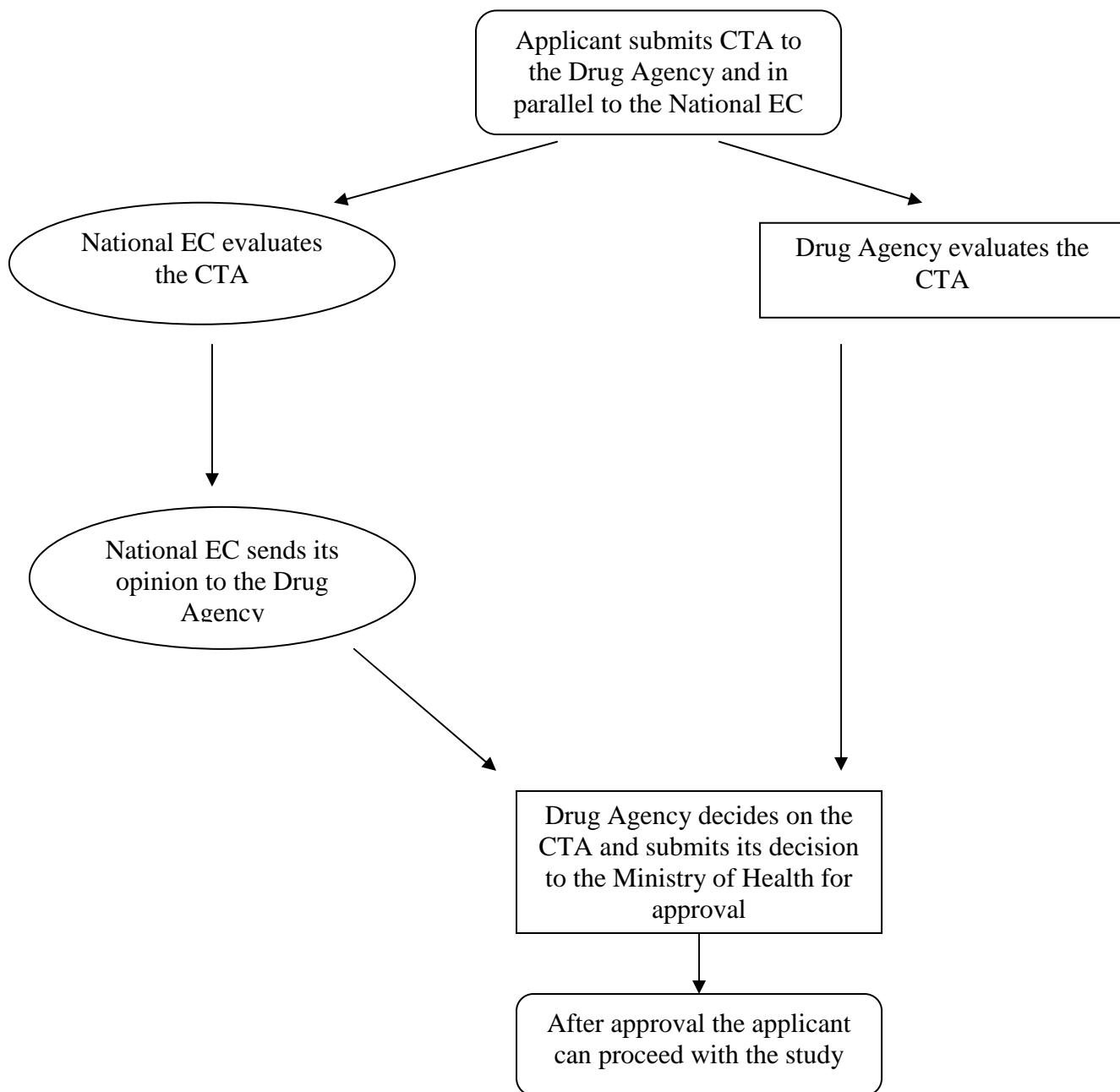


- Steps to be omitted for international multicenter and post-marketing studies

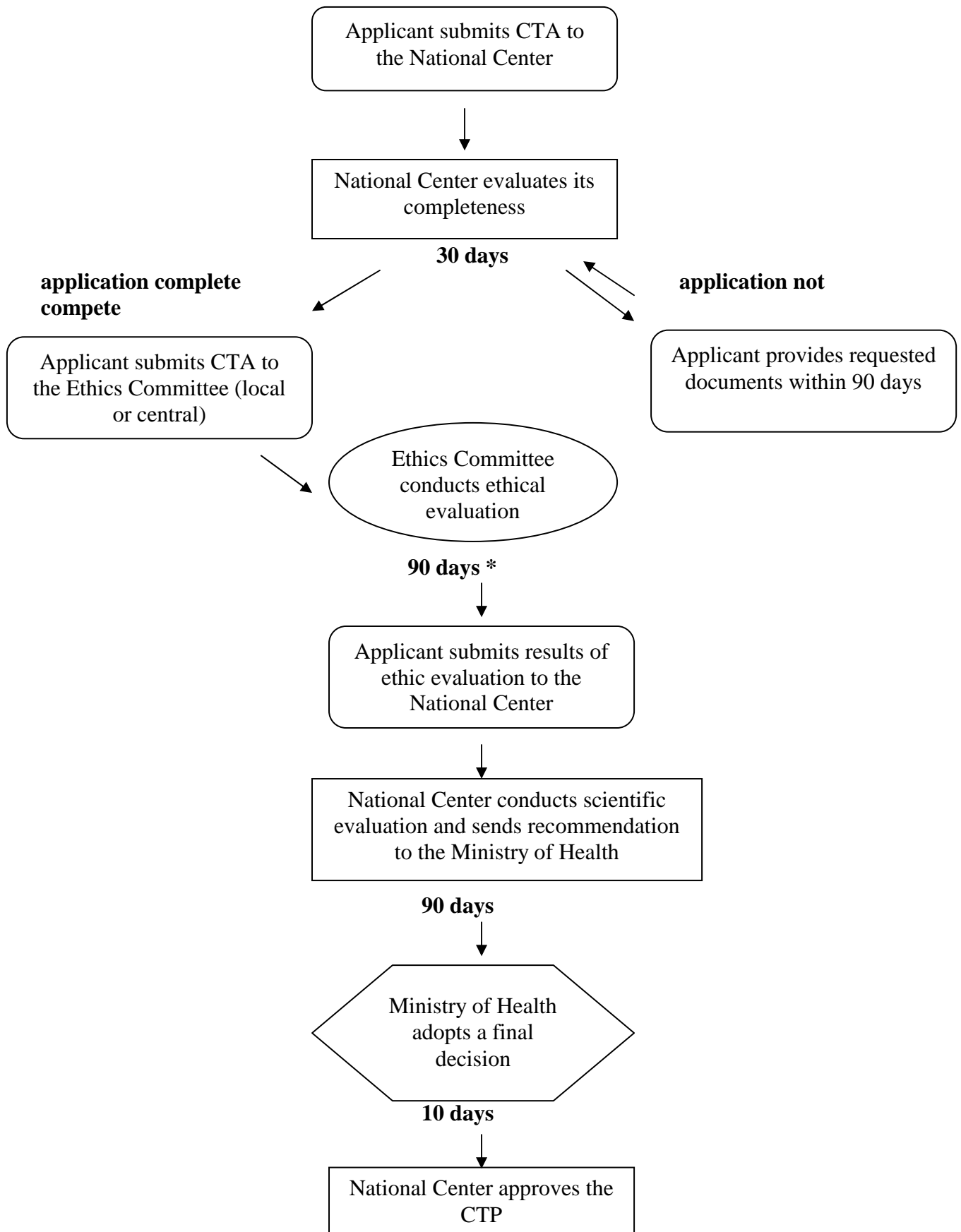
**Annex 4: Flowchart on Clinical trial approval procedure in Belarus**



**Annex 5: Flowchart on Clinical trial approval procedure in Moldova**



**Annex 6: Flowchart on Clinical trial approval procedure in Kazakhstan**



- For the Central Ethics Committee

## **Annex 7. Open Letter**

Deutsche Gesellschaft für Regulatory Affairs  
Master in Drug Regulatory Affairs course

### **Open Letter to the representatives of regulatory authorities and research organizations, active in clinical research**

Dear Ladies and Gentlemen,

There is a growing tendency for international research companies to choose Emerging Markets such as Latin America, Eastern Europe, Asia as a place to carry out clinical research. Emerging countries offer different regulatory and logistic provisions and being familiar with them helps research industry to understand advantages of each particular country and improve strategic planning. For national regulatory authorities is important to ensure a clear CTA\* submission and evaluation system and thorough supervision of trial conduct.

The purpose of our survey is to identify opinions of representatives of regulatory authorities and research organizations about regulatory systems in Eastern Europe. Countries included in the study are Russia, Belarus, Kazakhstan and Moldova. This study is performed within the framework of Master in Drug Regulatory Affairs course at the German Society in Regulatory Affairs and is supported by the European Forum for Good Clinical Practice (EFGCP).

Main goals of the study:

4. To describe CTA approval and ethical review process in every country;
5. To compare regulatory requirements and procedures between the countries;
6. To provide opinions of regulators and research organizations, operating in these countries, on practical aspects of clinical research conduct.

To answer these research questions we have developed a questionnaire that focuses on two main aspects: first, on the experience of regulatory authorities and research industry gathered in each country and second, on their assessment of existing regulatory systems (Questionnaire – Annex I). Survey can be conducted either by phone or by email.

Based on results of the survey practical recommendations for carrying out clinical research in respective East European countries and on strengthening cooperation between regulatory authorities and research industry will be made.

We invite you to participate in this survey and are looking forward to your collaboration!

Sincerely,

Volodina Anna, MsIH  
University of Bonn

Ingrid Klingmann, MD, PhD, FFPM, FBCPM  
Chair of the Clinical Research Module  
Master of Regulatory Affairs, University of Bonn, Germany  
Member of the Board, European Forum for Good Clinical Practice

\*Clinical Trial Application

## **Confidentiality and Ethical aspects**

This survey is completely voluntary. If you agree to proceed, you may choose to stop filling up the questionnaire or answering the questions during phone interview at any time. If you do not wish to answer a certain question please feel free to do so.

This survey is anonymous. Your answers will be seen only by me. I am interested in personal opinions and experiences. By publication of the results only research country (e.g. Moldova, Russia) and professional area of respondents (defined either as “regulatory authority” or “research industry”) will be indicated.

Results of the survey will be published in the Master thesis for Drug Regulatory Affairs course at the German Society for Regulatory Affairs (DGRA), University of Bonn. Before submission of Master thesis a working draft of the survey analysis will be sent to every respondent for comments and corrections.

Dissemination of information: final version of the thesis with analysis of regulatory requirements for clinical research in 4 East European countries and survey results will be sent to every survey participant.

## **Survey procedure**

You may answer survey questions (Annex I) either by phone or by email.

**Phone survey:** interview will be conducted on day and time specified by respondent. A phone call will be given on phone number provided by respondent, language: English or Russian.

**E-survey:** electronic version of the questionnaire will be sent to respondents by the email, language: English or Russian.

We have tried to develop a questionnaire as comprehensive as possible. However, we would be very grateful for any additional comments you may want to provide to any of the questions.

It will take about 15 minutes for you to fill up the questionnaire. Your input is very valuable for us and we would greatly appreciate your taking time to answer these questions.

For questions and comments please email: [anna.volodina@yahoo.com](mailto:anna.volodina@yahoo.com) Anna Volodina



## Annex 8. Questionnaire for the Competent Authorities

This questionnaire serves for carrying out research project for master thesis within the Master of Drug Regulatory Affairs course at the University of Bonn in cooperation with the German Society for Regulatory Affairs (DGRA) and with the support of the European Forum for Good Clinical Practice.

### Section I. Current experience with clinical trial applications

1. How many clinical trial applications have been submitted for approval in 2007, 2008 and 2009 in your country? Please provide data at least for one year. If you can not provide exact numbers, please give us approximate figures.

	Total number of Clinical Trial Applications		Among them Phase I trials		Among them Phase II trials		Among them Phase III trials		Among them Phase VI (post-marketing trials)	
	Exact number	Approx. number	Exact number	Approx. number	Exact number	Approx. number	Exact number	Approx. number	Exact number	Approx. number
2007										
2008										
2009										

#### Comments:

2. How long does it usually take from submission to approval of a CTA by RA and EC(s)? Where possible, please specify usual approval time for each type of trial.

Approval time for CTA in general	Approval time for Phase I trials	Approval time for Phase II trials	Approval time for Phase III trials	Approval time for Phase VI trials
Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)

#### Comments:

3. In cases when sponsor and investigator are two different organizations, who shall submit an application?

<b>Answer:</b>
----------------

4. Based on your experience please identify the most common reasons why CTA have been rejected.

<b>Reasons for rejecting a CTA</b>
<ul style="list-style-type: none"><li>•</li><li>•</li></ul>

Section II. Regulatory environment

1. What regulatory aspects may serve as an attractive point for the industry to conduct clinical research in your country? (E.g. quick approval process, clear requirements, availability of regulatory information)

<b>Answer:</b>
----------------

2. According to your experience are there any areas of improvement in the regulatory system for clinical research (compare maybe to other countries)?

<b>Areas of improvement of the regulatory system</b>
<ul style="list-style-type: none"><li>•</li><li>•</li></ul>

3. Are there any cultural specialties that you consider to be important for an international company, wishing to perform a clinical study in your country?

<b>Cultural specialties important to consider for clinical trails</b>

## Annex 9. Questionnaire for the Pharmaceutical Industry and CROs

This questionnaire serves for carrying out research project for master thesis as a part of Master of Drug Regulatory Affairs course at the University of Bonn in cooperation with the German Society for Regulatory Affairs (DGRA).

### Section I. Current experience with clinical trials

1. Every year, more trials are placed in CEE. How do you see the recent development of the clinical research market in this county, and what does the future hold?

**Answer:**

2. Are you planning to increase the number of studies in this country for the next 2-3 years from the current level? If yes, to what extend?

**Answer:**

3. Based on your experience, how long does it usually take from submission to approval of a CTA by RA and EC(s)? Where possible, please specify usual approval time for each type of the trial.

Approval time for CTA in general	Approval time for Phase I trials	Approval time for Phase II trials	Approval time for Phase III trials	Approval time for Phase VI
Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)	Days / weeks / months / years (please underline)

### Comments:

4. In cases when sponsor and investigator are two different organizations, who usually submits a CTA?

**Answer:**

5. Based on your experience, what are the most common reasons for rejection of clinical trials application?

#### Most common reasons for rejecting a CTA

- 
-

6. Where industry can find information/advice on regulatory requirements and procedure when they want to submit a trial?

**Answer:**

\Section II. Regulatory environment

1. Are there any regulatory/tax/financial incentives that attract your company to conduct clinical trials in this particular country (compare to other countries)?

<b>Regulatory incentives</b>
<ul style="list-style-type: none"><li>•</li><li>•</li><li>•</li></ul>
<b>Tax/financial incentives</b>
<ul style="list-style-type: none"><li>•</li><li>•</li><li>•</li></ul>
<b>Other incentives</b>
<ul style="list-style-type: none"><li>•</li><li>•</li><li>•</li></ul>

2. Based on your experience, are there any requirements for CTA and conduct of a trial that are laid down in the regulations but are not working smoothly in the practice?

**Answer:**

3. What are the main challenges you usually face when conducting a clinical trial in this country? (study approval process, requirements for IMP, ethical approval, inspections, reporting)

<b>Main challenges in CT conduction</b>
<ul style="list-style-type: none"><li>•</li><li>•</li></ul>

4. What changes in the regulatory system, if any, would you like to see in this country in the coming years?

**Answer:**

5. Are there any cultural specialties that you consider to be important for an international company, wishing to perform a clinical study in your country?

<b>Cultural specialties important to consider for clinical trails</b>

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben