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# CLINICAL STUDIES IN COMMON WEALTH INDEPENDENT STATES: CRITICAL ASSESSMENT OF THE REGULATORY REQUIREMENTS.

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**Abstract:** 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. Duration of the study approval as per legislation of Russia and Kazakhstan corresponds to 7 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. 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. 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).

**Keywords:** Ethical committee, Clinical trials, Clinical research, Regulatory amendments

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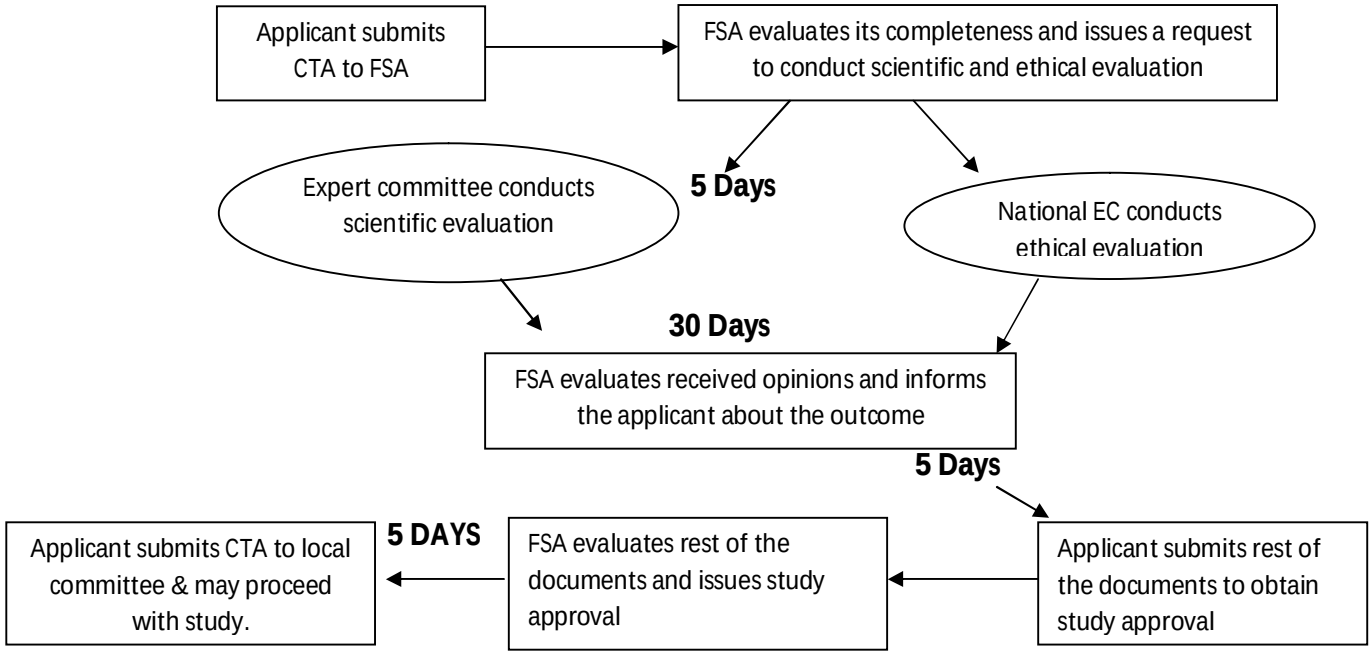
## INTRODUCTION

Eastern Europe along with Latin America and Asia is viewed as an emerging market in clinical research. 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 naive populations and low number of dropouts[1,2]. According to some analysts, pharmaceutical industry currently utilizes only 15% of the clinical study enrolment potential in Eastern Europe[1,3,4]. 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[5,6,7,8] .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). 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[9,10]. Four countries like Russia, Belarus, Kazakhstan and Moldova were chosen to study the countries' regulatory and national particularities relevant for clinical research.

### 2.1 CLINICAL RESEARCH IN RUSSIA

**Flow Chart on Clinical Trial approval procedure in Russia**



**Following Laws governs the Regulations and Amendments in Russia**

| Stage | Law related | Comments |
|---|---|---|
| **National legislation in Clinical research** | Federal Drug Law no. 61 | Regulates clinical research in Russia; |
| | Order no. 232 of Sep 2005 | National standard on Good Clinical Practice |
| | 5th Oct 2009 | Guideline on monitoring of adverse drug events during clinical studies |
| | Order of Ministry of Health no. 2314-IIp/07 | National Ethics Committee |
| | Order of Ministry of Health no. 235 | Organization of Departments for conduct of Clinical studies in healthy volunteers |
| | Regulation no. 291-22/101 | Responsibilities of local committees and their role in clinical research |
| | 10th Aug 2004 | Guideline on conduct of Bioequivalence studies |
| | 915000.14.0001-2002 | Industry standard on clinical –economical studies |
| **Clinical trial authorization** | Drug Law no. 86 | Transfers functions of study approval and supervision to FSA |

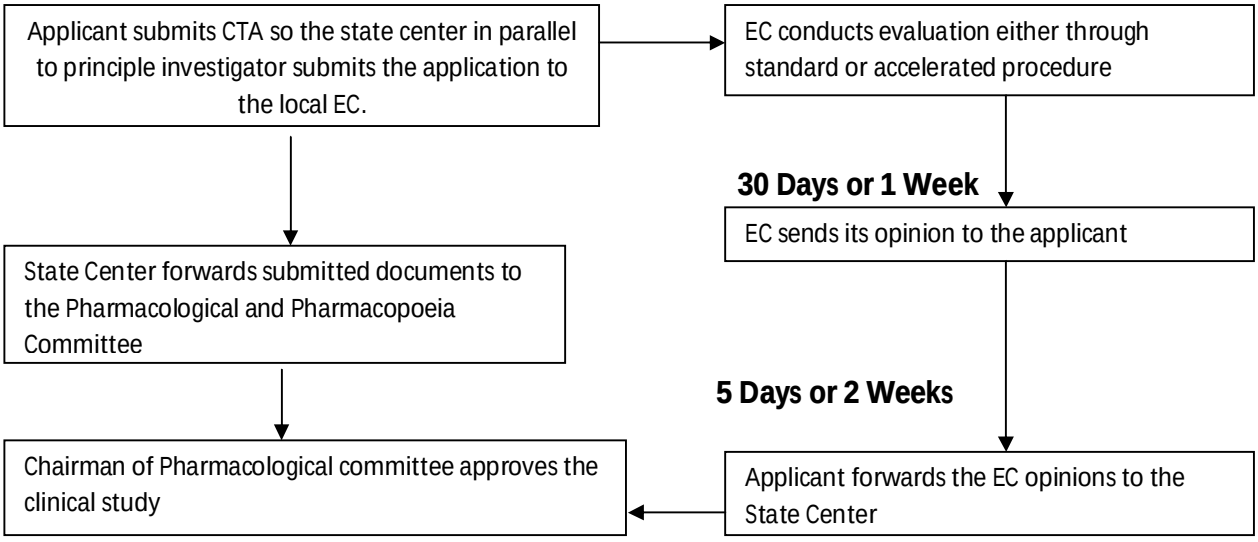
**2.2 CLINICAL RESEARCH IN BELARUS:**

**Following Laws governs the Regulations and Amendments in Belarus**

| Stage | Law related | Comments |
|---|---|---|
| **National legislation in Clinical research** | Public Health Law no. 2435-XII | |
| | Drug Law No. 161-3 | Procedures on pre-clinical and clinical studies, import and export of medicinal products, rights and responsibilities of |

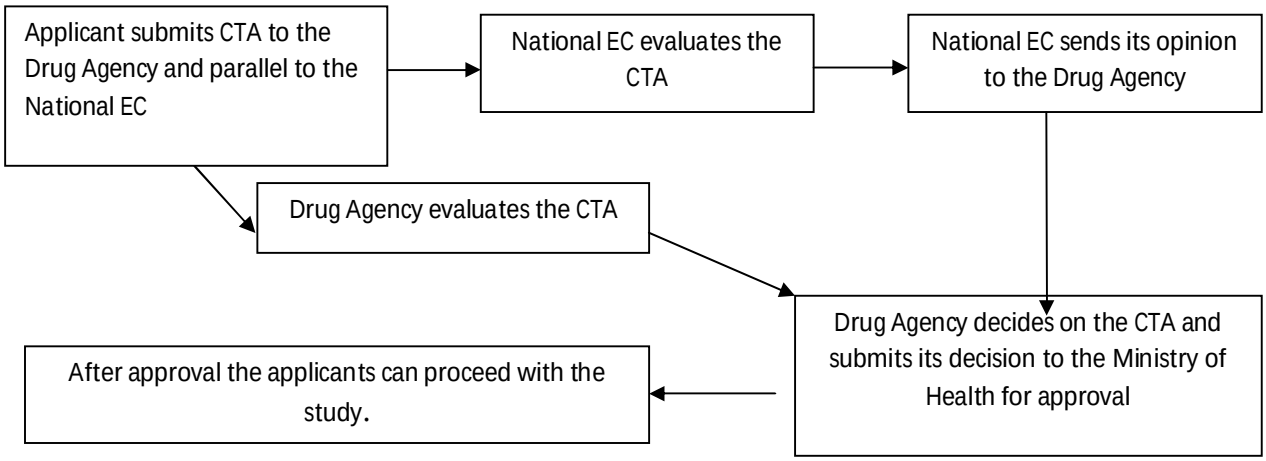
| | |
|---|---|
| | study subjects. |
| Resolution of Council of Ministers No. 1677 | Quality control of Medicinal Products |
| Resolution of Ministry of Health No. 50 | Good Clinical Practice of Belarus |
| Guideline on Ethics Committee No.57-0004 | Principles and procedures of EC's including clinical trial authorization, review of amendments, inspections. |
| Order of Ministry of Health no. 88 | Pharmacological and Pharmacopoeial Committee |
| Instruction of Ministry of Health no. 50-0504 | Accreditation of health facilities and health specialists to conduct clinical studies of medicinal products and devices. |
| Order of Ministry of Health no. 274 | National Bioethics Committee. |

**Flow Chart on Clinical Trial approval procedure in Belarus**



## 2.3 CLINICAL RESEARCH IM MOLDOVA:

**Flow Chart on Clinical Trial approval procedure in Moldova:**



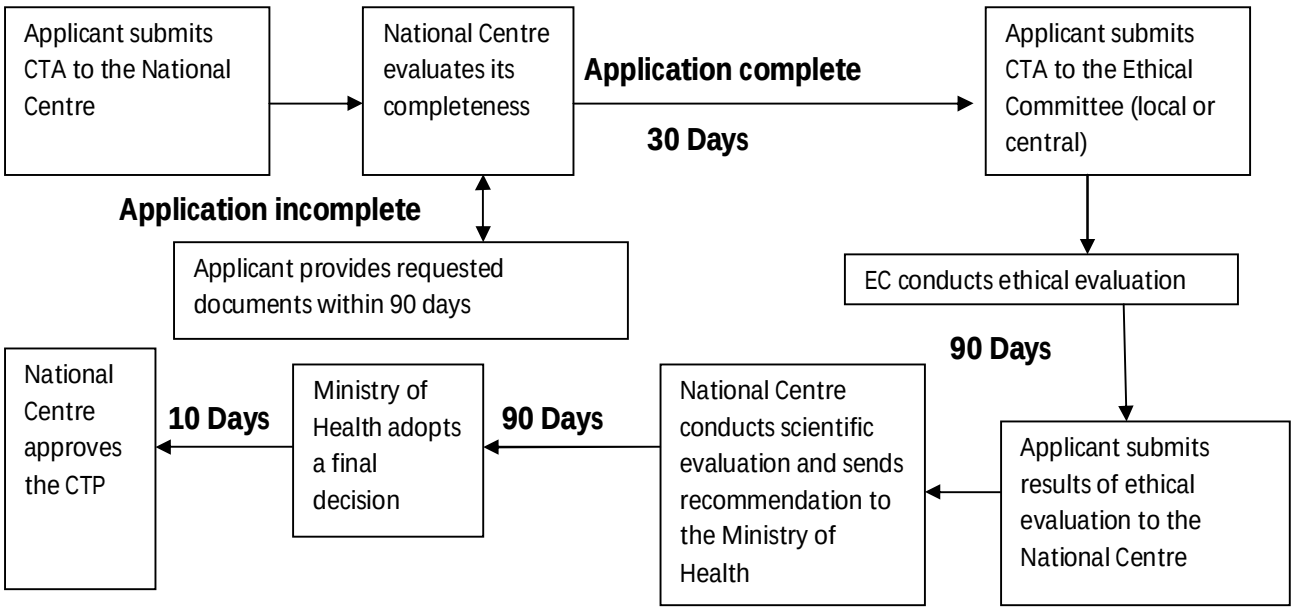

**Following Laws governs the Regulations and Amendments in Moldova**

| Stage | Law related | Comments |
|---|---|---|
| **National legislation in Clinical research** | The Drug Law No. 1409 - XIII | 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. |
| | Law No. 1456-XII | Pharmaceutical practice |
| | Law No. 552-XV | Accreditation in healthcare system |
| | Law No. 263-XVI | Rights and responsibilities of the patient |
| | Law No. 264-XVI | Medical profession |
| | Resolution of the Parliament No. 1352 | Public policy on medicines |
| | Order of the Ministry of Health No.10 | Guideline on conduct of clinical studies in Moldova. |

| | | |
|---|---|---|
| | Order of the Ministry of Health No. 54-p12 | National Ethics Committee |
| | Order of the Parliament No. 10 | State Surveillance in Public Health |
| | Law No. 185-XV | Reproductive health and family planning |
| **Declaration of end of the trial** | Order No. 10 | Stipulated procedure on how to end the trial declared in Moldavian. |

**2.4 CLINICAL RESEARCH IN KAZAKHSTAN:**

**Flow Chart on Clinical Trial approval procedure in Kazakhstan:**



**Following Laws governs the Regulations and Amendments in Kazakhstan**

| Stage | Law related | Comments |
|---|---|---|
| **National legislation in Clinical research** | Comprehensive Code on Public Health & Healthcare system of Kazakhstan | Harmonizes national regulations in public health and reduces subordinate legislative documents |
| | Order of the Ministry of Health No.442 | Conduct of medico-biological experiments, pre-clinical and clinical studies in Kazakhstan |
| | Order of the Ministry of Health No. 53 | Defines of the study phases (I-IV) |
| | Order of the Ministry of Health No. 52 | Monitoring of adverse drug events |
| | Order No. 425 on Central EC | Lays down goals, rights and responsibilities of the Central EC, its structure and procedures. |
| | Order No. 304 | Establishment of orphan drugs list |
| | Order No. 442 | Guideline on conduct of clinical studies in Kazakhstan |

**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.

**DISCUSSION**

*Structure of the competent authorities*

Belarus, Moldova and Kazakhstan have one competent authority within the Ministry of Health which is responsible for scientific evaluation and approval of the CTA. FSA will issue the study approval when the submitted documentation is complete, and will rely on the scientific assessment of the Expert Commission.

*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). 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 earlier procedure (15 weeks on average). 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 [4,8] and 4-12 weeks in Belarus[3].

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[46]. 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[10].

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 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 fulfill 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[1,2]. 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 cannot 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 annually3,5.

*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 counties it is not clear what regulatory procedures apply to non-observational studies.

**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.
3. 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).
4. 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.

5. The company should consider cultural particularities when setting up a procedure for informed consent, collection of bio-specimen, ensuring privacy and confidentiality of the subjects.
6. 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.

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