Drugs' Marketing Authorisation and Clinical Trials Regulations in Ukraine

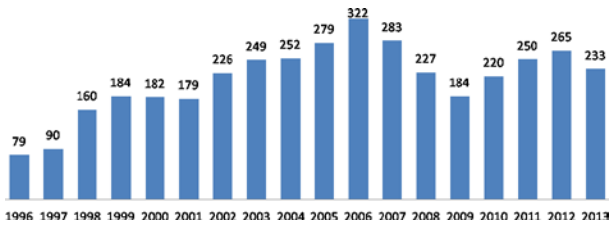
PEER REVIEWED

Despite the difficult political and economic situation, Ukraine is still open for pharma business and clinical trials in particular. Along with a vast population concentrated in several large cities, a wide range of investigative sites and qualified research personnel, Ukraine provides for foreign pharmaceutical companies and sponsors a regulatory environment mostly based on the principal provisions of the corresponding EU legal acts and guidance governing particular areas of drug marketing and clinical study authorisation.

Unlike Russia, which prefers to go its own way, including in terms of regulations in the sphere of drugs' marketing authorisation (MA) and clinical trials, Ukraine moves along the beaten track and creates its legislative framework on the basis of the European legal documents. Despite that, the number of clinical trials initiated in Ukraine by European and other foreign sponsors has not yet approached the level of Russia.

Figure 1

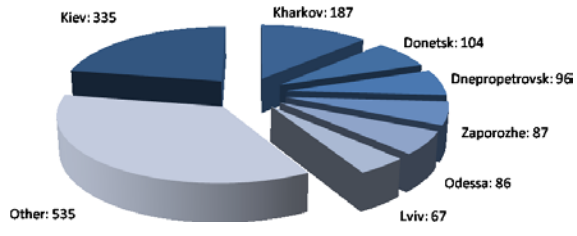
Clinical trials in Ukraine (1996-2013)



Nevertheless, Ukraine is one of the most attractive regions of the post-Soviet area in terms of clinical research because of its vast population which is concentrated in several large cities (about 46 million people), well-equipped investigative sites (1476 as of January 2014), qualified and GCP-trained medical personnel, as well as a favourable legal landscape with regulations compliant with the European standards.

Figure 2

Number of Investigative Sites in Major Cities



The competent authorities engaged in MA and clinical trial authorisation are represented by the Ukrainian Ministry of Health (MoH) and its subordinate expert advisory board – the State Expert Center (SEC). The MoH grants MA for drugs and issues clinical trials authorisations. SEC conducts expert evaluation of MA applications and clinical trial documents, and carries out clinical trial audits and drugs safety monitoring. The Ukrainian Central Ethics Committee responsible for ethical expertise of clinical trials documents and clinical trials authorisation was abolished in 2012. The ethical support for clinical trials is now provided by numerous local ethics committees (LECs) established at various medical, scientific and educational institutions[2].

Pharmaceutical companies or CROs can request scientific advice, either during the initial development of a pharmaceutical product before submission of MA application, or later on, throughout the validity period of the MA certificate. Scientific advice is free of charge[4].

The MA procedure includes three stages of expertise. The first stage (lasting up to 21 working days) aims to determine that the drug is not forbidden in Ukraine and to classify the type of application. After the first stage is successfully completed, the applicant should pay out the registration fee and expertise cost. The objective of the second stage expertise (preliminary expertise), the duration of which is 14 working days, is the compliance of the submitted package of documents with established legal requirements. A complete application is needed in case of claiming for an innovative drug MA. An abridged application is prepared when submission is made for MA of generic drug, fixed combination of previously registered drugs and other dosage form/therapeutic indication of previously registered drug. In the course of the second stage expertise SEC could request for additional (or missing) data and documents, and the applicant has to respond in 90 working days[4].

The cost of expertise depends on the type of MA application and the nature of the drug. In case of a complete MA application (standard application) the expertise cost is about 2750 Euro, and about 2200 Euro if the chemical drug (substance) is well evaluated in Ukraine, about 2600 Euro for expertise of biosimilar drug, about 1250 Euro for expertise of orphan drugs, about 2300 Euro for expertise of single component generic drug, and 2600 Euro for a multi-component generic drug. An applicant is also obliged to pay state registration tax of 100 Euro for each dosage form, 10 Euro for each additional dosage strength, 10 Euro for each additional package of the drug (except radiopharmaceutical, diagnostic products and herbal drugs)[3].

Specialised expertise is performed by SEC within 210 working days in case of a complete application, and 90 working days in case of an application for selected situations (some drugs for treatment of HIV, tuberculosis, hepatitis, rare diseases; generics, biosimilars, orphan drugs, some others). In the course of specialised expertise, SEC could request additional (or missing) data on quality, safety and efficacy of the assessed drug and the applicant has to respond in 60 working days. In cases where documents and data submitted by the applicant do not fully provide justification of an MA application, the SEC could request additional non-clinical or clinical testing of the drug[4].

The SEC expert report prepared at the end of specialised expertise is the basis for the MoH decision whether to grant MA for pharmaceutical product or reject the MA application. Data on quality, safety and efficacy of the drug needed for expert evaluation should be presented in CTD format, which comprises five modules, according to the EU requirements CPMP/ICH/2887/99. The submission package, besides CTD, should also include:

- Proof of drug registration status (i.e. MA certificate issued by the country of applicant/manufacturer; list of countries where the drug is already registered),
- Finished product manufacturer authorisation (licence), GMP certificates or other GMP statements,
- Flowchart and description of manufacturing process and process controls,
- Qualitative and quantitative composition of the drug and proposed analytical procedures for its control,
- Summary of product characteristics (SmPC),
- Mock-ups and specimens[4].

The MA is initially valid for five years and may be renewed after this period on the basis of a re-evaluation of the risk-benefit balance by the SEC[4].

The information contained in the MA application and its annexes shall be subject to public disclosure and protection against unfair commercial use. In case a generic drug is submitted for MA within five years since the original drug has been registered in Ukraine, an applicant has to provide MoH with document evidencing that reference drug MA holder gave consent to use its non-clinical and clinical data for MA purposes[4].

The MA holder should notify SEC of all the changes in the technological process, utilised equipment or manufacturers engaged in APIs and excipients production. An appropriate type of variation should be chosen. Type 1A/1B and Type 2 variations represent minor changes (e.g. a change of MA holder name or location, a change of proprietary drug name (trade name), a change of ATC code, etc.) that have a low risk of compromising quality, safety and efficacy of the pharmaceutical product. All the variations listed above are subject to a two-stage expert evaluation that is performed by SEC on the contract basis. The first-stage expertise, lasting five working days, represents a preliminary assessment of the submitted package of documents in terms of compliance with legal requirements and the type of variation application. The second-stage expertise, lasting 60 working days, represents specialised expertise aimed at justification of proposed changes and absence of their impact on the quality, safety or efficacy of the pharmaceutical product. In the course of specialised expertise, SEC could request additional (or missing) data, and the applicant has to respond in 30 working days. The expertise cost varies depending on type of the variation and the nature of drug: e.g. about 240 Euro in case of a Type 1A variation that doesn't affect the primary package of biotechnological drug, or about 400 Euro in case of a Type 2 variation that affects the primary package of biotechnological drug[4].

All other changes, e.g. a change of the API to a different API, inclusion of an additional API, or removal of one API from a multi-component product, a change in the dose of one or more of the APIs, a change in dosage form or route of administration, a change in the recommendations for use, etc., are so major that they constitute a new pharmaceutical product. These should be considered to be an application for a new product and should not be accepted as a variation[4].

The procedure for clinical trial authorisation is the same for both international multi-centre (IMCT) and local clinical trials. Clinical trial authorisation is issued by MoH based on the results of expertise carried out by SEC. The list of documents that should be submitted to SEC for expertise is presented in Table 1.

Table 1

List of documents for clinical trial authorisation

Cover letter	Ukrainian language
Application form	Ukrainian language
Power of attorney with Apostille that specifies CRO's activities on behalf of sponsor	English language (notarised translation into Ukrainian language is mandatory)
Clinical trial protocol	English language
Protocol synopsis	Ukrainian language
Investigator's brochure	English language
Investigational medicinal product dossier (IMPD)	English language
Case report form (except IMCT)	English language
Informed consent form	Ukrainian and Russian languages
Patient-related documents (diaries, checklists, questionnaires etc.) and promotional materials needed for recruitment	Ukrainian and Russian languages
IMP labels	Ukrainian and Russian languages
Certificate of IMP batch analysis	English language
GMP certificate	English language
Principle investigator's application	Ukrainian language
List of clinical sites + information on clinical sites to be involved in clinical trial	Ukrainian language
Documents confirming establishment of clinical sites' LECs	Ukrainian language
Signed and dated investigators' CVs	Ukrainian language
Investigators' GCP certificates	
Compulsory insurance policy	Ukrainian language
Information on measures to be taken by investigator in case of insured event	Ukrainian language
Information on payments and compensations to healthy volunteers or patients (if any)	Ukrainian language
EudraCT number (if applicable)	English language
List of competent authorities of other countries involved in expertise of IMCT (if applicable)	English language
Brief information on other clinical trials with use of IMP (if applicable)	English language
TSE certificate (if applicable)	English language

Duration of expertise is 50 calendar days, and time needed for MoH to authorise the results of SEC expertise is 10 calendar days. The cost of expertise is about 3300 Euro in cases where the investigational drug is not registered in the country of origin, and about 2000 Euro if it has been already registered in the country of origin. In the course of expertise, SEC could request additional (or missing) data, and the applicant has to respond in 60 calendar days[5].

The clinical trial documents should be submitted for ethical assessment at every clinical site that is going to participate in the clinical trial. Ethical assessment may be performed before, simultaneously with, or after SEC expertise. The list of documents submitted for ethical expertise is shorter than the list of documents submitted to SEC: IMPD and other drug-related documents (certificates, labels, etc) are not necessary for LEC assessment. It is also not necessary to submit the full text of the protocol, and a summary of this document is absolutely enough for ethical consideration. Ethical expertise is free of charge and its duration is 30 calendar days. In the course of ethical expertise, LEC could request additional (or missing) data, and the applicant has to respond in 30 calendar days[2, 5].

If involvement of children is anticipated in the clinical trial, informed consent signed by both parents is mandatory. The information on investigational drug and planned clinical trial acceptable for minors' understanding should also be provided for the child's personal consideration and assent (written for older children or oral for younger children). Moreover, the information on the involvement of children in a specific clinical trial should be addressed by the investigator in writing to the the Ukrainian guardianship and custody agencies at the place of permanent residence of the child[5].

In case a clinical trial has been authorised by MoH, a sponsor or CRO may apply for an import license for investigational drug and study materials (laboratory kits, needed equipment, etc.). The import license is issued in a two-step procedure. At the first stage, a sponsor applies for reconciliation of the total amount of investigational drug and study materials that should be imported for the whole study period. The appropriate document – so-called "umbrella" permission – is issued by SEC in 10 business days. At the second stage, a sponsor applies for permission to import definite shipments of investigational drug or study materials within the limits specified by the "umbrella" permission. The permission to import an exact shipment of clinical study drug or materials (import license) is issued in 10 business days by the State Drug Control Agency, which is subordinate to MoH[5].

All the investigational drugs, including matching placebo, are charged VAT of 20 % in accordance with the provisions of the Tax Code of Ukraine. It is expected that in the first half of 2015 the VAT rate will be decreased from 20 % to 7 % in order to boost the country's attractiveness in terms of conduct of IMCTs.

Licence for export of biological samples is not needed. Any medical institution can participate in conduct of clinical trial as a research (investigative) centre in the case of:

- Proof of appropriate medical qualification (medical licence and accreditation certificate issued by MoH),
- Proof of LEC availability,
- Proof of metrological control implementation,
- Proof of storage areas' availability (patients' source documents should be stored at least 15 years after clinical trial is completed at clinical site).

An investigator has to be an employee of a clinical site that is involved in a definite clinical trial. In case an investigator is an employee of a medical educational institution based at a clinical site, a corresponding contract between the educational institution and clinical site should be in place. It is also mandatory that the investigator should be GCP-trained. Payment of the research centre's and investigator's services is performed under the contracts signed between the research centre and sponsor/CRO, and between investigator and sponsor/CRO[5].

The volunteers or patients who participate in a clinical trial (those who have signed an informed consent form) should be insured by the local Ukrainian medical insurance company.

The essential or non-essential amendments may be implemented in the course of the clinical trial. Both types of amendments should be submitted to SEC. The essential amendment is considered by SEC in 30 calendar days and addressed to MoH for issuing of a corresponding authorisation in case of a positive result of SEC expertise. The time needed for MoH to issue an amendment authorisation is five calendar days. In the course of expertise, which costs about 370 Euro, SEC could request additional (or missing) data, and the applicant has to respond in 30 calendar days. The non-essential amendment is submitted to SEC only for notification and the procedure is free of charge. All the amendments should also be submitted to LEC; essential ones for consideration and non-essential ones for LEC notification. The essential amendments should be considered by LEC in 10 calendar days[5].

SEC is the Ukrainian competent authority whose competence includes drug safety monitoring issues, and sponsors or CROs are obliged to provide SEC with appropriate information. All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. SEC should be notified of all fatal or life-threatening unexpected ADRs occurring in a clinical trial as soon as possible, but no later than seven calendar days after first knowledge by the sponsor that

a case qualifies, followed by as complete a report as possible within eight additional calendar days. Serious, unexpected ADRs that are not fatal or life-threatening should be reported to SEC as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. In case of a long-term clinical trial, the sponsor should provide SEC with periodic safety update reports at least once per year. In the course of safety data expertise SEC could request additional information if the benefit/risk ratio of investigational drug has changed from its point of view. If the sponsor has not provided SEC with the requested information in seven calendar days, SEC could temporarily or completely stop the trial[5].

In the current 2014 year the political situation in Ukraine has been unstable, affecting the perspectives of ongoing and future clinical trials. The Ukrainian MoH, like other state agencies, has been under intense pressure because of a severe budget shortfall and major distractions. Nevertheless, regulatory approvals have remained in line with legislative timelines and study submission and consideration procedures have not changed. Furthermore, in 2015 the VAT rate for the import of investigational drugs, medical devices and equipment for approved clinical trials is expected to be cut from 20 % to 7 %, which should be regarded as a substantial step forward for Ukraine to improve its international image and attract additional clinical trials.

Some CROs that are operating in the clinical research market in Ukraine suppose that the economic constraints faced by the country will lead to shortages of certain high-priced medicines and hospital supplies, such as CT/MRI intravenous contrast dyes. The other companies believe that no significant changes will affect research sites or the ways they operate. Some CROs have stated that new studies should not be authorised in Crimea, recruitment of new patients into current studies should be ceased, and monitoring should not be done there, while others propose sponsors should ask Russia for study approvals for Crimean sites. CROs are quite unanimous in their assessment of prospects of the Ukrainian South-East region: sponsors should avoid research sites in this critical area. Such measures as thorough checks of logistic partners and local banks that are carrying out site payments, in terms of their inclusion in the sanctions lists, seem to be also quite reasonable[1, 6].

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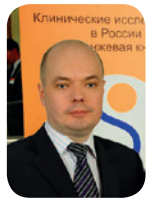

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