Specifics of drug registration in Common Customs Zone countries

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The transformation of the Common Customs Zone (CCZ) into the Common Economic Zone (CEZ) has been scheduled for January 2012. According to expert forecasts, the aggregate size of the pharma market of this alliance's countries may reach 26 bn USD by the end of 2012 and 30 bn USD by early 2014 (Fig. 1).

Fig. 1. Forecast of pharma market development in CCZ (CEZ) countries, 2011—2013

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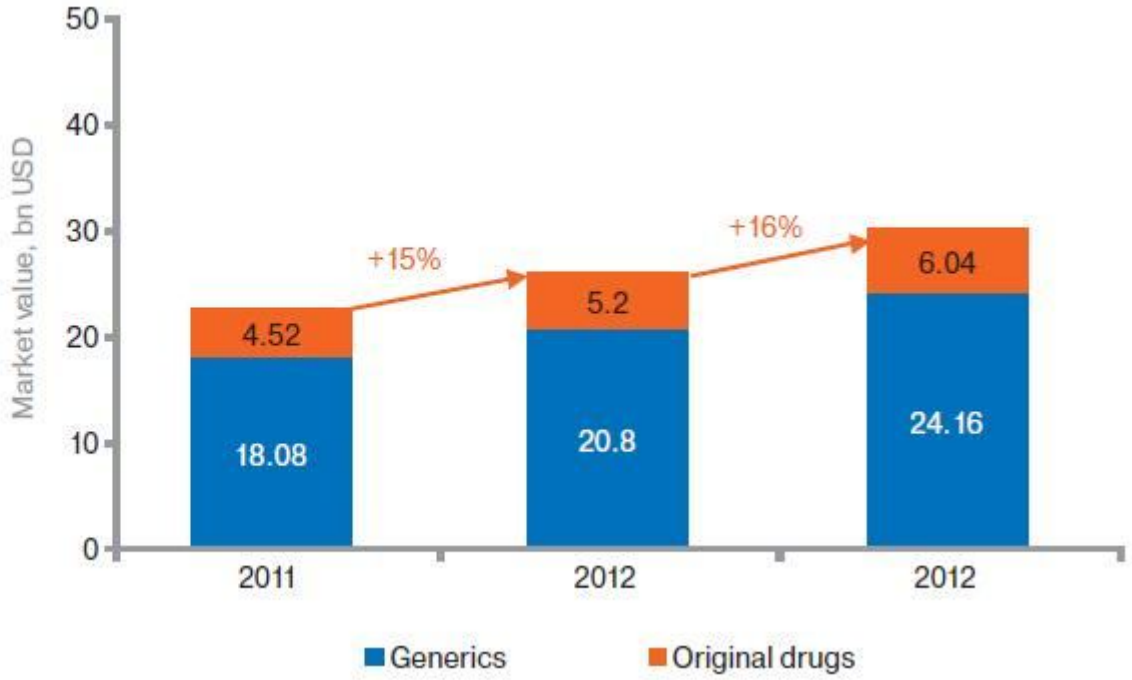
Source: Pharmexpert — Monitoring of retail drug sales and hospital purchases in Russia, Kazakhstan, and Belarus



In this respect, the market shares of the CEZ countries will remain the same as in the CCZ. Russia will account for 91% of the aggregate market, while Kazakhstan and Belarus — for 5% and 4%, respectively. The growth rates and structure of their respective pharma markets will not change much either. The drug market in each specific country as well in general will remain a generic market, although the share of this drug group will go up.

What the pharma industry is expected to benefit from the three countries' economic integration?

Within the CEZ, local drugs will receive in the countries the status of "domestic goods" for the purposes of participation in tenders. This will probably facilitate the growth of local drug share on the CEZ pharma market. However, this is likely to happen in the future, since the legislation in the three countries is still differs a lot. The period of the legislative framework harmonization and mutual recognition of drugs seems to be rather long.

Drug registration: general provisions

Today, the CCZ countries have different regulations governing the drug circulation on their domestic markets. The drug registration is a procedure aimed at the authorization of (permit for) the circulation of the drug itself within a particular country and the confirmation of the drug safety, effectiveness, and quality in accordance with applicable regulations. If the drug registration is approved, the Marketing Authorization (MA) for that drug will be issued.

In the countries under review, the drug registration procedures are somewhat similar and somewhat different, being the responsibility of the appropriate authorized government bodies and agencies acting pursuant to local legislation (**Table 1**). The key regulator in each country is the government ministry: In Russia, it is the **Ministry of Health and Social Development** (**Minzdravsocrazvitiya**), in Belarus — **Ministry of Health** (**RB MOH**), and in Kazakhstan — **Ministry of Health** (**RK MOH**). Today each of the above government authorities has a web-site, so that everyone can get familiar with the requirements for drug registration procedure, monitor the status of the applications etc.

Table 1. Authorized drug registration agencies in the CCZ countries

Country	Authorized expert institution	Web-site
Russia	Federal State Budgetary Agency "Scientific Center for Assessment of Medica Products" of RF Minzdravsocrazvitiya (FSBA SC AMP)	www.regmed.ru
Belarus	Republic's Unitary Enterprise "Center for Assessment and Trials in Healthcare" of RB MOH (RUE CATH)	www.rceth.by
Kazakhstan	National Center for Assessment of Medical Products, Medical Goods, and Medical Equipment of RK MOH	www.dari.kz

Based on public data

In general, the drug registration procedure may be viewed as quite transparent. The key legislative acts applicable in the countries under study are provided in **Table 2**. They contain the description of the registration phases in each of the countries.

Table 2. Key legislative acts applicable to drug registration in CCZ countries

Country	Key legislative acts
Russia	Federal Law "On Drug Circulation in the Russian Federation" No. 61-FZ dated 12.04.2010
Belarus	Law of Republic of Belarus "On Drugs" No. 161-Z dated 20.07.2006
Kazakhstan	Code of Republic of Kazakhstan "On People's Health and Healthcare System" dated 18.09.2009

Based on public data

However, the registration regulations are not limited to the above legislative acts. There are local orders, resolutions, and standards that also govern the registration procedure. Their lists are also available on the web-sites of the health ministries of the respective countries (**Table 1**). There are three main phases in drug registration:

1. Assessment of documents;

2. Assessment of the drug (quality, effectiveness, safety);

3. Making a decision on state registration.

The phases of the drug registration procedure in the CCZ countries are shown in Figs. 2, 3, and 4.

Fig. 2. RF drug registration chart

Source: Olga Zasypkina, Pharmexpert Analytics and Consulting, based on public data

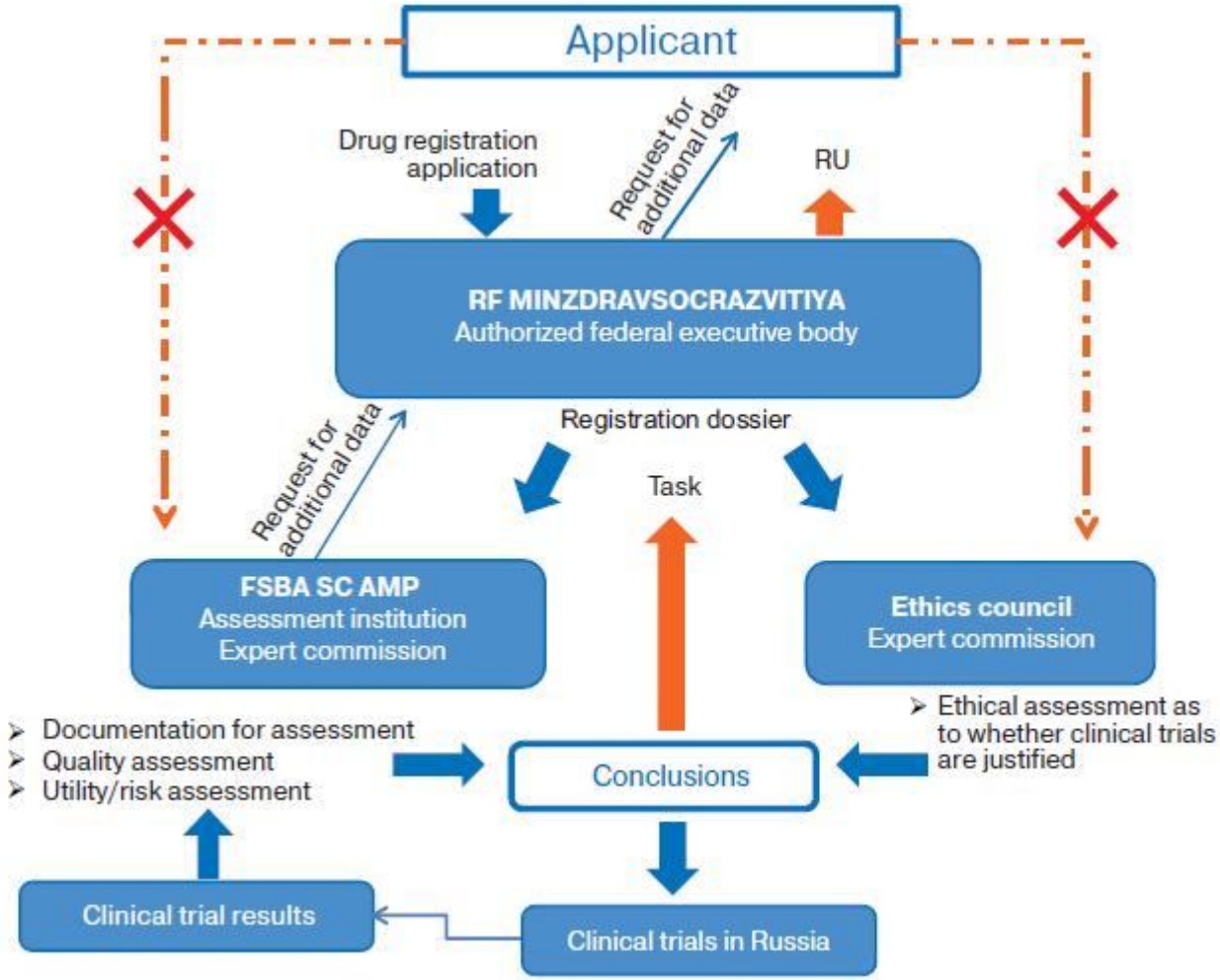


Fig. 3. Belarus drug registration chart

Source: Olga Zasypkina, Pharmexpert Analytics and Consulting, based on public data

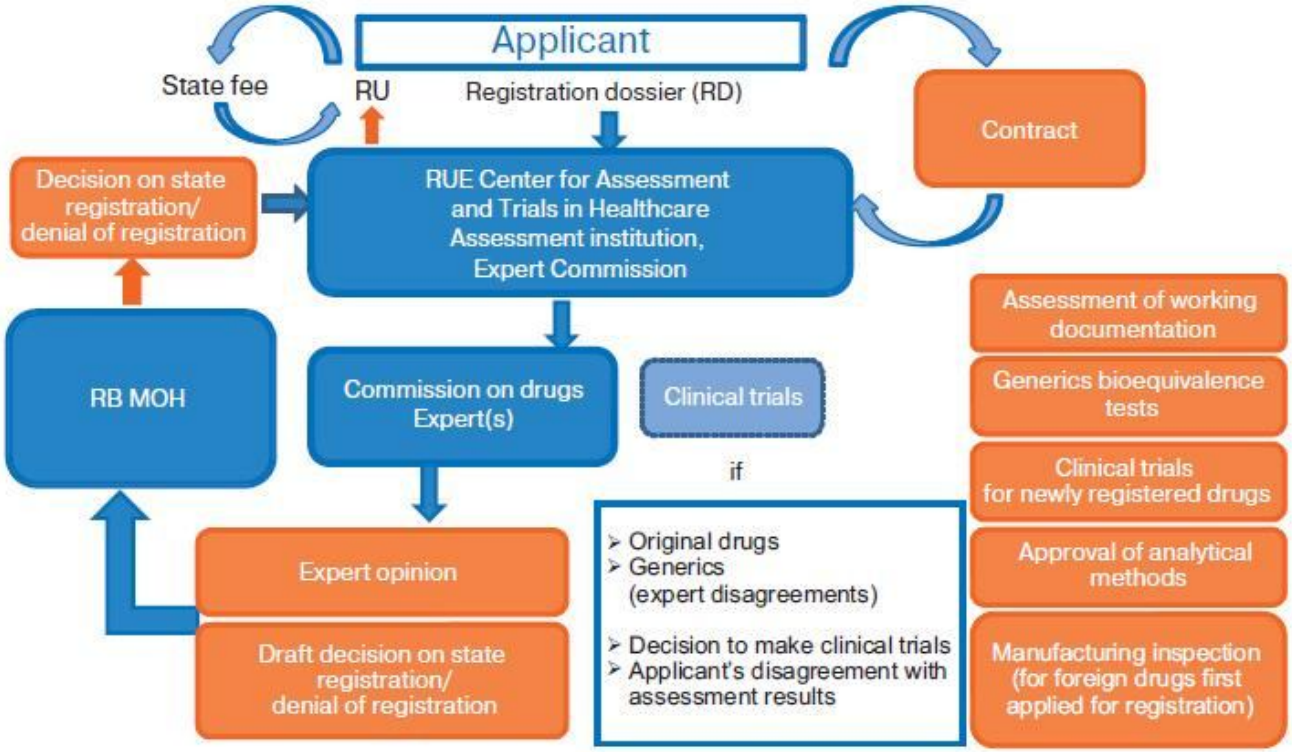
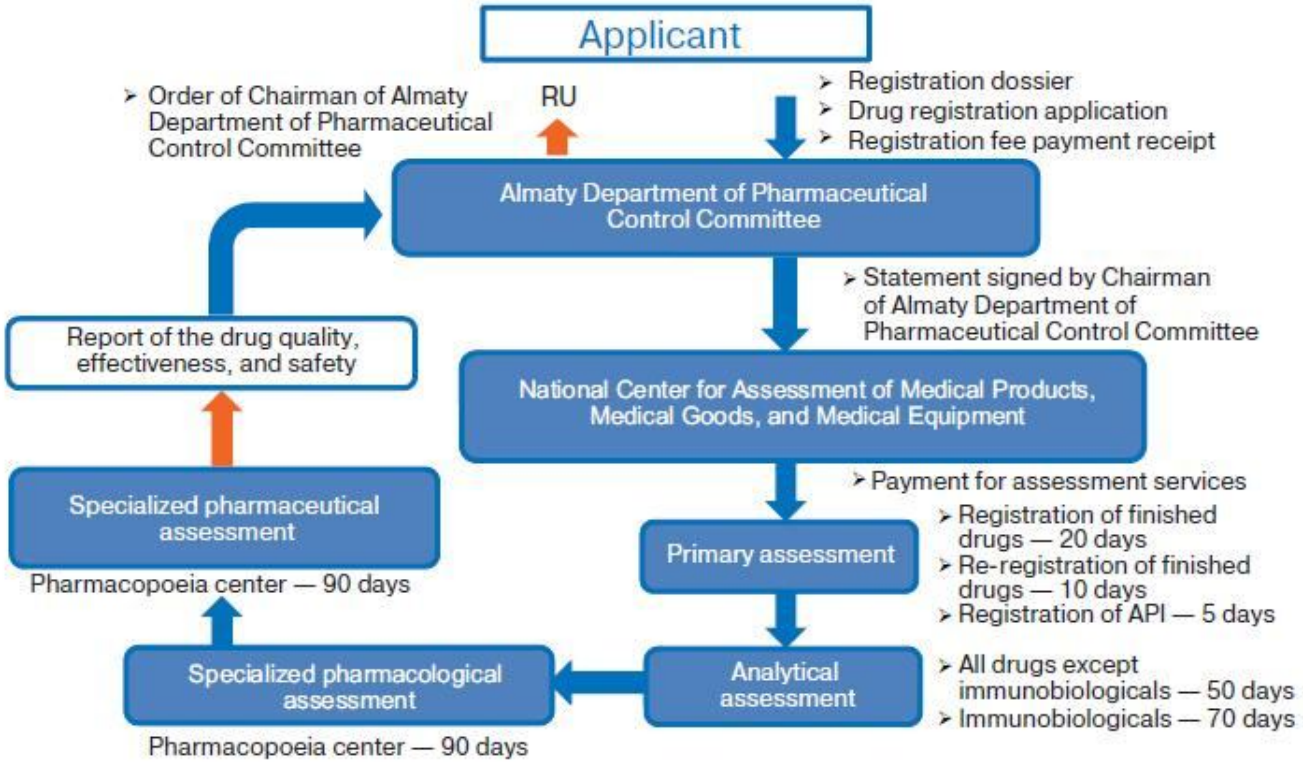


Fig. 4. Kazakhstan drug registration chart

Source: Olga Zasypkina, Pharmexpert Analytics and Consulting, based on public data



Drug quality standardization

The drug quality control is one of mandatory phases in their registration process. The corpus of regulations and other documents, which prescribe the quality of drugs in each of the countries under study, is the pharmacopoeia. In Russia, this is the State Pharmacopoeia [1], in Belarus — the National Pharmacopoeia of the Republic of Belarus (2007), and in Kazakhstan — the State Pharmacopoeia of the Republic of Kazakhstan (2007). These national formularies differ a lot. Although all of these three states are official observers in the European Pharmacopoeia Commission, it is the National Pharmacopoeia of Belarus that has achieved the maximum harmonization with the international requirements. Numerous international pharmacopoeias have been recognized in the territory of Kazakhstan. The wording of the State Pharmacopoeia of Kazakhstan has made it very close to the European Pharmacopoeia, but still there are significant differences which make it possible to characterize that pharmacopoeia as a national document. Russia proceeds from the concept of developing an original State Pharmacopoeia. Such differences determine whether the methods of the drug quality control are available to foreign manufacturers in these countries; therefore the issue of international harmonization of the pharmacopoeias remains open so far.

Registration timeframes

The timeframes for drug registration in each of the CCZ countries, as well as the cost of this procedure, are primarily dependent of the type of the drug and the assessment scope (Table 3).

Table 3. Timeframes for and specifics of drug registration procedures in CCZ countries

Country	Maximum allowable registration timeframes	Compact registration procedure
Russia	210 business days from the date of acceptance of the drug registration application	60 days from the date of acceptance of the drug registration application (second-entry drugs). Exceptions: Compact registration procedure cannot be used for the registration of biologics, insulin preparations, and the drugs which are newly registered for RF
Belarus	180 days	90 days (orphan drugs and herbal raw materials). The registration of local drugs may be completed within a shorter timeframe upon order of an authorized body, e.g. if the drug is put out to tender
Kazakhstan	227 days	137 days (drugs to prevent emergencies and used for the national security purposes; orphan drugs; authorized generics; APIs and bulk products; drugs made from the bulk product registered in Kazakhstan)

Source: Olga Zasypkina, Pharmexpert Analytics and Consulting, based on public data

In all countries under study the timeframes for registration do not include the time of clinical trials. Where the Expert Commission makes a decision on additional clinical trials, the timeframes for drug registration increase significantly.

Clinical trials

The decision on, and procedure of, clinical trials in the three countries under study are determined by the primary legislative act. By all means, clinical trials make the registration of drugs a longer and a much costlier process but, at the same time, their results are necessary to ensure and guarantee the drug quality, safety, and effectiveness. In accordance with the Federal Law "On Drug Circulation in the Russian Federation" No. 61-FZ, clinical trials in Russia must be made fully or partially in the Russian territory (for all drugs, except those whose circulation period exceeds 20 years and second-entry drugs with published clinical trial results). To make a clinical trial, an assessment of the documents is required for obtaining a permit, as well as ethical assessment.

In Belarus and Kazakhstan, the decisions on whether a clinical trial is necessary are made by expert commissions.

Summary: The drug registration procedures as well as their cost and timeframes differ significantly in the CCZ countries. It is, however, obvious that each country tends to support the national manufacturers (by streamlining the procedure, lowering the price or reducing the timeframes). The registration of generics in these countries, exactly as elsewhere in the world, is much simpler as compared to original drugs.

An intensive economic integration of the three nations will eventually bring the harmonization of requirements for the procedure and mutual interstate recognition of drugs in the territory of all CCZ countries. This will facilitate growth of the aggregate size of the three countries' pharma market and an intensive progress of the 'domestic pharma industry' of this alliance.

Drug registration in ex-USSR countries: common features and specifics

Expert, in 2001-2010 — Director of a Western pharma company for Central Asia and Transcaucasia; used to work in Uzbekistan and Kazakhstan as Head of representative offices of foreign pharma manufacturers.

Nearly 20 years have passed from the USSR disintegration, and it may be stated that all CIS nations are now living and working according to their own rules.

For a number of reasons (a civil war in Tajikistan, a most difficult economic situation in many countries), the national drug registration services did not emerge simultaneously in all ex-USSR countries. There is, nevertheless, certain similarity in their regulatory processes.

1. Format of dossiers submitted: CTD — preferable, NTA — acceptable.

2. Fortunately for Russian manufacturers, a Russian translation of the dossier is required in most countries (e.g. in Belarus and Central Asia countries). The Caucasus countries also except an English-language version of the dossier.

3. The registration of a drug in the manufacturing country is required (CPP). This rule complicates the life of export-oriented pharma manufacturers.

4. Texts on the secondary and primary drug package in the national language (alternatively, a bilingual text) are required in Ukraine and Kazakhstan. Most other countries accept the package with the text in Russian or in either of the internationally used languages, although English is preferable.

5. The directions for use in the national language inside the package are required (in basically each country). Some countries (e.g. Georgia, Armenia, and Azerbaijan) do understand the difficulties of the preparation of the leaflet in the national language and agree that the directions for use may be inserted later, in the drugstore chain.

6. In most countries, the legislation sets forth the maximum admissible timeframes for registration but the more attractive is the market for manufacturers, the longer and tougher is the registration.

The most dramatic difference is a simplified registration system (recognition procedure) adopted in Georgia for the pharmaceuticals manufactured in the European Union, the USA, and Japan. The situation that now prevails is paradoxical indeed: any legal entity may register any drug made in the above countries, in any packaging and in any language. This “innovation” has drastically reduced foreign manufacturer interest in the Georgian market. The neighboring Armenia plans to follow suit shortly, but, let’s hope, with lesser radicalism.

Considering the patent protection of drugs, it should be noted that for major manufacturers most countries with small pharma markets are not much interesting from the expansion standpoint, since such countries are full of cheap generics made in third countries.

There are odd situations, too: Azerbaijan, for example, had discontinued the acceptance of new dossiers for about a year, claiming that the reasons were just operational. Today, the situation has got back on track.

Hence, each country, even a small one, has its own specifics, and local agents or employees are therefore necessary to ensure the high-quality registration of drugs.

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[1] The 12th edition of the RF State Pharmacopoeia (Part 1) was published in 2008 and came into force in 2009. The 12th edition will consist of five parts.