Overview of Regulatory Requirements for Marketing Authorisations of Pharmaceutical Products in Countries of Eurasian Economic Union

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Dr. rer. nat. Valeria Ziemann

aus Minsk

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Betreuer und 1. Referent: Dr. Birka Lehmann

Dedication

To the memory of my dearest Mom -
Voronetskaya Ludmila Mixailovna

To my loved ones - husband and son, who bring a smile in my life

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1 List of abbreviations

CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CMC	Concerned Member State
CPP	Certificate of Pharmaceutical Product
CTA	Clinical Trial Application
CTD	Common Technical Document
DCP	Decentralized Procedure
EAEU	Eurasian Economic Union
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference on the Harmonization
MA	Marketing Authorization
OTC	Over the counter pharmaceutical product
PAES	Post Authorization Efficacy Studies
PASS	Post Authorization Safety Studies
Ph. Eur.	Pharmacopoeia Europe

PIL	Patient Information Leaflet
R&D	Research and Development
RMS	Reference Member State
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
USP	United States Pharmacopoeia

2 Establishment of the Eurasian Economic Union: main facts

The Eurasian Economic Union (EAEU) is an international organization for regional economic integration between several former republics of the Soviet Union. The Treaty establishing the Eurasian Economic Union was signed by the Heads of Belarus; Russia and Kazakhstan on May 29, 2014 in the capital of Kazakhstan Astana and came into effect on January 1, 2015. EAEU has international legal personality (1; 2).

The history of the Eurasian integration is over 20 years. The EAEU is a result of several integration projects among former soviet republics. President of the Republic of Kazakhstan N. Nazarbaev has firstly proposed the economic integration in 1994. Creation of the Custom Union and Common Economic Space forewent the establishment of the EAEU. The main steps of the integration process are presented and explained in more details in the table 1 below (based on (2)):

Date	Structure/Organization	Main Characteristics
1995	Custom Union between Belarus Russia and Kazakhstan	Limited form of integration. Establishment of a single custom territory with the common tax and tariffs for mutual trade of goods.
2012	Common Economic Space	Increased form of integration in comparison to the Custom Union. Coordinated policies for tax, fiscal, and custom. Cooperation between parliaments business and citizens in culture and foreign policy.
2015	Eurasian Economic	High level of integration.

	Union	Full economic integration expected to the 2025. Coordination and unification of policies for • energy • transport • industry • agriculture Free movements of • goods • services • capital • labor Cooperation in major infrastructure projects, creation of common markets.

Table 1 The main steps of the integration process of the EAEU

According to the Treaty on the Eurasian Economic Union, the goal of the EAEU is the establishment of a powerful association based on coordinated economic policies intended to rise the living standards of the population of the member states. To achieve the goal mentioned above the integration and expanding of domestic markets and creating proper conditions and new opportunities for business and investors are proposed as main strategies (4).

2.1 Member States of the Eurasian Economic Union

The EAEU is a large association in frame of global economy. Member States of the EAEU cover territory of 20 million km^2 with 182, 1 million populations (1).

The Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan and the Russian Federation are the member-States of the Eurasian Economic Union. Treaty including Republic of Kyrgyzstan to the EAEU was signed on December 23, 2014 and Kyrgyzstan become a full-member of EAEU on August 12, 2015.

Tajikistan is considering the membership in EAEU. Geographical map of the EAEU member states is presented on the figure 1 (cited from (5)).

Figure 1 Member states of the EAEU

The main information about the member states of the EAEU is summarized in the table 2 (based on (6)).

Country		Millions of habitants	GDP in 2014	Domestic pharmaceutical manufacturers
Armenia		3 million	USD 10.9 bn	18 local manufacturers 2 are GMP certified (7)
Belarus		9.5 million	USD 71.0 bn	30 local manufacturers 20 are GMP certified (8)
Kazakhstan		17.4million	USD 212.2bn	78 local manufacturers 2 are GMP certified (9)
Kyrgyzstan		5.9 million	USD 7.4 bn	40 local manufacturers No one is GMP certified No international companies with localized manufacturing(10)
Russia		143,7 million	USD 2,097.9 bn	350 local manufacturers Most of them are small and not GMP certified (11)

Table 2 Characteristics of the member states of the EAEU

Many countries demonstrating their interest for the cooperation with EAEU. Among them are China, India, Israel and Egypt (12).

Currently EAEU negotiates over the free trade zone agreements with several countries. Free trade agreement has been signed between EAEU and Vietnam in May 2015 (13).

2.2 Governance and Supranational Institutions

The administrative structure of the EAEU is presented by the following institutions (14):

Body/Institution	Function/ Structure/ Main Characteristics
Supreme Council	Supreme governing body. Comprised of the Heads of the EAEU member-states. Defines strategy, directions and perspectives of the EAEU. Adopts decisions binding for member states (this is different from the EU, where the European Council has no legislative power). The Supreme Eurasian Economic Council sessions are held at least once a year.
Intergovernmental Council	Heads of the Governments. Decided about strategically issues which remind without consensus after discussion in the Commission Council.
Eurasian Economic Commission	Supranational regulatory and executive body of the EAEU. Ensure functioning and development of the EAEU. Decisions are taken on collective basis and are obligatory for execution in the territory of member countries. EEC is formed by:

	Commission Council: prime-ministers of the member-states; Commission Board: 15 members (3 Members from each member country) and Chairman. The board takes decisions by vote. The organizational structure of Eurasian Economic Commission consists of 23 departments and 18 consultative committees
Court of the Eurasian Economic Union	Juristic body. Ensures implementation of the Treaty and other international agreements

Table 3 Administrative structure of the EAEU

It is underlined that EAEU is purely economic and not political or military union. For this reason creation of supranational authorities and parliament are not foreseen in the EAEU.

3 Creation of the common market for medicinal products in the EAEU

The pharmaceutical market of EAEU is one of the most fast-growing in the world. The cumulative growth on the medicinal products market in three member states of the EAEU: Belarus, Kazakhstan and Russia in 2011and 2012 made 15,6 and 7% respectively, and reached the level of 32,4 billion dollars (15).

The pharmaceutical market of EAEU is characterized by the following main features typical for the emerging markets:

Growth	vast and fast growing market (since 2003 Russian pharmaceutical market increased by 10-12% (16))
Structure	➢ dependence from importation of medicinal products: the share of imported pharmaceutical products (according to (17)) - 75% in Belarus - 88% in Kazakhstan - 82% in Russia ➢ orientation for generics and cheap OTC products
Legislation	➢ Heterogenic legislation and not harmonized regulatory requirements for pharmaceuticals products in the member states of the EAEU ➢ diverse, complicate and time-consuming procedures for marketing authorization in the member states ➢ different quality safety and efficacy standards in the member states
Pricing	➢ national price regulation systems ➢ low level of reimbursment which covers only small number of medicinal product
Domestic pharmaceutical industry	➢ small domestic pharmaceutical industry (share in GDP of each country makes no more than 0,5%) ➢ low investments in R&D, screening and pre-clinical research ➢ technological and infrastructural gaps in the domestic pharmaceutical industry ➢ deficiency of qualified personal and lack of experts

Table 4 Main characteristics of the EAEU pharmaceutical market

The first standards for Quality, Safety and Efficacy of pharmaceutical products in countries of EAEU were established during Soviet Union time based on Soviet Pharmacopeia and Gosstandard=State Standard with the purpose to safeguard public health.

After the collapse of the Soviet Union countries created their own national systems for regulation of medicinal products based on the both: the former Soviet Union standards and approaches accepted by the ICH countries. But due to the difficult economic situation and national specifics of development such as lack of financing, deficiency of qualified personal and experts, immature legislation and many other full harmonizations with the best global practice was not achieved.

The national regulatory requirements for marketing authorization of pharmaceuticals in the countries of the EAEU are significantly different from the EU/ICH requirements. Main of these specific regulatory requirements including, but not limited the following and presented below:

Legislation	➢ Immature and not harmonized legislation accompanied by frequent changes and amendments (as example usually several times per year in Russia) ➢ separation of responsibilities between several regulatory bodies ➢ lack of compliance with the best global practice and ICH requirements ➢ different understanding of product liability (manufacturer was legal responsible in most of countries before 2015) ➢ lack of detailed guidance and transparency of the MA procedure ➢ no or low implementation of GxP ➢ no or low implementation of pharmacovigilance ➢ not sufficient post-marketing control
Special requirements for	obligatory requirement to submit Certificate of Pharmaceutical Product: CPP establishes the status of medicinal product and

the documentation	of the applicant • format approved by the WHO • issued for single product only • valid for 2 years The content of CPP consists: • exporting country • importing country • name and dosage form of the product • registration status in the exporting country • marketing status in the exporting country • details on the applicant • information on inspection of the manufacturing site • attached SmPC ➢ Power of attorney, CPP, GMP Certificate, and Manufacturing License issued by the country which is member of the Hague Convention need to be apostilled; otherwise legalization from the national embassy is required ➢ CEP is not accepted ➢ MA in the country of origin/manufacturer is necessary
Quality standards	➢ National Pharmacopoeias are not harmonized between EAEU member states and with Ph.Eur. and USP ➢ Use of quality control instead of quality assurance: • laboratory expertise for the registration • laboratory control before import of each batch after MA (still valid in Belarus and Kazakhstan, recently deleted from Russian legislation) ➢ Requirements for the stability studies are not harmonized

	with the ICH: • extrapolation is not accepted • bracketing and matrixing are not accepted
Safety standards	➢ Lack of detailed requirements and guidance for non-clinical studies
Efficacy standards	➢ Requirement to conduct local clinical trials in Russia, Belarus and Republic of Kazakhstan
Dossier: content and format	➢ local specific document „Normative Document“ (local format of the dossier which is equal to the reduced Module 3 P of the CTD) Normative Document includes documentation on the finished product only: • analytical methods • specifications • shelf-life • PIL and labelling Normative Document should be approved and used for quality control of medicines and custom clearance before importation ➢ No eCTD submission
Variations to MA	➢ Most of variations are subject of approval

Table 5 Specific national regulatory requirements for marketing authorization of pharmaceutical products in countries of EAEU

In Armenia, Belarus, Kazakhstan, Kyrgyzstan and Russia, despite the common history and the common period in development of the pharmaceutical legislation, various requirements for the marketing authorization of medicinal products are established. Existence of different regulatory requirements and marketing

authorization procedures, lack of the mechanism of mutual recognition of registration certificates leads to the delayed market access of the new and effective medicine and high expenses of the pharmaceutical companies.

The current trends in the international relations and interdependence of the post-Soviet economies which were previously the parts of the common and centralized economic system demanded to search for further cooperation and integration of pharmaceutical markets. Formation of a common market of medicines and medical products was declared by one of priorities of the Eurasian Economic Union on a short-term outlook.

The six base principles establishing the common rules for the common market of pharmaceuticals are outlined in the Article 30 of the Treaty on the EAEU and cited below (2):

1) harmonization and unification of the legislation of the Member States in the sphere of circulation of medicines;

2) ensuring the uniformity of mandatory requirements for the quality, effectiveness and safety of circulation of medicines on the territory of the Union;

3) adoption of common rules in the sphere of circulation of medicines;

4) development and application of identical or comparable research and monitoring methods to assess the quality, effectiveness and safety of medicines;

5) harmonization of the legislation of the Member States in the field of control (supervision) over circulation of medicines;

6) exercising licensing and supervisory functions in the sphere of circulation of medicines by the relevant authorized authorities of the Member States

From January 1, 2016 the uniform market of drugs and medical products newly registered in the Eurasian Union was declared to start operating (2).

The common pharmaceutical market means that the medicines conforming to the standards of the appropriate pharmaceutical practice (GMP; GLP; GCP; GVP) and authorized in accordance with the uniform rules will freely move within the EAEU.

Harmonization of regulatory requirements for marketing authorization of medicinal products in member states was announced as the main objective for the EAEU in 2015.

It is supposed that member states of the EAEU will carry out registration of the medicines intended for the circulation on a common market of the union according to the uniform rules of registration and examination of medicines approved by the decision of Eurasian Economic Commission. Is also planned to accept uniform requirements for labelling of medicines and to instructions on use of medicines.

However, the work on creation of conditions for formation of a common pharmaceutical market does not cancel suddenly the existing national systems of registration of medicines: a long 10-year transition period until 2025 - when all countries have to comply with the uniform requirements and rules of the union, is established.

Creation of common pharmaceutical market is expected to provide optimum conditions for development of local pharmaceutical industry, increase of competitiveness of the drugs and investments in the pharmaceutical sector. These are the objects set by the leaders of the EAEU (18).

Establishment of the common pharmaceutical market is connected with a lot of legislation harmonization and its subsequent implementation by the member states of the EAEU.

3.1 Regulatory requirements for marketing authorization of medicinal products in the EAEU

The EAEU countries signed agreement defining the unified rules and standards for the circulation of pharmaceutical products (19).

In order to harmonies requirements for the common pharmaceutical market, Pharmacopeia and Expert Committees as well as registers and databases of pharmaceutical products authorized and rejected in the EAEU have to be established and maintained by the Eurasian Economic Commission.

The list of regulations necessary for implementation of the common market of pharmaceuticals was prepared and approved by the working group of Eurasian Economies Commission. The working group has been established from the representatives of the regulatory bodies of all member states, pharmaceutical industry, business communities, patient´s groups and research institutes (19). In 2015 based on the documentation developed by the working group, EAEU Commission Board completed more than 30 legislative acts aimed to implement unified regulatory requirements for the common pharmaceutical market (20).

In accordance with the draft document adopted (21) the main requirements for the marketing authorization of medicinal product are listed below:

Subject of registration	• medicinal products intended for the circulation on the common the market of the EAEU or in the territory of one union member state
Out of scope	• medicines made in drugstores • pharmaceutical substances • medicines intended for carrying out preclinical and clinical trials • medicines imported for personal application • radio pharmaceutical medicines made directly in the medical organizations

	• samples of medicines intended for registration purposes and standard samples • orphan medicines • preparations intended for treatment the heavy diseases for which clinical trials of the III phase are on-going in accordance with the special permissions
Dossier requirements	CTD • Electronic format • Module 1 in paper format
Scientific/Procedural advise	Questions, connected with • carrying out analytical tests • preclinical and clinical trials • procedure of registration • submission of samples and reference standards • other
Q, S, E standards	GxP
Laboratory control	Initiated by RMS during Module 3 assessment in cases if: • analytical method is not describe in any Pharmacopeia • there are considerable differences from a method or a technique described in a Pharmacopeia of the EAEU • insufficient validation data
Inspection of the manufacturing site	Initiated by RMS Based on the dossier submitted Performed • during the registration procedure (not more than 180 calendar days)

	• during the first three years after the registration of medicinal product <u>Decision to carry out inspection in following cases:</u> • lack of GMP Certificate • lack of registration of medicines produced on this manufacturing site in the member state of the Union (including registration of the medicinal preparations before coming into effect of the Agreement) • lack of registration in the country of origin of the medicinal preparation • identification of unreliable data during assessment procedure
Inspection of clinical trials	Initiated by RMS Based on the submitted dossier and the possible risks Performed • during the registration procedure (not more than 180 calendar days) • during the first three years after the registration of medicinal product Authority decides to carry out inspection in cases: • lack of information on approval of clinical trials by the independent ethical committee • inadequate process of receiving of the informed consent or inadequate information provided to participants of trials • complicate administrative structure of the clinical trials (participation more than three legal entities) • essential amendments to the protocol during clinical trial (change of primary end points, or statistical methods, introduction of the multiple amendments to the protocol • doubts concerning quality of the studied medicinal product and preparations of comparison including placebo • absence of data describing indicators of efficiency and (or) safety • exception of subjects of research from the statistical analysis without justification of the reasons • results contradictory with the data published in literature or results of other researches • identifications during dossier assessment unreliable facts and data and doubtful results (medic/biological contradictory between researches or between the research centers) • justification of the safety and efficacy and benefit/risk assessment of the medicinal product based on the results obtained in one clinical study only or on the small groups of subjects • if medicine is interfaced to the large-scale influence (for example, a vaccine intended for the children population)

	• new way of treatment (including the new therapies) • if the probability of emergence of ethical problems is high (participation in research of vulnerable groups of the population: children; persons with cognitive violations, patients, with diseases without alternative therapy, institutionalized patients; etc. according to requirements of the appropriate clinical practice of the Union) • insufficient experience of inspection by the national pharmaceutical inspectorates of member states of the EAEU clinical centers of the geographical region, from which results of clinical trials are presented • the sponsor was not inspected earlier by the authorities of EAEU or there are data on the non-compliance to GCP available from the authorized bodies of other countries
Inspection of the results of bioequivalence studies	Initiated by RMS in cases: • presented data of bioequivalence studies are too uniform /too non-uniform • amount of the passed /dropping-out values does not correspond to estimated values for this active substance or type of measurements • improbability/inconsistency of the presented clinical, statistical or analytical data • contradictory results between researches concerning pharmacokinetic parameters or inter individual/intra individual variability • results contradict the published and known data (for example, distribution and (or) characteristics of volunteers) • doubtful results (for example, improbable or results contradictory from the medico biological point of view between researches or between the research centers) • high probability of emergence of ethical problems (participation in research of vulnerable groups of the population: children; persons with cognitive violations; patients, with diseases without alternative therapy; the institutionalized patients; etc. according to requirements of the appropriate clinical practice of the Union) • there is an insufficient experience of inspection by the national pharmaceutical inspectorates of member states of the Union clinical centers of the geographical region from which results of clinical trials are presented • the sponsor was not inspected earlier by the authorities of EAEU or there are data on the non-compliance to GCP available from the authorities of other countries • this application for registration is the first request for registration of generic product in EAEU • there are other circumstances provided by rules carrying out pharmaceutical inspections of the EAEU

MA procedures	• Mutual recognition • Decentralized procedure • National procedure (until 2025)
Renewal	• Re-evaluation of the benefit/risk ratio • Application to be submitted to the RMS and all involved CMS 6 months before the MA expiry date in the RMS • Duration:120 days
Conditional MA	RMS may grant conditional MA and request that applicant • complete ongoing or conduct new PASS and/or PAES • include certain measures in risk-management plan to ensure safe use of medicine • submit information about all suspected undesirable reactions Requested conditions and timelines are specified in • Registration Certificate • EAEU database • SmPC and PIL. The holder of the registration certificate has the right to submit written explanations in response to the requested obligation. On the basis of the written explanations authority of the RMS has to remove or confirm the obligation. Conditional approval is granted for one year
Re-registration	Applicable to medicinal products registered in EAEU member states before coming in force of Agreement on Unified Rules for Registration of Pharmaceuticals Timeline: until 31.12.2025 Duration:100 calendar days

	Applicant submits: • Application form in electronic and paper format • Proof of payment • CTD Modules 1-3 in electronic format • Module 1 in paper format • CTD Modules 4 and 5 in form of reports without obligatory compliance with the requirements provided in the annexes to these rules

Table 6 Draft regulatory requirements for the marketing authorization of pharmaceutical products in the EAEU

In addition to the draft regulatory requirements for the marketing authorization of pharmaceutical products at the moment already prepared and adopted following regulations: good pharmacovigilance practice, good manufacturing practice (GMP), appropriate laboratory practice (GLP), appropriate clinical practice (GCP) and appropriate distributor practice.

The concept of harmonization of national pharmacopeias is developed and other normative documents regulating circulation of medicines in the conditions of the common pharmaceutical market of the Euroasien Union are finalized.

Transition period for the medicinal products registered before January 1, 2016, is established and contains 10 years, to this term all medicinal products in the EAEU countries need to be in compliance with the uniform requirements and rules established within the Union.

In accordance with the Article 100 of the Treaty (2) the common pharmaceutical market was expected to start operating from January 1, 2016. However, the real launch of the common pharmaceutical market will be possible after the approval of all necessary regulations by the Council of EAEU and their implementation by the member states of the EAEU.

3.2 Procedures for Marketing Authorizations in the EAEU

Examination and registration of the medicines in the countries of the EAEU assumes three types of marketing authorization procedures (21):

- the procedure of mutual recognition
- decentralized procedure
- national procedure (will be valid until 2025)

Mutual recognition and decentralized procedures for marketing authorization in the EAEU are significantly similar to the procedures in the EU. Centralized procedure is not foreseen in the EAEU.

Primary registration certificate within EAEU is planned to issue for a period of 5 years then in case if renewal procedure is successfully completed it becomes termless.

Procedures for marketing authorizations should be approved before common market of pharmaceutical products will start operating.

3.2.1 Mutual Recognition Procedure

Procedure of mutual recognition represents consecutive registration of pharmaceutical product in the EAEU countries with recognition of results of the expertize which is carried out by the RMS (one of EAEU member states which is chosen by the applicant) by all other countries of EAEU (21).

Procedure of mutual recognition of medicinal product will be carried out within 300 days.

The flow chart and separation of the responsibilities between RMS; CMS and applicant are presented in the figure.2.(in accordance with (21)).

3.2.2 Decentralized procedure

During the decentralized procedure it is anticipated that registration procedure will be carried out simultaneously by reference and concerned member states.

During the decentralized procedure the regulatory authorities at the same time carry out expertise within 105 days and the next 105 days are consider for the assessment and discussion of controversial issues with the applicant. This procedure should not exceed 210 calendar days, but can be carried out to shorter terms if consensus is reached.

The timetable for the decentralized procedure is presented below (in accordance with the (21).

Day 0	Start of the procedure
Day 105	Discussion between RMS and CMS. Issue of Request for Additional information/Documentation
Clock stop	Applicant has 90 days to answer deficiencies
Day 120	RMS provides preliminary Assessment Report, Normative Document, PIL and Labelling
Day 149	CMS send remarks and comments to the documentation provided by RMS
Day 150	Procedure may be finalized in case of consensus
Day 180	Start of national procedures to issue Registration Certificates
Day 210	Close of procedure

Table 7 Timetable for the decentralized procedure

3.2.3 National procedures

National procedure is kept for those applicants for the marketing authorization to whom the pharmaceutical market of one country is sufficient, and will be carried out until 2025 according to the national legislations of the member states of the EAEU.

The national specific requirements for the registration of medicinal products in the different EAEU member states are presented in more details on the following pages.

All sectors which regulation is not provided by the Agreement on the Uniform Principles and Rules of the Circulation of medicines within the Eurasian Economic Union (20) will still be regulated by the national legislation of the states. For example, obtaining licenses for manufacturing of medicines, activity of drugstores, advertising of medicines, formation of lists and price control for drugs from the List of vital and essential medicines will continue to be regulated by the national pharmaceutical legislations of the member states.

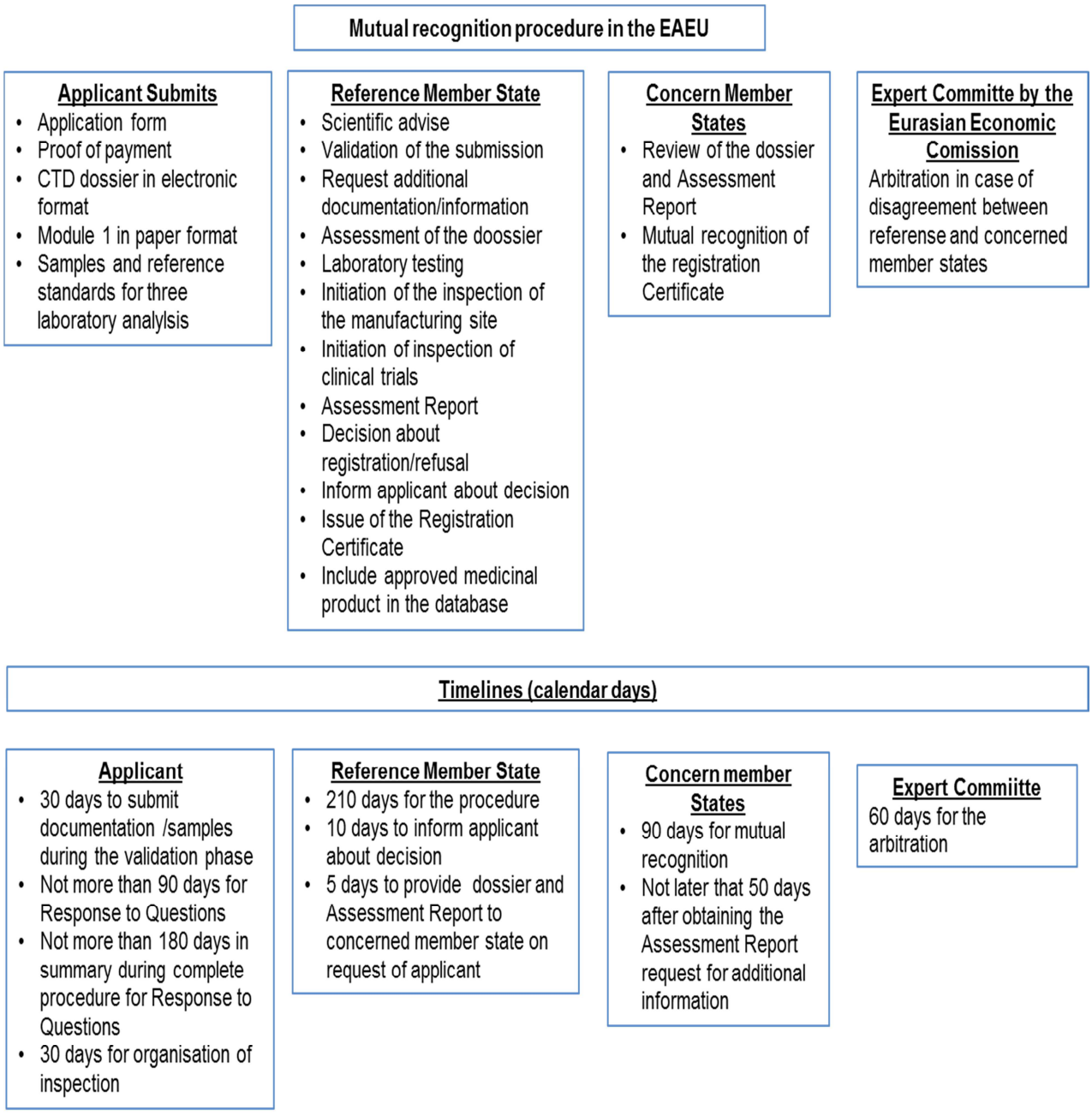

Figure 2 Mutual recognition procedure in the EAEU

3.3 Challenges of the creation of the common market of pharmaceuticals

Establishment of the common market of pharmaceuticals is very ambitious project. The agreement on the common pharmaceutical market came into force from January 1, 2016 therefore 2015 was effectively used for the preparation of harmonized requirements for the registration of medicinal products.

Leaders of EAEU postulated expanding of domestic pharmaceutical market and making it more transparent and more attractive for business community and investors as the main intentions of this project (18). This is very challenging task and is expected to have mixed effect considering the following observations:

- member states of EAEU have similar but still very different legislation, resources and experience in the area of pharmaceutical registration and regulation. The process of harmonization of regulatory requirements for the marketing authorization is expected to be time-consuming and will require considerable resources and trained stuff. To achieve a harmonization of regulatory requirements a lot of scientific guidelines and detailed instructions should be developed, approved and implemented. Thus harmonization of requirements for the clinical trials, stability studies and microbiological purity of the finished products are differs a lot and have to be agreed between member-states of EAEU.

- the legislative base of the common market of EAEU is expected to take the advantage of the most successful and advanced model of the EU, but nevertheless will be significant different due to huge dependence from the national environment and resources available. For example, creation of the centralized authority responsible for the marketing authorization similar to EMA is not foreseen in the EAEU. This is justified by the following reasons: first of all no supranational authorities will be created in the EAEU, secondly the main focus of the EAEU member states is and will be concentrated on

the assessment of local and imported generic drugs, while EMA is responsible for the assessment of the innovative products with high risks.

To overcome these and other challenges during the establishment of the common pharmaceutical market a lot of strategically planning and resources will be required from all parties involved: regulators, pharmaceutical industry and business.

4 National Requirements for Marketing Authorization

4.1 Specific of Russia

4.1.1 Legislative Base and Regulatory Framework for the Marketing Authorization of Medicinal Products in Russia

The most important legislative acts regulating and relevant for the circulation of pharmaceutical products in Russian Federation are available in Russian language at (22) and included in the table 8.

Law	Sphere of regulation
Federal Law No. 61	Legal basis of the pharmaceutical market
Federal Law No. 480	Fees to be paid for CTA and MA procedures
Federal Law No. 38	Advertising of medicinal products
Federal Law No. 99	Licensing of manufacturing of medicinal products, wholesale and retail sale
Federal Law No. 184	Declaration of conformity of medicinal products to national quality standards

Table 8 The most important legal acts regulating pharmaceutical market in Russian Federation

National regulatory framework for medicinal products in Russian Federation is complicated and consists of several authorities which main responsibilities in the area of pharmaceutical regulation are presented in the table 9 below:

Regulatory body/ Website	**Responsibilities** (including but not limited)
Ministry of Healthcare (Minzdrav) federal executive body (23) http://www.rosminzdrav.ru/	creating and implementing government policy and regulations in the area of healthcare register pharmaceutical products for human use publish State Pharmacopeia issue authorizations to perform clinical trials issue of Special Permissions for importation of • not-registered pharmaceutical products intended for the clinical trials • samples and standards for the MA procedure • non-registered drugs intended to care patient in extremely severe conditions

Scientific Center for Evaluation of Medicinal Products Federal State Budgetary Institution of the Ministry of Healthcare (24) www.regmed.ru	Evaluation of the • drug quality • analytical methods • submitted samples and standards • expected benefit/risk ratio during MA and CTA procedures, renewal of MA and submitted variations to the MA
Federal Service for Surveillance in Healthcare (Roszdravnadzor) subordinate to the Ministry of Healthcare (25) http://www.roszdravnadzor.ru	Issue licenses for the pharmaceutical activities and maintain their register state control of • pharmaceutical market by the inspections on compliance with the GxP • quality and safety of medicinal products circulated on the market • prices of the life-essential drugs
Ministry of Industry and Trade (Minpromtorg) federal executive body (26) http://www.minpromtorg.gov.ru	issue licenses for the manufacture of medicine maintenance of a register of licenses granted declaration of conformity and certification of medicinal preparations

Table 9 Regulatory bodies involved in the regulation of pharmaceuticals in Russia

Before starting the process of CTA or MA, applicant should arrange payments for the evaluation of quality safety and efficacy of pharmaceutical product in accordance with the Federal Law No 480 approved in December 29, 2014. The fees are different and depend from the type of expertise performed by regulatory authorities (22).

Expertise	**Fee, rubles**
To obtain permission to conduct clinical trials	110 000
To obtain orphan status for the medicinal product	25 000
To obtain permission to conduct multicenter clinical trials	210 000
To obtain permission to conduct post-authorization clinical trials	60 000
Benefit/risk evaluation of the new medicine	325 000
Benefit/risk evaluation of the medicine registered for more than 20 years	45 000
Renewal	145 000

Table 10 Administrative fees applicable for the CTA and MA procedures in Russian Federation

For the on-line submission of the dossier and application for marketing authorization of pharmaceutical product, applicant is required to be registered and receive a password for the state website http://grls.rosminzdrav.ru. Implementation of the on-line communication system with the authority during the marketing authorization process introduced more transparency in the MA process and established the possibility of the time-line tracking of the MA procedure and for these reasons was highly appreciated by applicants.

National regulatory requirements and registration procedure for pharmaceuticals have been significantly optimized and harmonized with the best global practice in

accordance with the amendments to the Federal Law No 61 „On Medicines Circulation“ approved by the Russian parliament by the end of 2014. The main significant requirements are outlined in the following table (based on the Federal Law No429 and (27)):

Subject for registration	• Medicinal products intended to be put on the Russian market for the first time • Medicinal products early authorized but manufactured in different dosage form • New combinations of medicinal products
Registration is not required	• Medicinal products imported on the patient name base • Pharmaceutical substances and finished products intended for export
Timelines	• MA procedure for original preparation: 160 business days • Accelerated MA procedure: 80 business days
Accelerated procedure	• <u>Applicable for:</u> - Orphan drugs - First three generic drugs - Preparations intended for use exclusively in pediatric population • <u>Excluded for:</u> - Biosimilars - New combinations of early registered - New dosage forms of early registered
Data exclusivity period	• 6 years for the protection of clinical results for the original product. • Possibility to submit for Marketing Authorization procedure: • after 4 years from the date of registration of original product for generic medicine

	• after 3 years from the date of registration in Russia of original biological product for bio similar products
Dossier	CTD format from July 2015
Clinical trials	• Local clinical trials are necessary for MA • CTA procedure is separated from MA procedure • From clinical trials are excluded orphan drugs and medicinal products intended for use only in pediatric populations.
Renewal	• Initially registration certificate is issued for 5 years. • After confirmation of registration it is unlimited. • Procedure for renewal 60 business days.
State registration of prices for life essential medicines	• List of essential medicinal products: - proposed by the MoH - approved by the government - adjusted on an annual basis • Price registration system - state registration in the federal database of the manufacturer´s maximal price - regional regulation of wholesale and retail price

Table 11 Summary of regulatory requirements for the marketing authorization of pharmaceuticals in Russian Federation

The updated requirements for the marketing authorization ensure more comfortable and transparent registration procedure than before. Nevertheless, the requirements for MA imply conduction of local clinical trials and inspection of the finished product manufacturing site.

4.1.2 Amendments to the Federal Law „On Medicines Circulation“

Recent years are characterized by intensive legislative changes in the area of pharmaceutical regulation in Russian Federation. The reform of the regulatory sector includes several amendments of the Federal Law No 61 „On medicines circulation“ introduced in 2010, 2011 and 2014. The Federal Law No. 429 approved on December 22, 2014 implemented the most significant amendments to the current pharmaceutical legislation in Russia with the purposes to

- harmonies national requirements with the best global standards and practice
- update, optimize and harmonies terminology
- implement important missing definitions
- improve and facilitate registration process
- separate CTA from marketing authorization procedure in compliance with the world practice

The most important and significant changes to the national pharmaceutical legislation approved with the amendments to the law „On medicines circulation“ among other includes the major following implementations:

- definition of the MAH – legal entity responsible for the quality, safety and efficacy of the pharmaceutical product
- definitions for orphan, biological, immunological, biotech, gene-therapeutic, homeopathic and biosimilar drugs
- GxP and Pharmacovigilance system
- procedure for scientific advice in form of written reply of MoH on the fee-basis
- procedure for definition of interchangeable drugs

4.1.3 Strategy Program „Pharma 2020“

Recent changes and amendments in pharmaceutical legislation of Russian Federation are results of the adaptation of the development strategy of pharmaceutical industry for the period until 2020 „Pharma 2020“ and based on the Order of the Government of the Russian Federation No. VZ-P12-1366 of March 6,

2008 and the protocol of meeting with the Russian Prime Minister of June 19, 2008 No. VP-P12-8pr (28).

The general trend of this import-replacement program is to ensure that 90% of the medicinal products included in the list of essential drugs should be produced domestically by 2020.The summary of the „Pharma 2020“ program is translated and presented below (in accordance with (28):

Goal	Change to innovative model of development of pharmaceutical industry of the Russian Federation.
Tasks	Increase of competitiveness of domestic pharmaceutical industry by harmonization of the national standards with the best international practice. Domestic development and manufacturing of innovative medicinal products and support of export of the domestic pharmaceuticals Additional funding mechanisms for research and development of pharmaceuticals Technological modernization of the pharmaceutical branch. Elimination of administrative barriers for registration of domestic drugs and ensuring appropriate control of their quality. Creation of new programs of professional training of specialists for

	pharmaceutical industry according to the international standards.
Main actions	Localization in the territory of the Russian Federation of hi-tech productions of medicinal products, chemical and biological substances Obligatory transition of the local manufacturers to the GMP standards.
Expected results	Ensuring medicinal safety of the Russian Federation according to the list of vital and life-essential medicines Increase in a share of production of a domestic production to 50% in value terms by 2020. Increase in export of pharmaceutical production by 8 times in comparison with 2008. Production of pharmaceutical substances in the territory of the Russian Federation in a size necessary for ensuring release of 50% of ready dosage forms in terms of money, including not less than 85% according to the list of strategic products

Table 12 Summary of Pharma 2020 program

In frame of the implementation of the „Pharma 2020“ program, the government of the Russian Federation encourage international pharmaceutical companies to localize manufacturing sites on the territory of Russia and supports domestic manufacturing by providing preferences. The resolution of the government of the Russian Federation adopted on November 30, 2015 restricts the participation of foreign manufacturers of medicinal products in the state purchase of the life-essential pharmaceutical products. In case of two local manufacturers from EAEU member states have applied for the participation in the tender, foreign manufacturer is not allowed to participate in the auction. Transitional period is granted for the

international pharmaceutical companies with partial localization of the manufacturing process (primary/secondary packaging) in EAEU: such foreign manufacturers are allowed to participate in the state tenders until December 31,2016. This restriction is intended to stimulate the foreign manufacturers to localize the full cycle of pharmaceutical manufacturing on the territory of the EAEU.

In the view of the current situation it could be postulated that realization of the of strategy of development of pharmaceutical industry in Russian Federation may be significantly affected by the geopolitics situation and sanctions.

4.2 National requirements for Marketing Authorization in Republic of Belarus

There are the legal provisions establishing requirements for the regulation of medicinal products and the power and responsibilities of the regulatory authorities in Republic of Belarus T

he major legislative acts regulating medicinal products are provided below and available in Russian and partially in English languages at (29):

Law of Republic of Belarus „ On medicines“ No.161-3 from July 20, 2006	General provisions of the regulation of medicinal products
Resolution of the Council of Ministers of the Republic of Belarus No. 1269, dated September 2, 2008	List of documents for new applications, renewals and variations; terms and responsibility
Resolution of the Council of Ministers of the Republic of Belarus No. 52 dated May 8, 2009	Scheme of registration process and forms for SPC, PIL, Artworks, application form

Table 13 The main legislative acts relevant for marketing authorization of medicinal products in Republic of Belarus

Two regulatory bodies involved in the procedure of registration of medicinal product in the Republic of Belarus are: Ministry of Health and Center for Examinations and Tests in Health Service Republican Unitary Enterprise.

Ministry of Health of Republic of Belarus realizes a state policy in health care and responsible for (in accordance with (30))

- state registration of medicines
- licensing of pharmaceutical activity
- monitoring systems of quality of medicines
- systems of a pharmacovigilance
- supervision of conditions of industrial production, pharmaceutical production, realization
- storages, transportation and medical application in the organizations of health care
- implementation of other functions provided by the legislation of Republic of Belarus.

The main responsibilities of the Center for Examinations and Tests in Health Service Republican Unitary Enterprise include but not limited to the following (cited from (29)):

- prepare and carry out expert examination of documentation included to the registration/re-registration dossier
- issuing permits for import of registered and unregistered medicinal products and/or pharmaceutical substances with restricted movement across the customs border of the Republic of Belarus for state registration (re-registration)
- making proposal for the amendments to the registration dossier for conducting pre-clinical studies and clinical trials
- services of arranging expert examination of documentation for clinical (bioequivalence) trials of medicinal products, clinical trials of medical devices and medical equipment

- reception, registration, and assessment of diagnosed adverse reactions to medicinal products
- quality control of medicinal products
- consulting services
- other activities in accordance with the legislation of the Republic of Belarus.

Main specific national requirements for the marketing authorization of pharmaceutical product in Republic of Belarus are listed below:

- Inspection of the foreign manufacturing site before/during MA procedure
- CPP, GMP Certificate, and Manufacturing License need to be apostilled
- Applicat must submit maximum sale price comparable with the price in the country of origin and EAEU countries. Price will be included in the registration certificate
- Decision to conduct local clinical trials is made by the Committee of the Ministry of Health
- Dossier and packaging materials need to be submitted in Russian or Belarussian languages
- Dossier should be submitted in the format of Normative Document

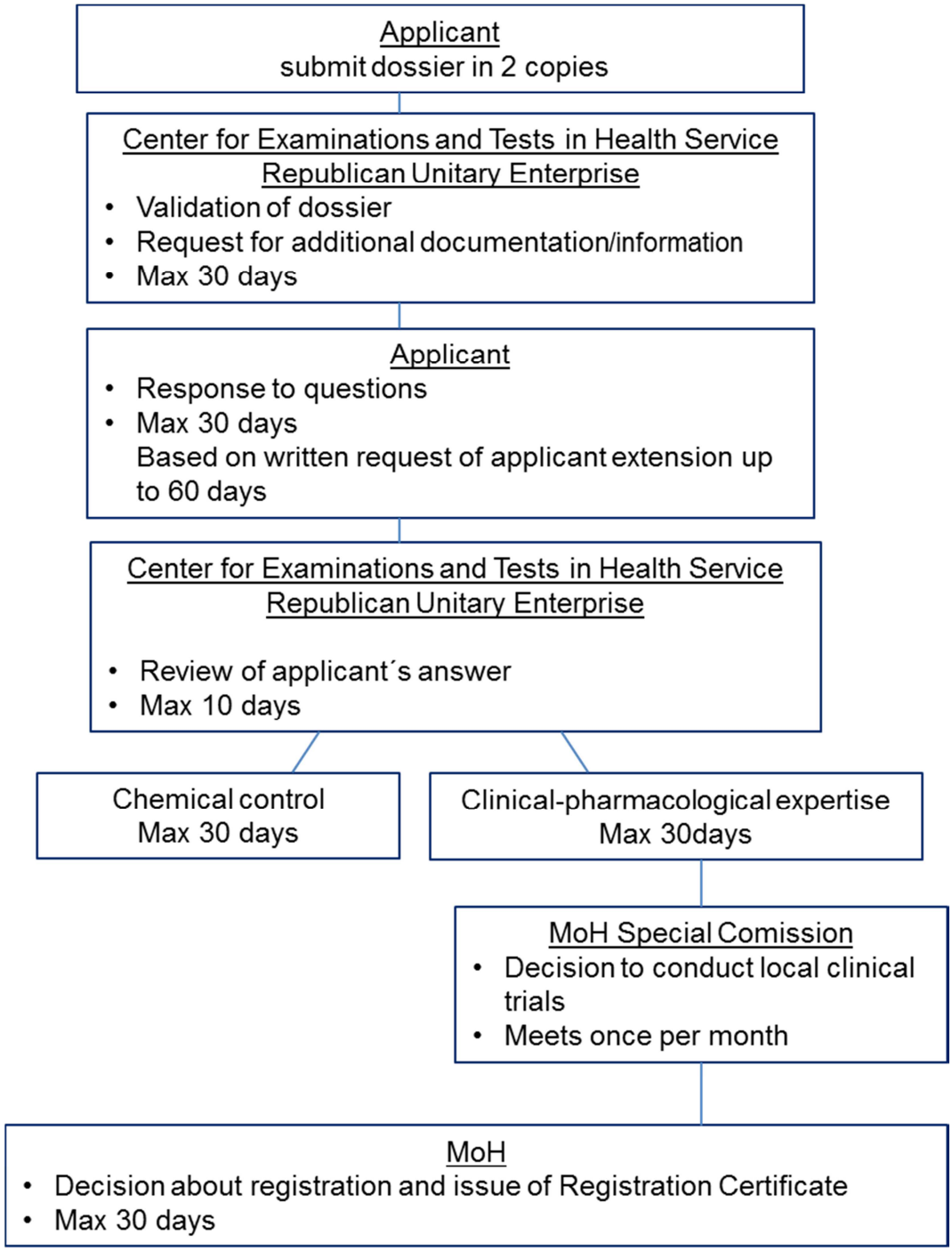

Figure 3 Procedure of Marketing Authorization in Republic of Belarus

4.3 Requirements for the Marketing Authorization in Armenia

The basis of Armenian regulatory system for medicinal products is established by several laws, decrees and orders. Most important of them are listed below and available at (31).

- The law „On medicines“; adopted on the National Assembly on October 27, 1998;

- Decree of the Government of the Republic of Armenia No 347 of 25 April, 2001 “On adopting the Rule of Registration of Medicinal products and Expertise Fees for Registration of Medicinal products in the Republic of Armenia”

- The Order No 123-N of the Ministry of Health of the Republic of Armenia dated 7 February, 2006 on approval of the Procedure of Expertise for Registration of Medicinal products in the Republic of Armenia, Form and Description of the Registration Certificate and the List of variations of medicinal products registered in the Republic of Armenia that do not require new registration.’’

Regulatory activities of pharmaceuticals are controlled by the Ministry of Health of the Republic of Armenia. The Scientific Centre of Drug and Medical Technology Expertise are responsible for the implementation of the national policy in healthcare and regulation of pharmaceuticals and conducting the expertise of medicinal products submitted for the state registration. (32).

Regulatory requirements for marketing authorization of medicinal products in Republic of Armenia are very comfortable for applicants.

Several pharmacopoeia standards are accepted in Armenia: Russian State Pharmacopoeia, the European Pharmacopoeia (Ph Eur), the International Pharmacopoeia (Ph Int), the American Pharmacopoeia (USP), the British Pharmacopoeia (BP), the German Pharmacopoeia (DAP), the German Homeopathic Pharmacopoeia (HAB), the French Pharmacopoeia (PhF).

Applicant has to submit simultaneously dossier, samples and reference standards for the registration of medicinal product.

Quality control is part of the registration procedure. In case of non-compliance applicant may resubmit new samples from the two different charges for the two additional testing analysis.

Dossier and samples may be submitted in Armenian, Russian or English languages.

Medicinal products which are registered at least in one of the ICH country undergoes simplified registration procedure without laboratory testing and clinical trials. Documentation to be submitted for the registration of such pharmaceutical product includes:

- CPP
- SmPC in English or Armenian language
- composition of the finished product
- analytical methods
- specifications
- shelf-life
- labelling and PIL in English or Armenian language.

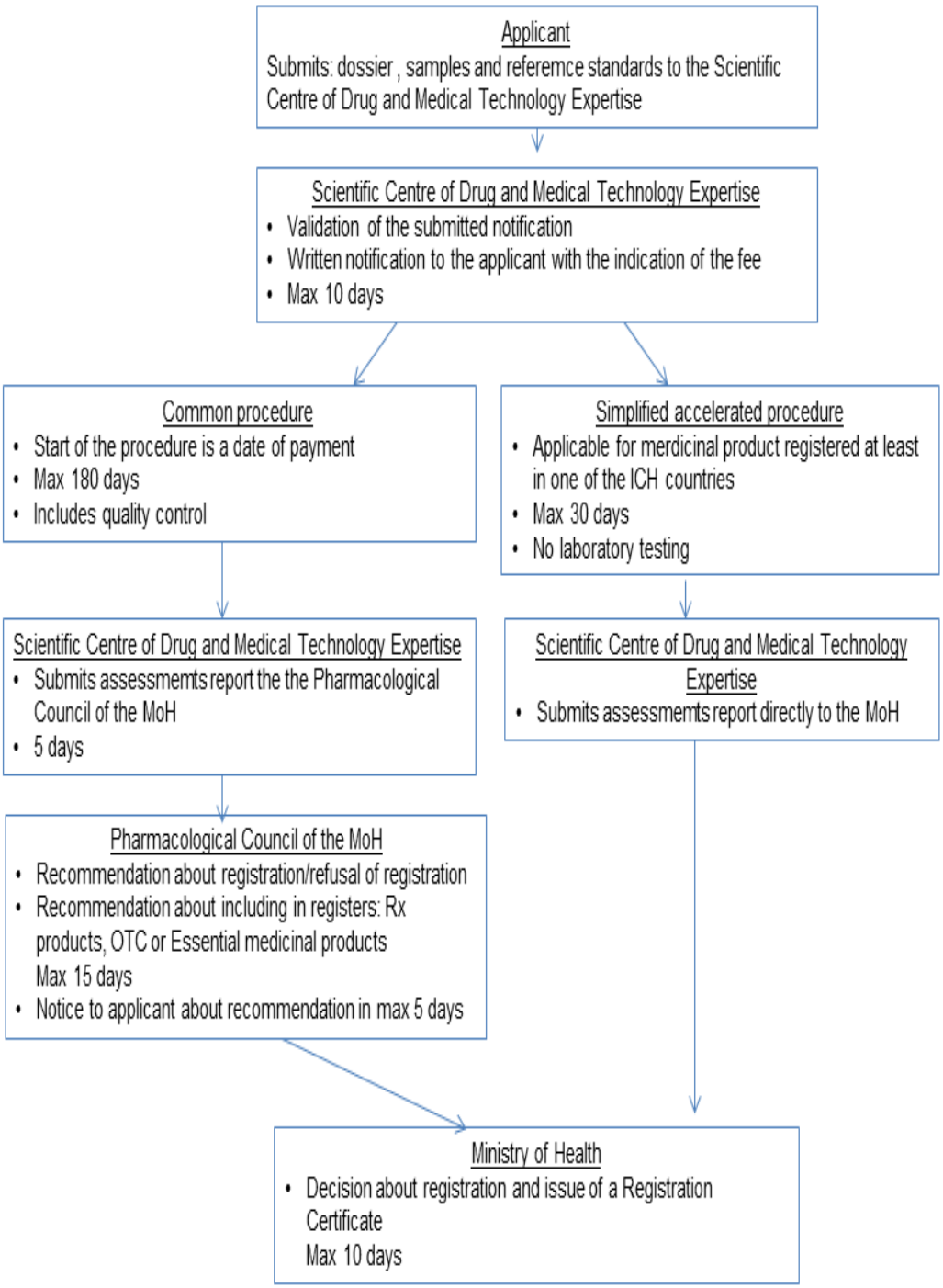

Figure 4 National procedure and timelines for Marketing Authorization of medicinal products in Republic of Armenia

4.4 Registration in Kazakhstan

Order of Ministry of Health № 735 from November18, 2009 “On approval of rules on state registration, re-registration and variations to the registration dossier of medicine, medical purpose products and medical equipment.”, amended on February 15, 2012 № 84 MOH is the legislative base for the marketing authorization of the medicinal products in the Republic of Kazakhstan (33).

Marketing authorization of medicinal products, rejection and withdrawal of registration is carried out by the Ministry of Health of the Republic of Kazakhstan (34).

Decision to register medicinal products is based on the results of the scientifically justified criteria and expertise of quality, safety and efficacy of medicinal products. Expertise of medicinal products for registration is carried out by the National Center for Assessment of Medical Products, Medical Goods, and Medical Equipment of Republic of Kazakhstan. The Center was established in 2002 and responsible for the following activities (cited from (35)):

- Conducting the evaluation of medicines, medical devices and equipment upon state registration
- Certification of medicines
- Development of the State Pharmacopeia
- Conducting the preclinical trials and bioequivalence studies of medicines
- Participation in the pharmacovigilance and monitoring of adverse drug reactions
- Participation in the development of legislation
- Conducting the expertise of advertisement/promotional materials on medicines
- Support and maintenance of the Medicine’s State register database
- Publishing the informational-analytical journal “Kazakhstan Pharmacy”
- Maintenance of the departmental dossier archives

Subject of registration in Kazakhstan are (in accordance with (35)):

- medicines, that are produced in the Republic of Kazakhstan
- imported medicinal products registered in the country of origin,
- bulk drug products imported into the Republic of Kazakhstan;
- new combinations of previously registered in the Republic of Kazakhstan drugs
- medicines previously registered in the Republic of Kazakhstan, but transferred to other manufacturer
- new dosage forms
- new type of packaging materials

There are five main stages in the marketing authorization procedure (35):

1. initial evaluation of the dossier
2. analytical expertise and chemical control
3. pharmaceutical expertise
4. pharmacological expertise
5. conclusions about the quality, safety and efficacy and issue of registration certificate /rejection of registration

Each subsequent step of the registration procedure is based on the positive conclusion of the previous step of evaluation.

The flow chart of the national registration procedure is presented on the figure 5 on the following page.

Specific national requirements of the marketing authorization procedure in the Republic of Kazakhstan

- The dossier should be submitted in the CTD format (from May 16,2011)
- Samples and reference standards should be submitted with the dossier simultaneously
- Requirement of the compliance with the national Pharmacopoeia which is significantly harmonized with the Eur Ph
- Packaging materials may be prepared in national or bilingual RUS/KZ languages

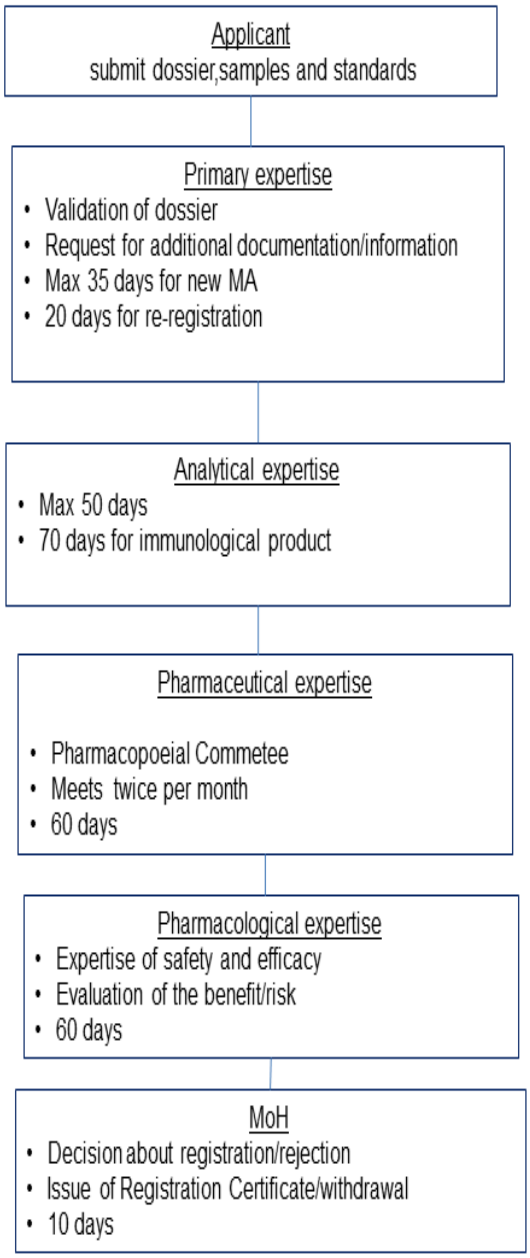

Figure 5 Marketing Authorization procedure in Republic of Kazakhstan

4.5 Marketing Authorization of pharmaceutical products in Kyrgyz Republic

Legal basis for the marketing authorization of pharmaceutical products in Kyrgyz Republic is provided by the law “On medicines” dated 30 April, 2003 and Resolution “On the safety of drugs for medical use” from April 6, 2011(36).

Authority responsible for the registration of medicinal products is Ministry of Health, Department of Drug Supply and Medical Technology (37).

Public information concerning regulatory requirements for the registration of pharmaceutical product which is provided on the official site of the Ministry of Health of the Kyrgyz Republic is very limited.

Documentation to be submitted for the registration of medicinal product (37):

- application form (2 copies)
- dossier (2 copies in paper format and electronic format)
- samples and standards for the three-fold analysis

Registration fees (in accordance with (37)):
foreign medicines: $1500

- every additional dosage, pharmaceutical form, packaging size:$500

preparations of domestic manufacturers: $500

- every additional dosage, pharmaceutical form, packaging size:$50

Duration of the procedure: 6 months.

Registration certificate is valid for 5 years.

5 Summary and Conclusions

Regulatory frameworks for the medicinal products in the member states of the EAEU are connected not only geographically but also by the common starting point and history of the Soviet Union, comparable development after independence finding, by

mentality of population and similar educational system. Significant similarities exist in the regulatory requirements for marketing authorizations in EAEU countries, however, due to different industrial development and economic situation establishment of national systems of pharmaceutical registration in these countries is characterized also by significant differences. For this reason national marketing authorization procedures were not harmonized in EAEU countries and there was no recognition of Registration Certificates for pharmaceutical products between countries before 2016.

The most significant national specific regulatory requirements for the obtaining marketing authorization for medicinal products in the EAEU countries are summarized in the following table 14:

Requirements	Armenia	Belarus	Kazakhstan	Kyrgyzstan	Russia
Alignments with the ICH requirements	No	No	No	No	No
Dossier format	CTD accepted Normative documentation accepted	Normative documentation	CTD from 2011, but Russian Normative documentation also accepted	CTD, but Russian Normative documentation also accepted	CTD from July 2015
Laboratory expertise during MA Procedure	Yes, but not needed for drugs originated from ICH countries	Yes	Yes	Yes	Yes
Pharmacopoei	Ph. Eur.;	Belarusian	Kazakh	Ph. Eur.;	Russian

a standard	USP; Russian Pharmacopeia	Pharmacopeia significa-ntly harmonised with the Ph. Eur.; Russian pharmacopeia is also accepted	national Pharmacopeia significantly harmonised with the Ph. Eur.	USP; Russian Pharmacopeia	State Pharmacopeia (not harmoni-sed with Ph.Eur.)
Local clinical trials	No	Yes, based on the Commission decision	Yes, based on the Commission decision	No	Yes
Timelines of MA procedure	220 days	180 days	225 days	180 days	160 days
Preferences for local manufacturers	Yes	Yes	Yes	Yes	Yes

Table 14 Comparison of the national requirements for marketing authorisations of pharmaceutical products in EAEU countries

Although the launch of the common pharmaceutical market in the EAEU was scheduled for January 1, 2016, the major process of regulatory harmonization is still far away from to be finalised. This harmonisation process and especially implementation of the adopted requirements are very challenging. The effectiveness of the harmonisation of the regulatory requirements for the marketing authorisation will be determined by the effectiveness of the requlatoty network between national health authorities of the member states, their ability to harmonise national legislation and their ability to implement decisions of Eurasian Economic Comission. An

effective and transparent regulatory network creation is of particular importance. Strong cooperation and interaction between authorities, clear decision making mechanism and implementation of the detailed guidelines and SOPs will have significant effect on the harmonisation process. Expected benefits from the harmonisation of the regulatory requirements will be among all stakeholdersand including reduction of the administrative barriers and unreasonable restrictions, cost effective use of resources, promotion of GxP, facilitation of cooperation between authorities, faster access to the quality safe and effective medicines. Development of a common pharmaceutical market and its regulatory system in the EAEU gives rise to many challenges among which the following factors are the most significant:

- discrepancy in regulatory requirements and possibilities of local pharmaceutical industry
- deficiency of qualified personnel
- general economic and global geopolitical situation (sanctions against Russia)

Nevertheless according to expert forecasts common pharmaceutical market in the EAEU is attractive and will represents a lot of opportunities (38).

The process of the harmonization of regulatory requirements is not expected to be finished overnight. Pharmaceutical companies wishing to benefit from the common pharmaceutical market are expected to develop long-term strategy, exercise patience and demonstrate flexibility.

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7 List of tables

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

Lübeck, 16.02.2016