“REGULATIONS AND REGISTRATION PROCESS OF GENERIC MEDICINAL PRODUCTDS IN COMMONWEALTH OF INDEPENDENT STATES”

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IN

REGULATORY AFFAIRS & QUALITY ASSURANCE

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CERTIFICATE

This is to certify that the dissertation work entitled "Regulations and registration process of generic medicinal products in Commonwealth of Independent States" submitted by Mr. Saurabh Vyas with Regn. No. (13MPH808) in partial fulfillment for the award of Master of Pharmacy in "Regulatory Affairs & Quality Assurance" is a bonafide research work carried out by the candidate at the Department of Regulatory Affairs & Quality Assurance, Institute of Pharmacy, Nirma University and at Aurobindo Pharma, Hyderabad under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Regulations and registration process of generic medicinal products in Commonwealth of Independent States", is based on the original work carried out by me under the guidance of Dr. Priti J. Mehta, Head of department, and I. Nagendran, General Manager, Regulatory affairs Department, Hyderabad. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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*Every time we remember to say **"thank you"**, we experience nothing less than heaven on earth."-- Sarah Ban Breathnach*

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LIST OF ABBREVIATIONS

ANDA	Abbreviated New Drug Application
ASEAN	Association of South East Asian Nations
ATC	Anatomical Therapeutic-chemical Code
AUC	Area Under Curve
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BP	The British Pharmacopoeia
CETHC	Center of Expertise and Testing in Health Care
CFC	Chlorofluorocarbons
CIS	Commonwealth Independent States
CoA	Certificate of Analysis
CPC	Committee of Pharmaceutical Control
CPP	Certificate of the Pharmaceutical Product
CRO	Contract Research Organization
CTD	Common Technical Document
CV	Curriculum Vitae
DRA	Drug Regulatory Authority
F & D	Formulation and Development
GDQC	General Directorate for the Quality Control
GMOs	Genetically Modified Organisms
GMP	Good Manufacturing Practices
IP	Intellectual Property
MH RU	Ministry of Health of the Republic of Uzbekistan
MP	Medicinal Product
NAD	Normative Analytical Documentation
NCE	National Center of Expertise
NCES	National Center for Examination and Standardization of Drugs

NCEs	New Chemical Entities
PhEur	European Pharmacopoeia
PhF	French Pharmacopoeia
PhInt	International Pharmacopoeia
PIL	Patient Information Leaflet
PSUR	Periodic Safety Updates Reports
QOS	Quality Overall Summary
RA	Republic of Armenia
R & D	Research and Development
SCE	Scientific Center of Expertise
SEC	State Expert Centre
SPC	Summary of Product Characteristics
SmPC	Summary of Product Characteristics
UE	Unitary Enterprise
USSR	United Soviet Socialist Republic
WHO	World Health Organization
WTO	World Trade Organization

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Abstract

Two specific outlines have been notable in the development of organizational depiction in the CIS nations. Nation like Ukraine, try to obtain market registration as per European/ICH point of assessment, but others, for example Russian fedration and other Republic States wedged by the custom of the Soviet age.

Since Russia as well as Ukraine are the two chief and most attractive CIS markets. These two nations have their own specific governmental policies, this work is fundamentally concentrated on the regulations and registration procedures of generic drug products in the whole CIS.

Generic drugs in CIS nations are registered and marketed under varied registration conventions, because of divers administrative methodology among the CIS nations

The CIS market is massive, fast rising and clearly offers huge breaks for pharmaceutical companies. Though, this is an ambiguous flea market, with enormous growth as well as diverse pharma-economies.

In CIS region the ability to accommodate country specific requirements and understand regulatory variances will have a considerable effect on the achievement of its multicounty submissions rule. So, the correct submission plan in advance possibly will mark uniform assessment progression without any significant delays or failures in dossier submissions.

Introduction

The Commonwealth of Independent States (CIS), formerly was part of earlier USSR (United Soviet Socialist Republic) obligated differentiated in to self-governing countries in 1991. In the approved decree, the adherents of the Commonwealth affirmed their interaction on the base of self-sufficient egalitarianism. These democracies which were arose from the Soviet Unification, generally baptized as CIS countries.

Currently CIS unites; Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan and Ukraine.

In 1993 the characters from the CIS States manifest an accord on the foundation of Trade Union to blueprint standard money related freedom on free relationship of Pharmaceutical items and administrations, to enhance composed financial aspects, traditions, assessments, and fringe monetary methods, to bring mutually methods of amendable financial activity and generate sympathetic circumstances for the expansion of straight production dealings[1]. From that point forward all the CIS states have been concentrating on making efficient relationship with a mixed bag of nations alongside India, mainly in the field of pharmaceuticals in light of the fact that India has colossal development in the arena of pharmaceuticals as well as biotechnology. The CIS territories are massively probing open accesses for enhancing exchange associations with India. The Indian government is likewise consistently included in keeping up a long- term coordinated effort with the CIS.

Among the CIS countries, India's pharmaceutical fares have been spread through Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan and Ukraine. Dealings in the middle of India and the CIS countries have stayed close and cheerful since the Soviet epoch. Though, shared exchange and business relations have not become equivalently with these recently framed nations. At present-day CIS builds just 1.2 every penny parcel in India's amassed exchanges. The primary purpose behind this can be ascribed to elements alike remoteness, regional boundary, lacking transportation office and absence of data around business prospects. Between the real exchanging abettors, Russia, Ukraine, Kazakhstan, Uzbekistan, Kyrgyzstan and also Belarus constitute more than 90 every penny of India's summative consensual exchange with the CIS republics[2].

History of development

During the Soviet period, the entire pharmaceutical industry, all hospitals, clinics, scientific institutes and pharmacies fitted to the state domination. No system of marketing authorization for the medicinal products as established in the early 1960s or "post-thalidomide" in Soviet Union. Notwithstanding this, as early as 30 April 1964, Ministry of Health (MoH) of the Union of Soviet Socialist Republics (USSR) has issued a declaration establishing a formal registration procedure for medicinal products including registration certificate, which contained such data as registration number, manufacturer, product name, composition, posology and price.

This Decree also set up the first list of registered medicinal products allowed to be manufactured and used in the Soviet Union, which contained only 331 names of the active pharmaceutical ingredients.

The list was successively amended, e.g. in the year 1967, with a further 290 substances, from 1971 onwards, the MoH of the USSR collected information about registered medicinal products in the so-called State Register of Medicinal Products. The register included

- The name and registration number of the product,
- Registration certificate,
- Specification and analytical procedure,
- Product information (e.g. Patient Information Leaflet PIL),
- Pharmacological properties,
- Clinical studies conducted

By 1 January 1987, the register included 2612 medicinal products in different pharmaceutical forms, 439 herbal drugs and preparations, 61 radiopharmaceuticals, 70 excipients and reagents and, 129 reference standards.

After the drop of the Soviet Union in 1991, each of the new independent republics started to establish its own registration procedure.

In September 1993 the Heads of the CIS States signed an Contract on the creation of Financial Union to form common financial space grounded on free movement of goods, services, labor dynamism, wealth, to elaborate coordinated monetary, tax, price, customs, peripheral economic policy, to bring collected ways and means of amendable economics[3].

Commonwealth independent states and their MOH's

S.no	Country	Regulatory authority
1	Armenia	Scientific Center of Drug and Medical Technology Expertise
2	Azerbaijan	Republic Ministry of Health, Analytical expertise center for Medicines, Department of registration(MOH)
3	Belarus	Ministry of Health of the Republic of Belarus
4	Georgia	Medicines Agency, Ministry of Health (MoH)
5	Kazakhstan	The National Centre of expertise of medicines, Medical devices and medical equipment (Agency of Republic of Kazakhstan for Health Affairs)
6	Kyrgyzstan	MOH, Kyrgyzstan
7	Moldova	Medicines Agency, Ministry of Health (MoH)
8	Russia	Division of Drug Registration (MoH)
9	Tajikistan	Ministry of Health (MoH)
10	Turkmenistan	Ministry of Health (MoH)
11	Ukraine	State Pharmacological Center of the Ministry of Health of Ukraine.
12	Uzbekistan	Ministry of Health of Uzbekistan

Table 1: Commonwealth independent states and their MOH's

A fruitful regulatory filing approach needs close courtesy to local requirements, understanding with former regulatory conclusions and information of the country's remedial follows. It is often beneficial for chief pharmaceutical corporations to succumb their early marketing agreement requests in the CIS market.

The key to this plan is to improve a robust core dossier that can be adapted to accommodate the differing necessities of CIS nations. This tactic greatly cuts duplication of effort and lessens governing incompliances[2].

Aim

The present work aims to develop a robust core dossier of generic medicinal product for regulatory filing so as to reduce the risk of regulatory delays by anticipating the questions raised by the individual regulatory authorities in CIS nations.

Objectives

The objectives of the proposed work includes

- Review of regulatory framework in the countries of CIS pharmaceutical market.
- To understand the regulatory guidelines proposed by the respective countries.
- To review and develop a dossier according to the guidelines proposed by the government agencies of respective countries.
- To understand the regulatory requirements for preparing scientific dossier
- To review the scientific Technical data requirements of each countries
- To compare and contrast the regulatory aspects of the countries according to the regions in the CIS pharmaceutical market
- The study was conducted with an objective to produce a clear and systematic framework for the generic drug product registrations and guidelines in the respective countries of the CIS pharmaceutical markets.

Literature review

Literature review was done mainly by reviewing and collecting the guidelines and generic drug registration procedures in the different countries. The research was carried out by analyzing and collecting the data from different regulatory guidelines.

1. Understanding the pharmaceutical markets

Pharmaceutical industry usually categorizes different markets based on the market size, regulations in the country, economic conditions of the country and the growth opportunities available[4].

Regulated markets:

- US, Europe, Japan, Canada.

Semi-regulated or emerging markets:

- Brazil, Russia, Mexico, India, China, Turkey, South Korea (Emerging-7 countries).

ROW (Rest of the world countries):

- Latin American geographies like Venezuela, Peru.
- Asian geographies like Philippines, Malaysia, and Singapore.
- Central and Eastern Europe countries
- African nations, Australia & New Zealand.

Emerging pharmaceutical markets:

Currently, like never before anytime recently, life sciences organizations are swinging to developing markets for instance Brazil, Russia, India & China (BRIC nations) for new development and a maintained focal point over the opposition.

Developing markets comprise of 70% of the world's total fair, produce 31% of GDP and will represent 30% of worldwide pharmaceutical spending by 2016. Anyhow, notwithstanding the guarantee, numerous pharmaceutical firms have felt developing torments and have not yet possessed the capacity to get a significant a dependable balance in these districts.

New players soon find that offering and working in these business sectors displays various difficulties. Business sector access prerequisites, for example, store network arranging,

assembling and circulation can be multifaceted. They likewise find a managerial state of affairs, including levy and import administrations, which can be critical hindrances to development, both as far as meeting expectations transverse over outskirts.

2. Common Technical Document

The Common Technical Document is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities[5].

Module-1: Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module-2: Common Technical Document Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

Module 2 should contain 7 sections in the following order:

1. CTD Table of Contents
2. CTD Introduction
3. Quality Overall Summary
4. Nonclinical Overview
5. Clinical Overview
6. Nonclinical Written and Tabulated Summaries
7. Clinical Summary

As Module 2 contains information from the Quality, Efficacy and Safety sections of the CTD, the organization of the individual Module 2 summaries is discussed in three separate documents:

- M4Q: The CTD - Quality
- M4S: The CTD - Safety
- M4E: The CTD - Efficacy.

Module 3 *Quality*

Information on Quality is presented in the structured format as described in the guidance, M4Q.

Module 4 *Non-clinical Study Reports*

The Nonclinical Study Reports is presented in the order as described in the guidance M4S.

Module 5 *Clinical Study Reports*

The human study reports and related information is presented in the order as described in the guidance M4E.

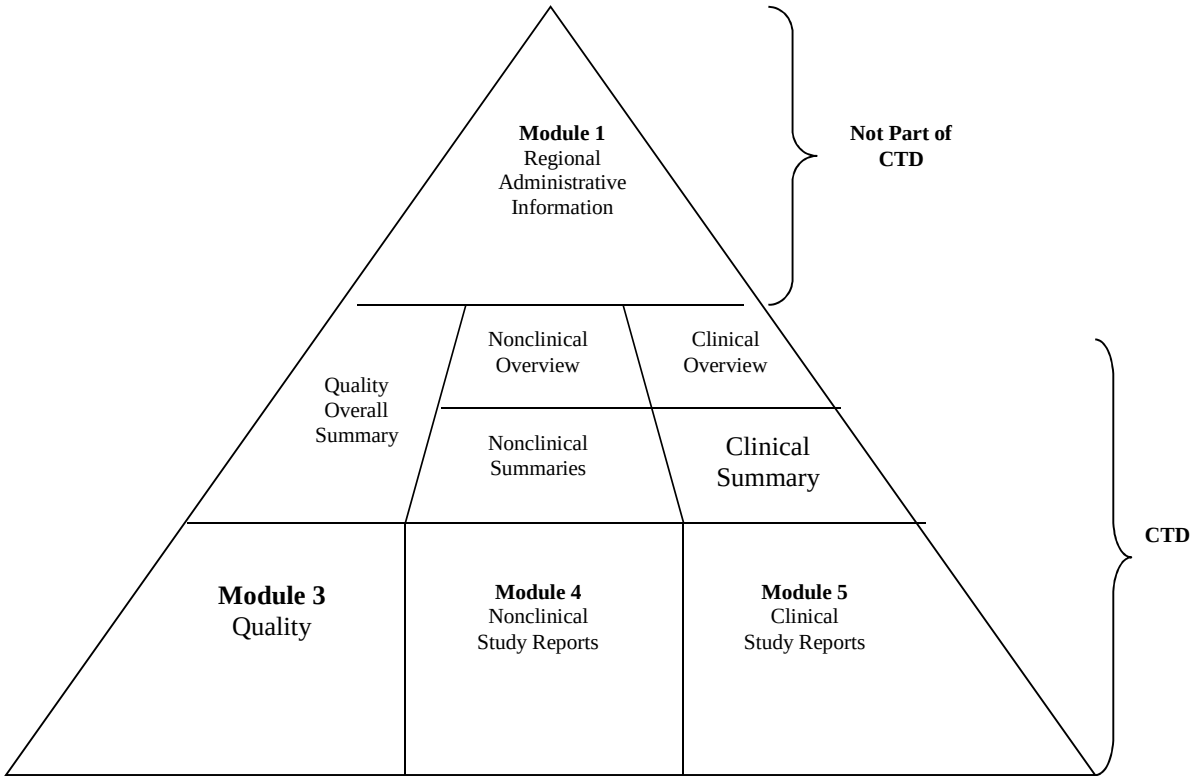


Fig 1: Structure of CTD[5]

3. Process of generic drug products registration:

The process of registration for generic products is similar to, but simpler than, the process of registration of NCEs. For a new generic product, a company develops a dossier that contains data primarily about the pharmaceutical chemistry of the product.

The assumption is that an innovator product exists (usually in the same market) and that the innovator has been shown to be clinically effective and safe (although in poorly controlled markets this may not be the case).

The data for the generic product is therefore designed to establish that it is clinically interchangeable with the innovator in terms of efficacy and safety. Such applications implicitly rely on the clinical data provided in the dossier for the innovator, even though there is rarely a direct comparison of the two dossiers during the evaluation. It is this implicit comparison of clinical information that may be constrained under TRIPs because of the requirements for data exclusivity, which may be interpreted as precluding reference to the clinical trials that originally established that a compound was effective and safe In some instances, a product can be registered on the basis of chemical and manufacturing data only (e.g. an injectable formulation for which there is a recognized pharmacopoeial standard , such as the British Pharmacopoeia, or the United States Pharmacopoeia), describing the method of synthesis and quality control for the product. The most rigorous test of interchangeability is a clinical trial comparing the proposed generic with the innovator and measuring the effects of both on clinical outcomes; these trials are rarely carried out.

Registration of generic products, as for innovator products, also requires inspection and quality control of manufacturing plants. This is particularly where manufacturing standards are critical and internationally, the benchmark for manufacturing standards is defined in the International Standards for Good Manufacturing Practice (GMP).

There have been unreliable reports from many developing countries that when GMP standards were introduced, many local manufacturers could not meet the standards required under GMP for documentation, process and management controls over the production of a product. This situation has led to debate about what are the appropriate standards for good manufacturing in resource-poor settings. In addition, local capacity to carry out GMP-standard inspections of facilities and processes is often limited, as the training and skills

required to become a certified GMP inspector are significant. Training programs have been developed, however, but need further support[6].

The time required to register a generic product varies. If it is a straight forward application with high quality data from a licensed and qualified manufacturer, then a dossier can be reviewed in 2-4 weeks. If, on the other hand, the substance is relatively poorly defined, the chemistry is complex and bioequivalence studies are needed as well as inspections of manufacturers, the process of evaluation and registration can and should take much longer. If a small DRA is registering large numbers of generic products rapidly, the quality of the evaluation and assessment of the products may well be compromised[4].

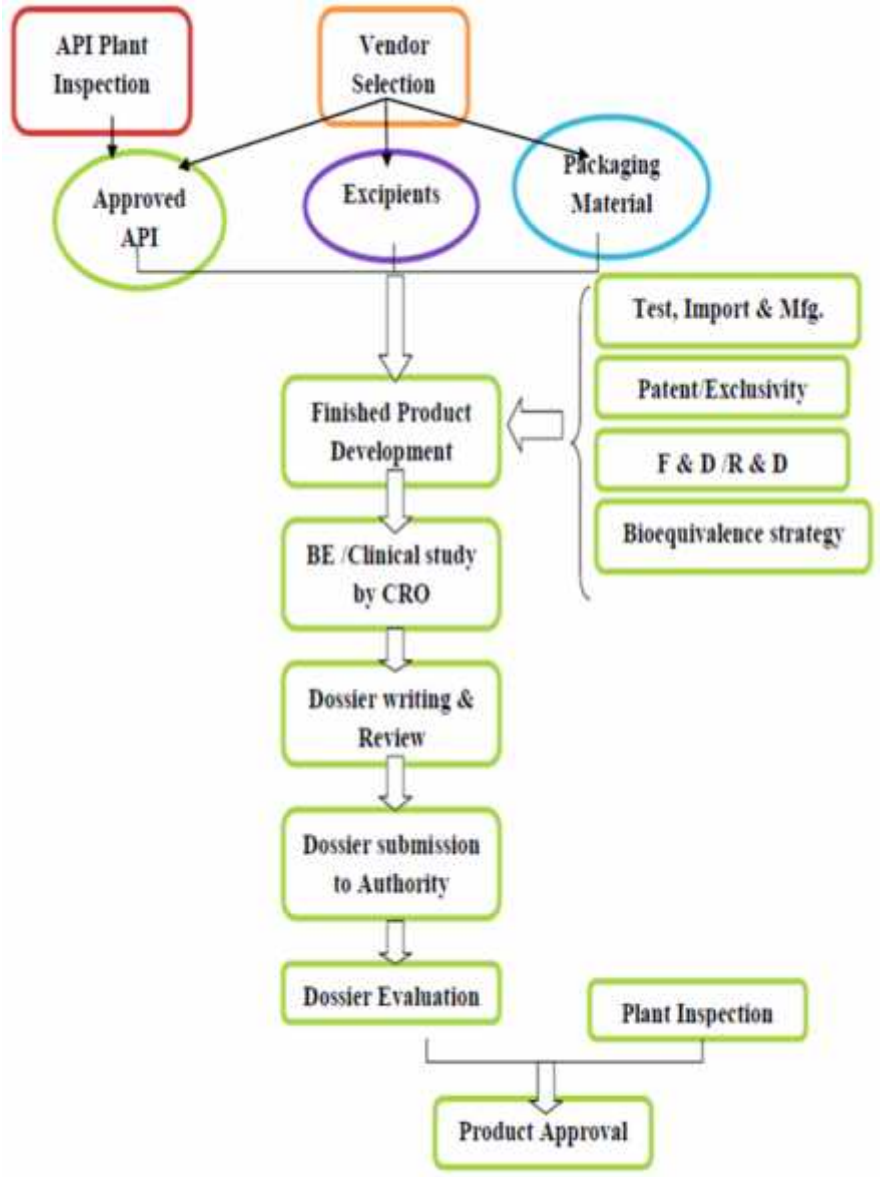


Fig 2: Regulatory Filing Procedure[4]

4. CIS (Commonwealth Independent States)

Since the mid-1990s, the new nations rising up out of the previous Soviet Union, ordinarily called CIS nations, have progressively pulled in the consideration of real players in the pharma business around the world.

Two particular patterns have been distinguished in the advancement of administrative enactment in the CIS nations, a few nations, as Ukraine, attempt to receive however much as could reasonably be expected of the European/ICH point of view, though others, for example, Russia, proceed all alone way, halfway impacted by the legacy of the Soviet period. Since Russia and Ukraine are the two biggest and most appealing CIS markets, yet seek after two particular administrative methodologies, this work is concentrated basically on looking at the enactment in the entire CIS nations[7].

S.No	COUNTRY	DOSSIER
1	Armenia	NON-CTD
2	Azerbaijan	
3	Belarus	
4	Georgia	
5	Kyrgyzstan	
6	Russia	
7	Tajikistan	
8	Turkmenistan	
9	Uzbekistan	
10	Kazakhstan	CTD
11	Moldova	
12	Ukraine	

Table 1: Classification of CIS on The Basis of Dossier Structure

In a few nations like Republic of Armenia, Tajikistan and Kyrgyz Republic, medication prices are not managed by the state, on the other side Russia, Ukraine, Kazakhstan, Belarus, Moldova and Uzbekistan utilize different government controlling apparatuses.

Regulations and Registration of medicinal product CIS (non CTD)

Countries

1. Armenia
2. Azerbaijan
3. Belarus
4. Georgia
5. Kyrgyzstan
6. Russia
7. Tajikistan
8. Turkmenistan
9. Uzbekistan

4. Regulations and Registration of Generic Medicinal Products in Armenia

4.1 Registration Regulations

On the terrain of the Armenia the production, import, sale as well as use of only registered drugs in the RA are permitted. The registration is conceded out conferring to the "Requirements for the state registration of medicines in the Republic of Armenia".

These necessities are intended according to the laws of the Republic of Armenia "On Drugs" and "On State Fee" On approval of the state registration of drugs and amount of payment for the examination of state registration of drugs in RA.

Registration of drugs, rejection in registration and invalidation of registration is steered by the Ministry of Health of the Republic of Armenia.

State registration of drugs is carried out on the basis of results of expert evaluation on scientific criteria of quality, effectiveness and safety of drugs.

The medicine expertise with aim to register is conducted by "Scientific center of expertise of drug and medical technology"("SCE")[7].

The quality of medicinal products registered in the Republic of Armenia shall comply with the requirements of currently used officially Pharmacopoeias in the Republic of Armenia:

- The XI State Pharmacopoeia of the former USSR,
- The European Pharmacopoeia(PhEur),
- The International Pharmacopoeia (PhInt),
- The American Pharmacopoeia (USP),
- The British Pharmacopoeia (BP),
- The German Pharmacopoeia (DAP),
- The German Homeopathic Pharmacopoeia (HAB)
- The French Pharmacopoeia (PhF)

In some cases temporary Pharmacopoeial monographs approved by the Ministry of Health of the Republic of Armenia.

4.2 Categories of medicinal products which are subject to state registration:

- New (original) and generic drugs
- Other doses, dosage forms and new indications drugs
- New combinations of drugs
- Changing the composition, production technology, international non-proprietary name of the drug that have received state registration, as well as the identification of new properties, new indications for use, new registration is required.

State registration is not required for drugs manufactured in pharmacies by prescription.

4.3 Registration procedure

Submission of Application for registration

For the purpose of registration of medicinal products, the manufacturer or its authorized representative (‘applicant’) submits a required documentation according to the approved lists of documents with respective samples of medicinal products and reference standards to the Scientific Centre.

Documents are submitted in Armenian, Russian or English and also on CD,

The applicant is responsible for the authenticity of documents and correctness of information.

The Applicant shall submit samples of medicinal products in packaging’s and labeling in Armenian, or in Russian, or in English (only for prescription medicinal products) packaging and labeling: two consumer packages (for checking-identification and laboratory-arbitrage) and in necessary quantities (in consumer packages) required for laboratory expertise complied with the specifications and methods of analyses (as per pharmacopoeial monographs)

Stages of the registration process

1. Preliminary examination of the materials submitted by the applicant will be made within a maximum of 10 days at the “SCE”.
2. After passing the examination the applicant is notified in writing of the result and receives an invoice for payment of examination.
3. Examination is carried out after the payment of fee by the applicant is done (in the form of deposit).
4. The beginning of examination period will be the date of payment.

5. The maximum duration of examination of drugs in RA is 180 days, except for the drugs that are registered in one of the countries full members of the EU, the U.S. or Japan, the examination period of which is 30 days under a simplified procedure without laboratory analysis.
6. In the case of simplified procedure for the state registration to the submitted application for registration the following documents in English and Armenian languages will be attached:
    - Certified copy of the registration certificate of drugs in one of the countries members of the EU, the U.S. or Japan, or the certificate of pharmaceutical product (CPP) according to the format approved by the World Health Organization, issued within the last 2 years;
    - General description of the drugs approved by the authorized body of the state that registered it;
    - Data on the qualitative and quantitative composition (including excipients);
    - Pharmacopoeia articles or documents defining control methods and specifications of the drug
    - The label, packaging, their color images, leaflet or instructions for medical use for professionals and consumers and their electronic versions of all release forms provided in the application in English or Armenian.
    - The periodical safety updates of the reports.

    In order to confirm the efficacy, safety, quality and compliance requirements for the production of the product, during the examination following works should be done:
    - The study of the pharmacological particulars,
    - Toxicological, clinical, laboratory researches,
    - Technological process,
    - Regulatory and analytical documentation evaluation,
    - Organization of production and quality control.
7. In compliance with normative analytical documentation requirements in the Republic of Armenia the laboratory testing of submitted samples begins.
8. With a negative result of the laboratory examination, the applicant has the opportunity to present two new samples of drugs of other series, in sufficient quantities for the new two laboratory tests.

9. For the provision of additional materials the period of 6 months is provided, the time needed for the preparation of documents in terms of examination is not included.
10. After completing the examination within five days the "SCE" provides the conclusion to the Pharmacological Council of MOH of RA.
11. In the case of examination of drugs under the simplified procedure, the expert report is submitted directly to the Ministry of Health of the Republic of Armenia.
12. After receiving the results of the examination, the Pharmacological Council of MOH of RA within 15 days provides the conclusion on registration the drug in RA or refusal in registration, as well as the inclusion of the drug to the RA medication lists (list of controlled drugs, list of medicines sold without a prescription, Essential Medicines List). Within 5 days, the applicant will be sent a notice of the conclusion of the Pharmacological Council.
13. The decision to register the drug in the RA will be taken by the MOH within 10 days after receipt of examination results and conclusions of the Pharmacological Council and after the applicant have payed the state fee in the prescribed manner and respected amount to the account of the State.
14. In the case of non-payment by the applicant of the state fee in the prescribed manner and amount within 30 days after notification of the positive conclusion of the Pharmacological Council, the registration process will be terminated and the subsequent examination of the purpose of registration of medicines is carried out on the same basis as appropriate.
15. Based on the decision of the MOH of RA drug registration within 10 calendar days, the applicant will be issued a Certificate of registration of medicines.

4.4 Denial of State Registration in Armenia

The registration of medicinal products is rejected if the following is available:

- A negative conclusion of the expertise.
- Alerts on the medicinal product received from international specialized sources
- The medicinal product contains chlorofluorocarbons (CFC)
- The submitted certificate is false.

The applicant is informed on the rejection of the medicinal product registration within 10 days.

The period of validity of registration of medicinal products in the Republic of Armenia is five years.

4.5 Documents required for the registration in the Republic of Armenia

Table 2: Documents required for the registration in the Republic of Armenia

S.No	Content
1	Application form
2	Registration certificate of the medicinal product delivered by the country of source (original or verified copy).
3	Certificate of Good Manufacturing Practice (GMP) delivered by the official body of the country of source.
4	Registration status in other countries.
5	Summary of Product Characteristics (SmPC).
6	Instructions for use for specialists and patients.
7	Qualitative and quantitative composition of the medicinal product (including excipients).
8	Pharmacopoeial monograph(s) and/or control method(s) or specification(s) of the finished medicinal product and its ingredients, packaging specification(s) (2 copies).
9	Quality certificates of the medicinal product and its active substances and excipients
10	Data on stability study and shelf life of medicinal product
11	Brief description of the technological process, chemical, technological and equipment schemes of the production, including controls of critical steps
12	Data on pharmacokinetic and/or bio-equivalence and/or limited clinical trials of the medicinal product.
13	Information on pharmacological, toxicological and Bio-equivalence
14	The label and packaging of the medicinal product
15	Certificate (verified copy) or verified extract from appropriate register about legal protection of trademark issued by the Intellectual Property Agency of the Ministry of Economy of the Republic of Armenia if available.
16	Periodic Safety Update Report.

Following Data should be included in the application form

1. Name of the medicinal product
2. International Nonproprietary Name

3. Composition
    - Active substances
    - Excipients
4. Dosage strength
5. Pharmaceutical form and route of administration
6. Anatomical-therapeutic- chemical code (ATC)
7. Presentation and packaging
8. Indications
9. Shelf-life
10. Storage conditions
11. Legal status for supply to the patient in the country of origin
12. Manufacturer (name, address, country)
13. Marketing authorization holder (name, address, country)
14. Number and expiry date of registration certificate of patent and trade mark
15. Applicant (marketing authorization holder in future), address, phone number(s), fax, signature, stamp or seal, date of signing

Table 3: The summary of the product characteristics

S.NO	Content
1	**Name of the medicinal product**
2	**Qualitative and quantitative composition** with indication of active substances (international nonproprietary name or chemical name), indication of other excipients knowledge of which is essential for safe and proper administration of the medicinal product.
3	**Pharmaceutical form**
4	**Clinical particulars**
	4.1 Therapeutic indications
	4.2 Posology and method of administration (where appropriate dosage adjustments in specific patient group should be stated)
	4.3 Contraindications
	4.4 Special warnings and precautions for use
	4.5 Interactions

	4.6 Pregnancy and lactation
	4.7 Effects on ability to drive and use machines
	4.8 Undesirable effects
	4.9 Overdose
5	**Pharmacological properties**
	5.1. Pharmacodynamic properties
	5.2 Pharmacokinetic properties
	5.3 Preclinical safety data
6	**Pharmaceutical particulars**
	6.1 Excipients
	6.2 Incompatibilities
	6.3 Shelf-life
	6.4 Storage conditions
	6.5 Nature and contents of container
	6.6. Special precautions for disposal
7	**Manufacturer (name, address, country)**
8	**Marketing Authorization holder (name, address, country)**
9	**Date of final revision of the text.**

4.6 Fees for registration of generic medicinal product in the Republic of Armenia

- In case of failing to pay the expertise fee within 6 month upon receiving the written notification on payment, the applicant has to submit a new application.
- The decision about registration of medicinal product is made by the Ministry of Health within 10 days on the base of the expertise results, conclusion of the Pharmacological Council and payment of state tax in accordance with established procedure and amount to the appropriate account of the State Treasury of the Republic of Armenia (in case the payment is made in foreign currency in accordance with the actual at date exchange rate established by the Central Bank of RA)
- The registration procedure will be suspended if the state tax is not paid in accordance with the established procedure and amount by the applicant within 30 days after notification about positive conclusion of the Pharmacological Council of the Ministry

of Health. In the future the Expertise for registration of medicinal product will be conducted due to the established procedure by applying new application.

Table 4: Fees payable for registration expertise in the Republic of Armenia

S.No	Type of application for registration	Expertise Fee (including VAT) (thousand Armenian dram)
1	The first dosage form and dosage strength of generic medicinal products	900
	Each additional pharmaceutical form	450
	Each additional dosage strength	240
	Each new indication	450
2	New combination of known medicinal products	1200
3	The first pharmaceutical form and dosage strength of the medicinal products containing new active substances	2250
	Each additional pharmaceutical dosage strength	1200

5 Regulations and Registration of medicinal product in Azerbaijan

5.1 Registration Regulations

Regulations about Medicinal Products are prepared on the basis of the Declaration of the President of Azerbaijan Republic.

Regulations do not concern medicinal products used for diagnostics, prophylaxis and treatment of diseases (such as medical devices, products, goods and materials, instruments and equipment's, medical reagents and optical devices).

The Ministry of Health of Azerbaijan Republic or its authorized organ (after the Ministry of Health) includes medicinal products after state registration into the register of medicinal products of Azerbaijan Republic and issues the permission for their import to Azerbaijan Republic, manufacturing, selling, and use for medical purposes on the territory of Azerbaijan Republic[8].

5.2 Categories of medicinal products which are subject to state registration:

According to the Law of Azerbaijan Republic "About medicinal products" the following medicinal products are to be registered:

- Original medicinal products;
- Analogues (generics) of medicinal products;
- New combinations of early registered medicinal products;
- Medicinal products with the expired period of state registration pharmaceutical substances used as active ingredients in the medicinal products manufacturing.

5.3 Procedure of Registration

Manufacturer's authorized person (applicant) addresses the Ministry of Health with a letter with the aim of state registration of medicinal products.

Applicant presents the letter confirming his/her authorities to the Ministry of Health.

The following documents are required for state registration;

- Application for the state registration of medicinal product in Azerbaijan Republic;
- Set of documents submitted of medicinal product manufactured in a foreign state;
- Set of documents for the state registration of medicinal product in Azerbaijan Republic produced in the country.

Documents are to be submitted in 2 copies:

- One copy is the documents compiled by manufacturer (along with copies of official documents certified notarially);
- Other copy is the set of the same documents translated into Azerbaijani or Russian languages and approved by the applicant.

Samples of medicinal product are to be submitted 5 boxes in number and in the form acceptable for selling, and pharmaceutical substance in the quantity sufficient for conduction of three analyses.

Applicant is responsible for authenticity of the documents presented and the information contained in the documents.

Ministry of Health is responsible for the confidentiality of the information presented by the applicant that concerns commercial secret the way provided for by the correspondent Legislation of Azerbaijan Republic.

A. Preliminary expertise of documents submitted for the state registration:

1. Application, documents provided for by the present Regulations and samples presented for the state registration are registered in the special book in case everything is correct, submitted for preliminary expertise and the applicant is informed about it.
2. After the applicant receives the notification provided for by the section of the present Regulations to conduct preliminary expertise, within 5 days the agreement is to be concluded with the Ministry of Health to conduct preliminary expertise. The agreement will reflect the volume, period of expertise along with the cost of services and other correspondent terms. After the agreement is concluded the applicant within 15 bank days makes a bank transfer to the bank account of the Ministry of Health for conducting preliminary expertise.
3. From the day of payment of the preliminary expertise within 15 calendar days the Ministry of Health is to conduct the expertise of documents and samples presented for the state expertise with the aim of state registration. During the preliminary expertise the expediency of state registration and completeness of the information submitted are studied.

   In case of a mistake or discrepancy revealed in the applicant's documents while conducting the preliminary expertise and in case not all documents are submitted to prove quality, safety and efficacy of medicinal products for state registration, the Ministry of Health can

demand from the applicant to submit additional documents to eliminate mistakes and discrepancy.

4. Applicant has 90 calendar days to organize the submission of additional documents, elimination of mistakes and discrepancy. This period does not concern the period of preliminary expertise provided.

   If additional documents are not presented and mistakes and discrepancy are not eliminated within 90 calendar days from the day of demand, the process of the preliminary expertise is suspended while documents and samples are returned to the applicant. In case of documents and samples return the cost of the preliminary expertise the applicant paid is not to be returned. Medicinal product with returned documents can be repeatedly submitted for the state registration by the applicant.

Base on the results of the preliminary expertise the Ministry of Health takes one of the following decisions:

- To send the documents and samples for expertise from the side of specialized expertise agency of the Ministry of Health of Azerbaijan Republic;
- To refuse from the state registration

In case the decision to send the documents and samples for the specialized expertise is taken the applicant is to be notified.

The Ministry of Health refuses from the state registration of the medicinal products basing on the results of the preliminary expertise in the following cases:

- While submitting another medicinal product for the state registration under the trade mark that has already undergone the procedure of the state registration in Azerbaijan Republic;
- While submitting the early registered original medicinal product for the state registration under the same name and from the third person side without agreement of the license holder (excluding the cases when the international nonproprietary name recommended by the World Health Organization is used) ;
- In case the documents and samples presented do not meet the requirements of the Law of Azerbaijan Republic “About medicinal products” and present Regulations.
-

B. Specialized expertise of the documents presented for the state registration:

After the applicant receives the notification indicated for the specialized expertise for the documents and samples medicinal product, within 5 working days the applicant is to conclude an agreement with specialized analytical expertise agency of the Ministry of Health of Azerbaijan Republic concerning conduction of expertise.

The agreement reflects the volume, period of expertise and also cost of services and other correspondent conditions. Once the agreement is concluded the applicant within 60 bank days is to make payment for conducting specialized expertise to the bank account of the Ministry of Health.

- Specialized expertise consists of laboratory tests of medicinal product, evaluation of normative-technical documents and results of clinical-pharmatoxicological trials
- Specialized expertise is to be conducted within 180 calendar days from the date the applicant makes payment for the expertise
- In the case of medicinal product with expired period of state registration, the specialized expertise of the documents of medicinal products presented for re-registration and information changes made to the documents of state registration is to be conducted within 90 calendar days
- If needed the Ministry of Health can demand the applicant to submit additional information and reagents
- Time the applicant spends on submitting additional information and reagents is not included in the time of specialized expertise
- If the additional information is not presented within 90 calendar days the conduction of the specialized expertise is to be suspended
- When the specialized expertise is suspended the documents and samples the applicant presented along with the payment made for the specialized expertise are not to be returned
- Medicinal product with the suspended specialized expertise can be repeatedly submitted for the state registration
- Report on the results of the specialized expertise is to be presented to the Ministry of Health from the side of specialized expertise agency of the Ministry of Health.

C. Additional Specialized expertise of the documents presented for the state registration.

In case the documents presented for the specialized expertise for the state registration of medicinal product are not sufficient for the medicinal products manufacturing, import to Azerbaijan Republic and use in the medical practice, and in case when quality, safety and efficacy of the medicinal product are not proved, the Ministry of Health takes the decision to send the results of the expertise within 10 calendar days from the date of report for the additional specialized expertise from the side of Expert Council on Pharmacology and Pharmacopeia.

One copy of this decision is to be presented to the applicant.

- Additional specialized expertise consists of the expertise of documents presented by the applicant, the expertise of report indices made by the specialized expertise and/or laboratory analysis of medicinal products
- Additional expertise is to be conducted within 30 calendar days
- If needed the Expert Council on Pharmacology and Pharmacopeia of the Ministry of Health can demand the applicant to submit additional information concerning the expertise
- Time the applicant spends on submitting additional information and reagents is not included in the time of specialized expertise
- If the additional information is not presented within 90 calendar days the specialized expertise is to be suspended.
- When the specialized expertise is suspended the documents and samples are not to be returned to the applicant
- Medicinal product with the suspended additional specialized expertise can be submitted repeatedly for the state registration.
- Report on results of additional specialized expertise is to be presented to the Ministry of Health from the side of specialized expertise agency of the Ministry of Health.

Applicant can refuse from the registration at any stage of state registration. In this case the documents and samples presented for the state registration are not to be returned.

Taking decision on the results of the additional specialized expertise:

Basing on the results of specialized expertise and in the cases of Additional specialized expertise of the present Regulations basing on the report made by the Expert Council on Pharmacology and Pharmacopeia of the Ministry of Health of Azerbaijan Republic, the Ministry of Health takes one of the following decisions:

- To approve state registration of medicinal product;
- To refuse from the state registration of medicinal product

5.4 Rejection of medicinal product from state registration:

Ministry of Health refuses from state registration of the medicinal product in the following cases:

1. If the composition of the medicinal product contains the substance forbidden for use in Azerbaijan Republic;
2. In case of discrepancy between quantity and quality indices to those presented in the documents;
3. When therapeutic efficacy is not proved;
4. In case of the negative result of clinical tests and other trials conducted to evaluate safety, efficacy and quality of medicinal product;
5. In case of serious side effects of medicinal product during registration process
6. In case of the negative conclusion on the results of the expertise of the manufactory;
7. In case of the negative conclusion on the results of the specialized expertise and/or additional specialized expertise of the Expert Council on Pharmacology and Pharmacopeia;

While taking the decision to refuse from the state registration of the medicinal product the applicant is to be provided with the sound answer in the written form.

5.5 List of Documents necessary for the registration of generic medicinal products Azerbaijan

Table 6: Documents necessary for the registration of generic medicinal products Azerbaijan

S No.	Content
1	Application for the state registration
2	In case of making amendments to the medicinal product dosage and submission of another dosage for the registration:
	2.1 Copy of document about the registration of medicinal product new dosage in the manufacturing country certified notarially;
	2.2 Report about pre-clinical tests and clinical trials of medicinal product in the new dosage (signed by tests and trials executor and approved by the head of agency).Copies for foreign countries are to be approved by the head of agency conducting the trials and the customer;
	2.3 Pharmacopeia article on quality control over medicinal product or normative document project;
	2.4 Quality certificate issued by the manufacturer for the new dosage of medicinal product;
	2.5 Indications for use of medicinal product;
	2.6 Samples of package and its drafts, indications for use and their electronic versions;
3	At the registration of changes in the package (dosage quantity per pack) and at registration of another package
	3.1 New indications for use of medicinal product;
	3.2 Samples of package and its drafts, indications for use and their electronic versions;
	3.3 Quality certificate issued by the manufacturer for the new dosage of medicinal product;
	3.4 Project of amendments to the normative documents on the quality control over the medicinal product;
4	In case medicinal product name is changed:

	4.1 Copy of document about registration of the medicinal product name in manufacturing country certified notarially;
	4.2 Reference grounding change in medicinal product name;
	4.3 New indications for use of medicinal product;
	4.4. Specimen of packaging and its sketches, guidelines on their use, as well as their electronic versions. If the name of the medicinal product does not coincide with the registered name of the same medicinal product in the producer country, in this case application on the registration of medicinal product is accepted only once the name of the medicinal product is agreed with the Ministry of Health
5	In case of introducing new indication for use, i.e. how to use medicinal product:
	5.1 New indication for use of medicinal product;
	5.2 Samples of package and its drafts, indications for use and their electronic versions;
	5.3 Report about medicinal product clinical trials on the new indication (signed by the tests and trials executor and approved by the head of agency). Copies for foreign countries are to be approved by the head of agency conducting the trials and the customer
6	In case the previous indications for use of medicinal product are excluded
	6.1 New indications for use of the medicinal product;
	6.2 Samples of package and its drafts, indications for use and their electronic versions;
	6.3 Information approving necessity to exclude previous indications and methods of use (revealed additional side effects, results of use, clinical indications, decision accepted by the competent organ concerning exclusion of previously provided indications and methods of use) ;
7	In case of making changes concerning coloring, stabilizing substances, aromatizers included into the medicinal product or changes in tablets and capsules covering:
	7.1 Comparative information on biological availability of early registered and being registered medicinal product;
	7.2 Information confirming medicinal product stability;

	7.3 Pharmacopeia article on composition of early registered medicinal products and comparative table of quality indices determined in normative documents;
	7.4 Quality certificate for one series of medicinal product;
	7.5 New indication for use of medicinal product;
	7.6 Samples of package and its drafts, indications for use and their electronic versions;
8	In case of making changes to the normative documents on quality control over active ingredient, auxiliary ingredient or ready medicinal product:
	8.1 New normative documents;
	8.2 Comparative table of previous and following trials;
	8.3 Quality certificate of pharmaceutical substance, auxiliary ingredient and ready medicinal product;
9	In case of changes to the preliminary package and at the registration of another kind of package:
	9.1 Normative documents concerning new packaging material;
	9.2 Comparative table of quality indices proving medicinal product stability in the package changed within the shelf life and determined in the normative documents;
	9.3 Indications for use of medicinal product
	9.4 Samples of package and its drafts, indications for use and their electronic versions;
10	While making changes and amendments to the manufacturing process:
	10.1 Brief description of the previous manufacturing process;
	10.2 Brief description of the new manufacturing process with indication on the changes made;
	10.3 Normative documents project (if mixture combination is changed)
	10.4 Quality certificate on ready medicinal product;
11	In case of change of medicinal product shelf life:
	11.1 All information proving medicinal product stability based on normative documents indices;
	11.2 New indications for use of medicinal product;

	11.3 Samples of package and its drafts, indications for use and their electronic versions;
12	In case medicinal product storage conditions are changed:
	12.1 Comparative table of quality indices proving medicinal product stability in the package changed within shelf life and determined in normative documents;
	12.2 New indications for use of medicinal product;
	12.3 Samples of package and its drafts, indications for use and their electronic versions.
13	In case the method (way) of quality control over the pharmaceutical substance or ready medicinal product is changed the results of new method validation proving equivalence with previous method or advantage over it are to be presented;
14	In case the name of medicinal product or the address of the manufacturer are changed and at another registration of each regular manufacturing branch:
	14.1 Explanatory letter;
	14.2 Manufacturing license;
	14.3 Certificate of reliable manufacturing practice;
	14.4 Samples of package and its drafts, indications for use

6. Regulations and Registration of medicinal product in Belarus

6.1 Registration Regulations

Registration, reregistration and variations to the registration dossier of medicinal products in the Republic of Belarus are determined by Resolution of CM RB № 1269 from 02.09.2008 "On Approval of the Regulation on State Registration (Re registration) Of Medicinal Products and Pharmaceutical Substances and the Provisions on State Registration (Reregistration) Of Medical Purpose Products and Medical Equipment" Expert evaluation will be provided by UE "Center of expertise and testing in health care" (CETHC) for the state registration of medicinal products, pharmaceutical substances the applicant submits to the “CETHC” registration dossier in two copies.

While on drugs, pharmaceutical substances of foreign production registration dossier is submitted in a foreign language with translation into Russian or Belarusian

The Centre of Examinations and Tests in Health Service, Republican Unitary Enterprise (the Centre of Examinations and Tests) shall perform the set of works for arrangement of and execution of works for the state registration (re-registration) of drugs and pharmaceutical substances, as well as for the technical maintenance of the State Register of Drugs of the Republic of Belarus (State Register) and its annual publication.

The Centre of Examinations and Tests shall maintain record-keeping and storage of the documents related to the state registration (re-registration) of drugs and pharmaceutical substances, under the procedure stipulated by the laws[9].

The State Registration Of Drugs, Pharmaceutical Substances Includes The Following Actions: The Centre of Examinations and Tests accepts the registration file including the documents necessary for the state registration of drugs and pharmaceutical substances, the administrative procedures to be executed by the governmental bodies and other organizations in relation to legal entities and individual entrepreneurs, as approved by the Council of Ministers of the Republic of Belarus.

6.2 Categories of medicinal products which are subject to state registration:

- New (original) and generic drugs
- Other doses, dosage forms and new indications drugs
- New combinations of drugs

6.3 Registration Procedure:

1. For the state registration of drugs, pharmaceutical substances the applicant shall submit the registration file in duplicate to the Centre for Examinations and Tests. The registration file for the drugs, pharmaceutical substances of foreign manufacture are to be submitted in the foreign language with translation into the Russian or Belarusian language. The examination of the registration file shall be made[10]:
    - At the state registration of original drugs – by two experts, at the least, of the Drug Commission
    - At the state registration of generic drugs – by two experts, at the least, of the Drug Commission
    - At the state registration of pharmaceutical substances – by an expert (experts) of the Drug Commission.
2. The outcome of examination of the registration file is made as the expert opinion of each expert who has made examination. If comments are available in expert opinions, the Centre for Examinations and Tests shall:
    - Familiarize the applicant with contents of the expert opinions and with the list of comments (without names of the experts);
    - Appoint the time for correction which is not to exceed 30 calendar days from the date of familiarization of the applicant with the comments.

    On the base a written application of the applicant this time may be prolonged till 60 calendar days.

    The applicant must:
    - Inform the Centre for Examinations and Tests in writing about corrections under the comments and submit the necessary documents by the time stated in the third paragraph of the first part of this clause. After corrections under the comments the repeated examination shall be made, its time is not to exceed 10 calendar days;
    - Make corrections under the comments and (or) submit the additional information (materials) within 40 calendar days, at the latest, before expiration of the time for the administrative procedures, if the comments are available and (or) it is necessary to submit the additional information (materials) after the repeated examination.
    - The applicant's failure to make corrections under the comments by the time stated shall be the grounds for denial of the state registration (re-registration) of a drug.

3. The Drug Commission shall give the final conclusion which is to be made as the minutes of the sitting of this Commission. After completion of the works stated, according to their results, the Centre for Examinations and Tests shall submit the draft decision on the state registration of the drug, pharmaceutical substance or the draft decision on denial of the state registration of the drug, pharmaceutical substance, with the reasons stated, to the Ministry of Public Health within 30 days from completion of the works, at the latest.

   The draft decision on the state registration is to be enclosed with the Registration Certificate for the drug

4. Within 11 days from the date of submission of the documents, by the Centre for Examinations and Tests, the Ministry of Public Health shall take the decision on:
   - The state registration of drugs, pharmaceutical substances and entry of the information into the State Register;
   - Denial of the state registration of drugs, pharmaceutical substances.
5. The decision taken is to be made as the order of the Ministry of Public Health, and this order is to be sent to the Centre for Examinations and Tests within the five-day period from its date. If the decision on the state registration of a drug, pharmaceutical substance has been taken, the decision is to be enclosed with the documents stated in the Regulations.
6. The Centre for Examinations and Tests shall notify the applicant in writing within 10 days about the decision taken and necessity for the applicant to pay the established state due.
7. Upon receipt of the written information about the state registration of drugs and pharmaceutical substances from the Centre for Examinations and Tests the applicant shall pay the state due for the state registration of drugs, pharmaceutical substances, as established by the laws
8. Within 5 days, at the most, from the date of confirmation of the actual payment of the state due to the republican budget the Centre for Examinations and Tests shall enter the information about the drugs and pharmaceutical substances into the State Register and issue the following to the applicant:
   - The Registration Certificate;
   - The pharmacopoeia monograph, medical application guidance and (or) insert, model of graphic presentation of the package – for a drug of domestic manufacture;

- The authorization for use of the drug manufacturer's normative document containing the drug quality control indices and methods, medical application guidance
- The authorization for use of the pharmaceutical substance manufacturer's normative document containing the pharmaceutical substance quality control indices and methods – for a pharmaceutical substance of foreign manufacture.

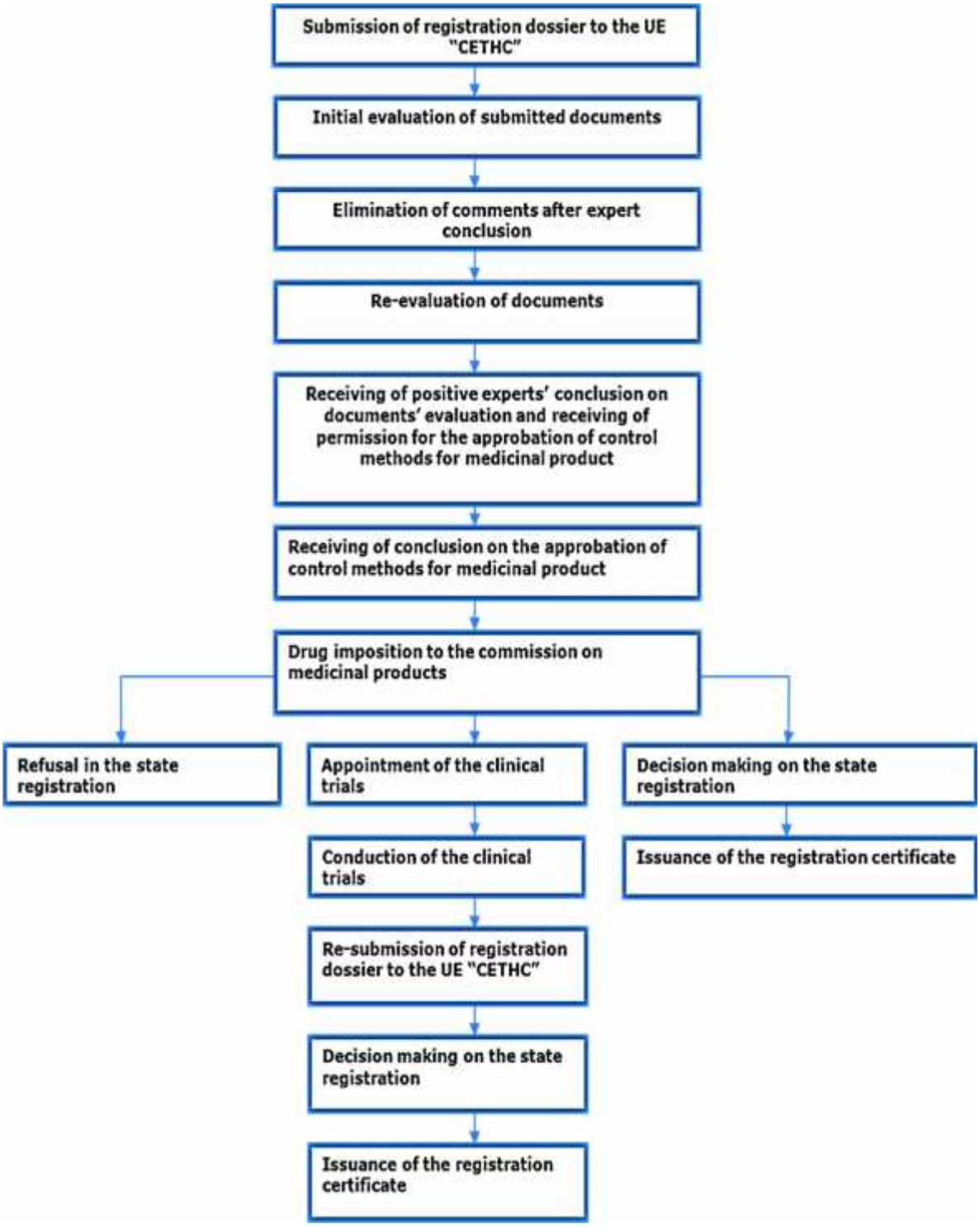
6.4 Denial of State Registration of Drugs

The Ministry of Public Health denies the state registration of drugs in the following cases:

- Availability of the substance not permitted for use in the Republic of Belarus, in the composition of the drug;
- The state registration (re-registration) of the drug registered earlier and entered into the State Register under a new name, provided that the existing registration of this drug is maintained;
- The state registration (re-registration) of the drug under the commercial name which has been registered earlier by other applicant and entered into the State Register;
- The applicant's failure to submit the documents stated in the course of the state registration (re-registration);
- Refusal to carry out the clinical trials appointed by the Ministry of Public Health or other trials stipulated by the laws;
- Availability of negative results of the clinical trials or other trials of the drug stipulated by the laws, in relation to the drug safety, efficacy and quality.

In the event of denial of the state registration (re-registration) of the drug, pharmaceutical substance the applicant may appeal against this decision under the procedure established by the laws.

Fig 3:Stages of the registration process in Belarus[10]



After the registration of medicines in MOH, the State Fee payment is done (for obtaining of the registration certificate) in sum established by the legislation of the Republic of Belarus. Registration certificate of medicines is valid for 5 years.

6.5 The list of documents submitted for state registration of drug

Table 7: The list of documents submitted for state registration of drug

S.No	Contents
1	Data on the official status of the drug:
	1.1. Document on the registration of the drug in the country where it is produced (certified copy);
	1.2. For medicines produced under license - permission from person, who issued the license (notarized copy);
	1.3. Manufacturing license or a document of the production of the drug in a Good Manufacturing Practice (GMP) (certified copy);
	1.4. Instructions for use of the drug and leaflet.
2	The short scheme of production process (synthesis) of a pharmaceutical substance. Documentation for the chemical, pharmaceutical and biological testing:
	2.1. The composition of the drug indication numbers of all ingredients, including excipients, colorants, flavors, stabilizers
	2.2. Brief scheme of production - a description of the process of production of the drug;
	2.3. Quality control of pharmaceutical substances and excipients;
	2.4. Data on the actual test at the intermediate stage of the manufacturing process,
	2.5. Quality control of the finished product;
	2.6. Information on the results of the validation of methods of quality control;
	2.7. Samples of quality certificates for pharmaceutical substances and finished medicine (one series);
	2.8. Samples of the packaging and brand labels in Russian or Belarusian;
	2.9. The results of stability testing of the drug (at least two series);
	2.10. Studies on bioavailability / bioequivalence (for generic drugs);
	2.11. Data to assess environmental risks relating to medicinal products containing genetically modified organisms.
3	Documentation on pharmaco-toxicological tests*(The documents referred to in paragraph 3, during the registration of generic medicines are not applicable.)
	3.1. Report on the toxicity study (after a single dose and repeated dose);

	3.2. Report on the study of reproductive function;
	3.3. Report on the study of embryonic, fetal and perinatal toxicity;
	3.4. Report on the Study of mutagenicity;
	3.5. The test report of carcinogenicity;
	3.6. Report on the study of pharmacodynamics;
	3.7. Report on the Study of pharmacokinetics;
	3.8. Report on the study of local tolerance (toxicity).
4	Documentation of clinical trials:
	4.1. Report on the clinical trials of the drug;
	4.2. Published data on the experiences of the drug;
	4.3. Safety report.
5	Sample of quality certificate of pharmaceutical substance provided by manufacturer.
6	Test protocol and the conclusion of an accredited testing laboratory for quality control of drugs of Belarus.

7. Regulations and Registration of medicinal product in Kyrgyz Republic

7.1 Registration Regulations

Registration, re-registration and variations for the registration dossier of medicinal products in the Kyrgyz Republic are determined by Article 35 of the Law from 30th April,2003 "On medicines" and Resolution of CM from 6th April, 2011 N 137 On approval of the Technical Regulations "On the safety of drugs for medical use."

According to the current law medicinal products can be made, sold and used on the territory of the Kyrgyz Republic only after the state registration procedure.

The aim of state registration procedure is the protection of the internal market from non-quality medicines.

The application (2 copies) and following documents to the Department of Drug Supply and Medical Technology at the Ministry of Health of the Kyrgyz Republic for the registration process[11]:

- Registration dossier (2 copies in the paper form and electronic format),
- Samples of medicines in sufficient quantity for the three-fold analysis of the test method and one the archival sample with the certificate of analysis;
- Reference standards, standard samples of drugs and impurities with the certificate of analysis of the manufacturer;
- Specific reagents (if necessary).

The registration period is 6 months (it does not include the time during which the manufacturer responds to requests).

Registration certificate of medicines is valid for 5 years.

7.2 The list of required documents for submission on the state registration (registration dossier)

Part I. Administrative Documents:

- Application;
- Document on the registration of the drug in the country where it is produced (certified copy or notarized copy);
- Document on the registration of the drug in the other country;
- Document of the production of the drug in a Good Manufacturing Practice (GMP) (notarized copy);

- Document of the safety of the drug (prion) for substances of animal origin;
- Certificate for the microorganism (used for vaccine production);
- Copy of the registration certificate (for reregistration process);
- Certificate of analysis (CoA) of the drug substances;
- CoAs of the three manufacturing batches or CoA of the one manufacturing batch with a letter of guarantee to provide CoAs of the next manufacturing batches;
- Draft instructions (in the paper form and electronic format);
- The color models of primary and secondary packaging labeled (in the paper form and electronic format);
- Samples of the drug.

Next, to test methods of quality drug may also be requested additional samples, reference substances with batch certificate, including the date of production, shelf life and storage conditions.

Part II. Chemical, pharmaceutical and biological documentation:

- Composition of the medicinal products;
- Description of manufacturing process and process controls;
- Batch formula;
- Validation of manufacturing processes;
- Container/closure system (with all CoAs);
- Specifications and analytical procedures of the control of medicinal product;
- Control of active substance(s) (specification and analytical procedures);
- Control of excipients (specification and analytical procedures);
- Methods for determining the stability of the medicinal product;
- The results of stability testing of the drug (at least 3 series);
- Information on the dissolution profile (solid dosage forms);
- Expert report on the chemical, pharmaceutical and biological documentation and / or the other additional information that confirms the quality.

Part III. Pharmacological and toxicological documentation:

- Toxicity:

* Toxicity study with a single dose;
* Toxicity studies with repeated administration;

- Reproductive function (fertility and general reproductive characteristics);

- Data regarding embryotoxicity and teratogenicity;
- Mutagenic potential;
- Carcinogenic potential;
- Pharmacodynamics (general pharmacodynamics and pharmacodynamic effects on proposed testimony);
- Drug interactions;
- Data on the pharmacokinetics;
- Local tolerance;
- Data on the allergenicity and the like;
- Information on the possible risk to the environment products containing genetically modified organisms (GMOs)
- For medicinal products of animal origin in the section should be given this additional information:

* Data on the type, age, diet of animals from which the raw stock;
* Data on the nature (category) of tissue taken as raw stock for the production
* Methods of control of raw materials, including methods to identify prions in the final vehicle (if necessary).

Part IV. Clinical documentation:

- Clinical Pharmacology (pharmacodynamics, pharmacokinetics);
- Clinical experience:

* Clinical trials Drug Application (reports of efficacy and safety);
* Post marketing experience;
* Published and unpublished data on clinical experience;

- Data on bioequivalence (for generic drugs)
- Periodic safety update reports (PSUR).

Note: * Data required only for registration of New medicinal product

The registration time period required is 6 months (it does not include the time during which the manufacturer responds to requests) and Registration certificate of medicines is valid for 5 years.

8. Regulations and Registration of medicinal product in Russia

8.1 Registration Regulations

State Regulatory Authority is called Federal Service on Supervision in Sphere of Public Health Services and Social Development ((RF MINZDRAVSOCRAZVITIYA).

RF MINZDRAVSOCRAZVITIYA takes the decision to register the product and issues Registration Certificate[12].

The expertise of all pharmaceutical products quality, efficacy and safety is done by National Center of Pharmaceutical Products Expertise (FGU).

The Russian regulatory system provides for certain control over the manufacturing process through a requirement to establish at the production plants in-house control laboratories which are inspected and accredited by the Ministry of Health. With Russia's transfer toward WTO accession, control over the manufacturing process in compliance with GMP standards has become important.

Russia's move to GMP is planned for 2005 and since new technical regulations on controlling pharmaceutical production through introduction of EU GMP standards are in the works and not yet ready, the Ministry of Health, has proclaimed an expensive voluntary certification of the manufacturing process as a means of effective control over production. At the same time, The Ministry of Health strongly supports the implementation of new certification rules for drugs, which was introduced in December 15, 2002. The new certification system was presented as a solution to such problems as low quality of drugs, incompliance of certain drugs with quality and safety requirements and counterfeits.

Drug registration–legislative acts[13].

The state structure that regulates registration issues structure, interaction with applicants. The first step of launching drug to the market of the Russian Federation is its registration. The registration is a state procedure of drug quality, efficacy and safety evaluation to obtain an approval for medical use of a drug in the Russian Federation.

The regulatory legal acts that regulate the medicinal product registration procedure[14]:

- Federal Law No. 61-ФЗ "On circulation of medicines" of April 12, 2010 (became effective on September 01, 2010).
- Order N 1413н of the Ministry of Health and Social Development of the Russian Federation «On approval of the Guidelines for contents and execution of documents required for creation of the Registration Dossier for a pharmaceutical product for medical use for the purpose of its state registration» of November 23, 2011.
- Order N 750н «On approval of the rules of pharmaceutical product for medical use evaluation and the form of an expert committee opinion» of August 26, 2010.

Fig 4: Structure of State Regulatory Authorities

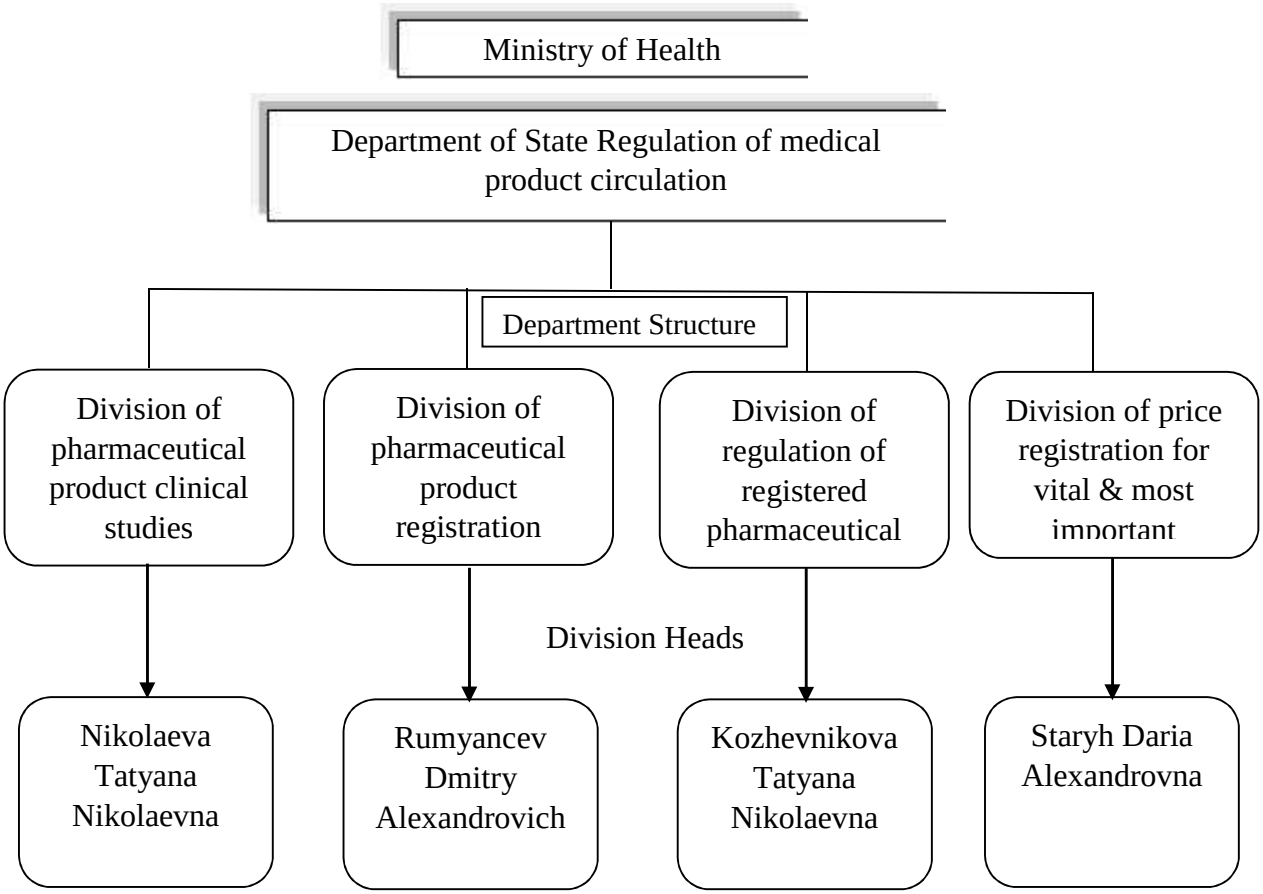


Fig 5: Registration Certificate Issuing Authority

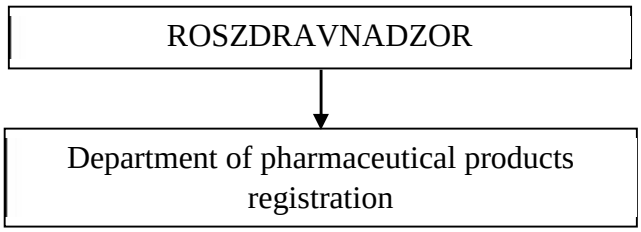
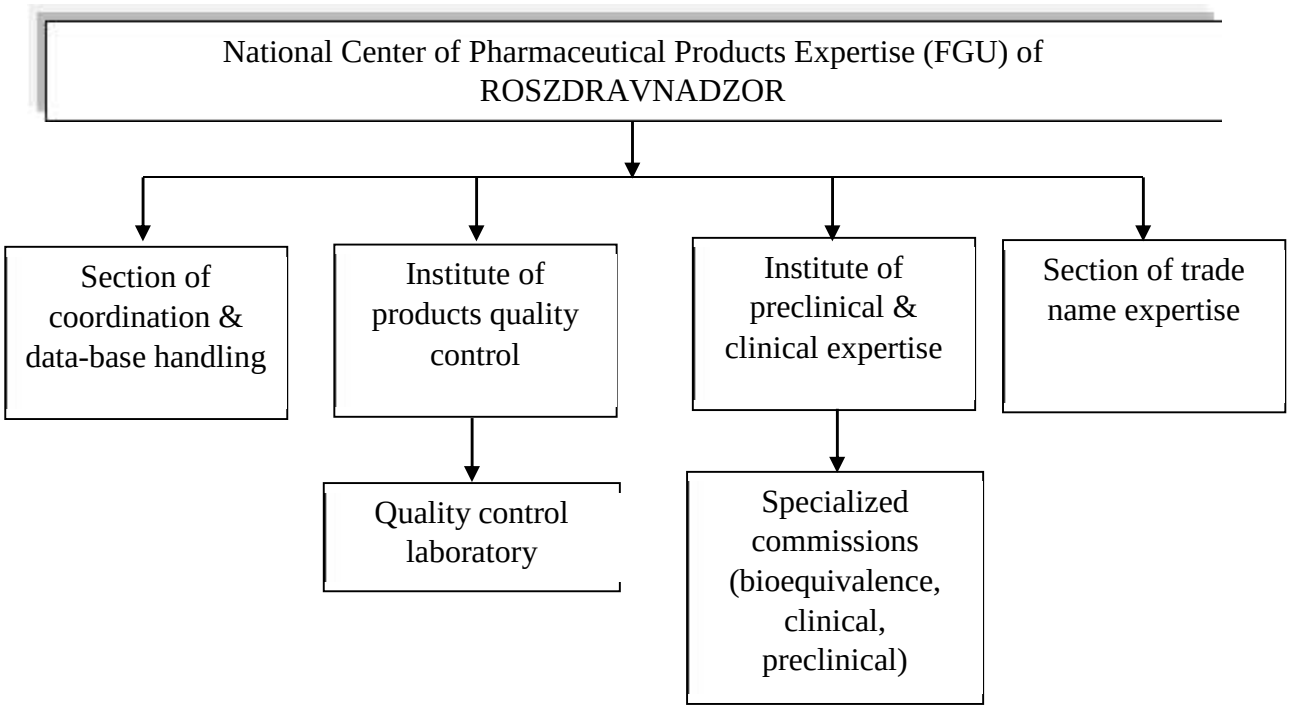


Fig 6: Pharmaceutical Products Efficacy and Safety Expertise Authority



8.2 The following medicinal product (MP) categories are subject to state registration[15]:

1) Original pharmaceutical products;
2) Generic pharmaceutical products;
3) New combinations of earlier registered pharmaceutical products;
4) Pharmaceutical products registered earlier but manufactured in other pharmaceutical forms, new strengths.

The following products are not subject to state registration:

1. Medicinal products made by pharmacies,
2. Medicinal (herbal) plant raw materials;
3. Medicinal products purchased outside the territory and intended for personal use;
4. Medicinal products intended for export;
5. Radiopharmaceutical medicinal products made in medical institutions directly.

8.3 Registration Procedure

Despite several positive developments to more openness and predictability, the registration procedure for Pharmaceuticals in Russia still lacks clarity and transparency. In addition, cultural and language barriers often become a challenge to foreign companies attempting to register pharmaceuticals by themselves without appropriate legal advice or help from experienced distributors or consultants[13, 16].

The Ministry of Health has launched a new web site devoted to regulatory issues: www.regmed.ru. It is a significant step forward because it publishes the list of documents necessary for registration of pharmaceuticals and provides contact information for the Division of Registration of Drugs, Pharmaceutical Substances and Immune biological Medical Preparations, which is the main Ministry of Health's office responsible for oversight of the registration procedure. However, the site does not have an English version. The registration procedure begins with the signing of a contract with and submission of number of required documents to a special entity affiliated with the Ministry of Health the Federal State Enterprise "Scientific Center for Expert Assessment of Medical Products". The "Center" conducts reviews and expert assessments of the registration documents and directs all required stages of the registration procedure.

The "Center" works in close cooperation with a number of expert committees, including the Pharmacology and Pharmacopoeia Committees, and the Committee on Ethics, as well as research institutes on conducting reviews of the documents, pre-clinical, clinical, toxicological, laboratory and other tests required for registering a drug. The cost of registering one foreign drug is $12,000 while the fee for a domestically made drug is $6,000.The registration is valid for 5 years.

Usually registration is a time consuming process and may take up to a year or more to complete. This fee does not include the cost of trials, which might be assigned to a drug. The registration certificate is issued by the Department of State Control over Drugs and Medical Equipment of the Ministry of Health. The registration cannot be done by phone, e-mail or any type of correspondence. A foreign manufacturer should perform registration either through an authorized agent or distributor, in-house Russian-speaking registration personnel or a regulatory contact permanently based in Russia. Registration involves establishing direct contact and diligent work with an expert from the above mentioned "Center".

The registration procedure consists of 4 sequential stages[16]:

1. Creation of a Registration dossier including documents necessary for clinical study initiation, and submission of the Registration dossier to the Ministry of Health of the Russian Federation.
2. Obtaining permission for the conduct of a clinical study in the Russian Federation.
3. Drug quality evaluation and evaluation of the expected benefit to possible risk ratio which is done after the clinical study of a drug:

a. Drug quality control at the FSBI SCEMP's laboratory and approval of a normative document (specification and analytical procedures);

b. Evaluation of the expected benefit to possible risk ratio and approval of Instruction for medical use of a drug.

4. Decision by the Ministry of Health of the Russian Federation on registration of the pharmaceutical product, it's entering in the State Register of pharmaceutical products and marketing authorization issuance.

STAGE 1. Creation of a Registration dossier

To apply for registration of a medicinal product, it is necessary to draw up a Registration dossier.

Document execution requirements:

All documents must be submitted in Russian or have a certified translation into Russian.

The documents are certified as follows:

A) The documents issued by official designated authorities of a foreign state (CoPP, GMP, manufacturing license, power of attorney, contracts) must be always legalized – by means of consular certification or apostille.

B) The documents prepared by the manufacturer (certificates of analysis, stability study reports) – original documents or their copies signed by the manufacturer's authorized person and sealed.

C) Pre-clinical and clinical study reports – original documents or their copies are submitted which must be seen and numbered and then signed and sealed on the last page by an authorized person.

D) Such documents as validation reports, description of manufacturing process, specifications and analytical procedures – copies of these documents are submitted.

STAGE 2: Obtaining permission for the conduct of a clinical study in the Russian Federation.

One of the main modifications introduced on September 01, 2010 in the registration procedure is that all pharmaceutical products must always undergo clinical studies during the registration process in Russia. The only exclusion that exempts from the obligation to perform a clinical study in the Russian Federation is when there is an analogous drug registered in Russia more than 20 years ago and it is impossible to conduct a bioequivalence (BE) study for this drug (e.g. metronidazole solution for infusions 5 mg/ml the original drug was first registered in Russia in 1982, i.e. more than 20 years ago, and no BE study is possible for this drug as it is intended for parenteral use; pancreatine tablets the drug was first registered more than 20 years ago, and no BE study is possible for this drug as it is not absorbed in the systemic circulation and is active in the GI tract). Such pharmaceutical products skip registration stage 2 (clinical/BE/therapeutic equivalence study) and after the Registration dossier is submitted to the Ministry of Health of the

Russian Federation, the pharmaceutical product skips directly to the third stage of registration.

STAGE 3: Drug quality evaluation and evaluation of the expected benefit to possible risk ratio which is done after the clinical study of a drug

The Ministry of Health of the Russian Federation makes a decision on a pharmaceutical product registration based on results of evaluations performed by the lower institution the Federal State Budgetary Institution “Scientific Center for Evaluation of Medicinal Products" of the Ministry of Health of the Russian Federation (FSBI SCEMP (www.regmed.ru). The FSBI SCEMP evaluates the proposed drug quality control methods and quality of submitted samples of a drug, and also evaluates the expected benefit to possible risk ratio which is done after the clinical study of a drug. To date, the FSBI SCEMP of the Ministry of Health of the Russian Federation has been prohibited to render services on pharmaceutical product evaluation directly to applicants in the course of the registration process. As a budgetary institution, the FSBI SCEMP only performs evaluations for the Ministry of Health of the Russian Federation upon receipt of their instructions.

For interaction with applicants, a new state portal grls.rosminzdrav.ru was created. The portal contains public (accessed without a password) and restricted information (accessed via a personal account protected by a password assigned). The public information is the State Register of pharmaceutical products and the State Register of selling price limits.

3a. Drug Quality Control at the FSBI Laboratory

After the clinical study is terminated, the applicant submits a report on the clinical study results together with a state duty payment receipt (225000 rubles) and an application for renewal of the state registration procedure to the Ministry of Health of the Russian Federation. The registration procedure is renewed and the Registration dossier is forwarded to the evaluation institution of the Ministry of Health of the Russian Federation FSBI SCEMP (www.regmed.ru) to perform drug quality evaluation and evaluation of the expected benefit to possible risk ratio of a drug. The second important modification introduced in the registration procedure on September 01, 2010 refers to prohibition of communication between the manufacturer’s representatives and experts of the FSBI SCEMP. The registration process stages are reflected in the applicant’s personal account

accessed on-line on the website of the Ministry of Health of the Russian Federation (grls.rosminzdrav.ru). All inquiries are answered via the on-line personal account with provision of a paper version through the forwarding department of the Ministry of Health of the Russian Federation.

The amount of drug samples, reference materials and chromatographic columns necessary for testing could be seen on the site of Scientific Center (www.regmed.ru) after submission to this Scientific Center of the Power of Attorney.

To import drug samples and reference materials, it is necessary to obtain an Import License for an unregistered drug which is issued by the Ministry of Health of the Russian Federation. Such Permission is issued free of charge.

The Import License» is a document authorizing the import of an unregistered batch of a pharmaceutical product to evaluate its quality for the purpose of registration or clinical studies. This License does not exempt the shipper from customs clearance of the imported product. A customs broker's assistance is required for the customs clearance. The period during which the samples may be imported is 1-2 months (taking into account the period of obtaining the Import License).

3b. Evaluation of the expected benefit to possible risk ratio and approval of Instructions for medical use.

Based on Registration dossier, data of the drug clinical study conducted in the Russian Federation and on experience of medical use of the drug, the FSBI SCEMP experts evaluate and correct the draft Instructions for medical use of a drug, and give their opinion on drug efficacy and safety.

STAGE 4. Decision by the Ministry of Health on registration of the pharmaceutical product.

The evaluation institution (FSBI SCEMP) forwards the expert opinion with results of evaluations performed (3a and 3b) to the Ministry of Health of the Russian Federation. In case of the positive opinion, the experts of the Ministry of Health of the Russian Federation enter a drug in the State Register of medicinal products and issue a Marketing Authorization. If the drug quality or efficacy/safety cannot be confirmed by results of the evaluation performed, a decision to refuse the state registration of a drug is issued.

The Marketing Authorization is issued for 5 years for a pharmaceutical product first registered in Russia. Upon expiration of this period, the manufacturer applies for confirmation of drug registration, thereafter the Marketing Authorization is issued for an unlimited period of time.

Registration Timeframe

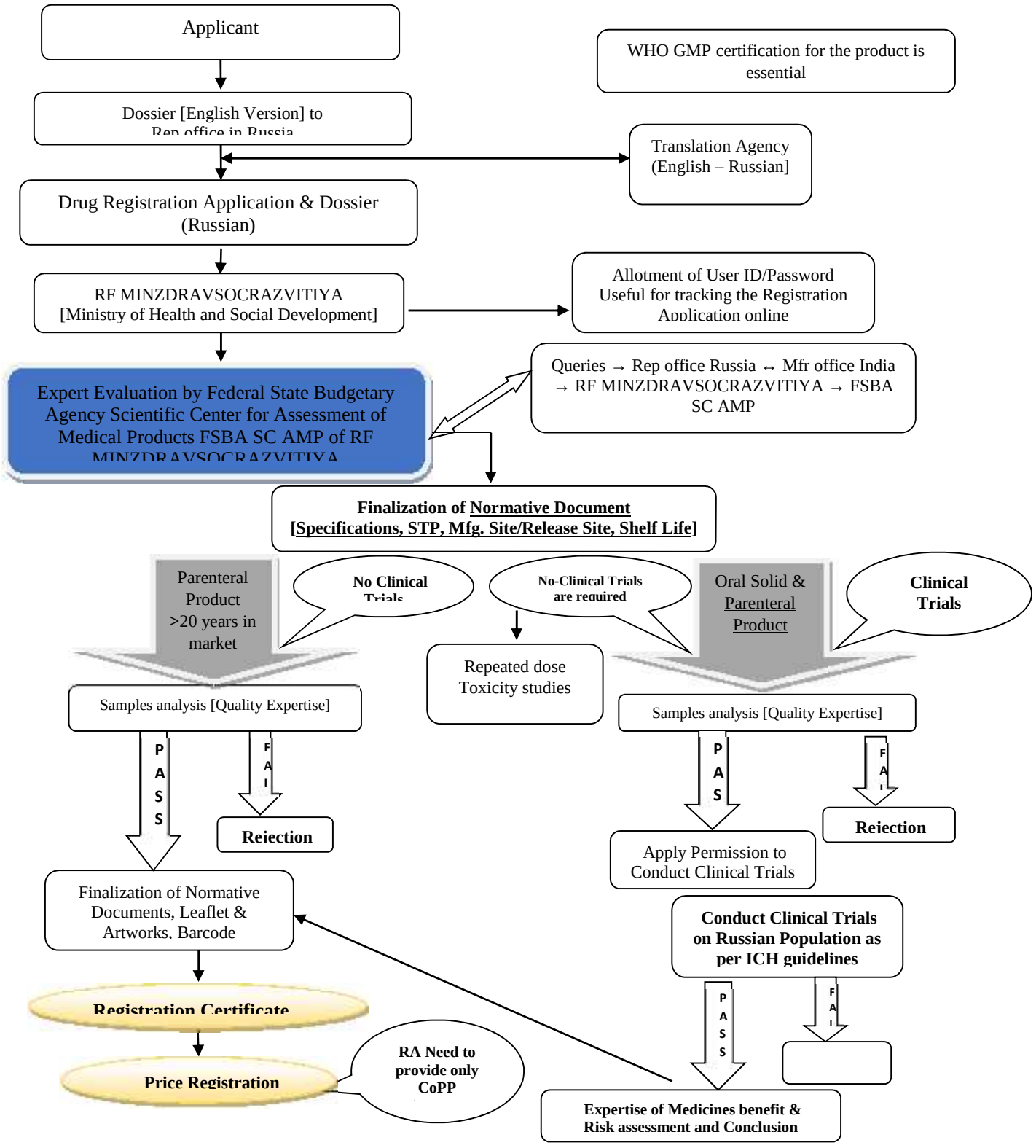
On circulation of medicines, the period of the registration procedure is 210 working days. This period does not include the time required for conduction of a clinical study. The total registration period for a medicinal product that requires a clinical study in the Russian Federation is at least 18 months. The total registration period for a medicinal product that does not require a clinical study in the Russian Federation is at least 9 months.

The total registration period for a medicinal product that does not require a clinical study in the Russian Federation is at least 9 months:

Fig 7: Registration Timeframe for generic product in Russia

STAGE I	STAGE II	STAGE III	STAGE IV
Creation of DMF including documents required for clinical study initiation & submission of the DMF to the MoH & social development of the Russian Federation	-	Drug quality & evaluation of the expected benefit to possible risk ration performed after the clinical study of the drug	Decision by MoH & social development of the Russian Federation on inclusion of the drug in the state register of medicinal products & marketing authorization
1 month	-	5.5 months	3 months

Fig 6: Registration procedure In Russian Federation



8.4 Rejection of Registration of Drugs

Authority of the federal registration denies registration of drugs in the following cases:

- Availability of the substance not permitted for use in the Russian federation
- The applicant's failure to submit the documents stated in the course of the federal registration (re-registration)
- Refusal to carry out the clinical trials appointed by the Ministry of Health or other trials stipulated by the laws

8.5 The list of necessary documents for the registration of foreign drugs in the Ministry of Health of Russian Federation

1. Application for the State registration of a pharmaceutical which includes the name of the pharmaceutical preparation, the name and the contact information for the manufacturer
2. The name of the pharmaceutical preparation, including international non-proprietary name, scientific name in Latin, trade name and main synonyms
3. List of active ingredients and components
4. Recommended dosage, instruction for use
5. Description of the drug and its packaging, shelf life and storage conditions
6. Power of Attorney issued by the manufacturer to the authorized company for carrying out registration procedure (notarized original with apostil)

Certificates:

7. A copy of the Free Sales Certificate (must be notarized and apostilled)
8. A copy of the license of pharmaceutical manufacture (must be notarized and apostilled)
9. A copy of the GMP certificate (must be notarized and apostilled)
10. A copy of the Certificate of manufacturer registration in their own country (must be notarized and apostilled)
11. The original Certificate of analysis of the drug and its active substance (must be signed and stamped by manufacturer)
12. A copy of the Certificate of trade mark (must be signed and stamped by the manufacturer)

13. Information of registration of the drug in the country of manufacture and other countries

Information and test reports:

14. The summary of method of the drug manufacturing (must be signed and stamped by manufacturer)
15. The complete description of the quantitative and qualitative control methods with references to the pharmacopeia and specification (must be signed and stamped by manufacturer)
16. Stability data of three drug series - by date
17. Patterns of the spectrums and chromatograms of the drug
18. Report of the pharmacological (specific) activity study substantiating the indications for use which are formed and described in the instruction
19. Test report of the drug toxicity (acute, sub-acute, sub chronic, chronic toxicity)
20. Test report of the specific influences (cancerogenity, mutagenic and teratogenic effects, embryo-toxicity, allergic and local-irritative effects)
21. Clinical trial report of the medicine usage in clinic (the information which concerns only the drug which is produced by this manufacturer)
22. Copies of publications of the medicine usage in clinics after its registration in the country of origin (the information which concerns only the drug which is produced by this manufacturer)
23. Report of pharmakinetics of the pharmaceutical study and its bioequivalence to the original drug
24. The summary information of the side effects, in comparison with other analogous medicines, used at the same indications
25. Instruction for use (must be signed and stamped by the manufacturer)

Samples and package:

26. Information of the material used for package: Certificates of the packaging materials (must be signed and stamped by the manufacturer)
27. The colour design of internal and external packages (Original and Russian version)
28. Samples of active substance for quality control
29. Standard and referenced samples of the drug for the binding examination of quality (must be in the standard package).

The documents necessary for registration include a certificate of analysis of the drug in the country of origin of the manufacturer, GMP certificate and information on registration of the drug in the foreign country.

8.6 Registration Fee

The cost of registration of one medicinal product that does not require clinical studies in the Russian Federation due to the existence of an analogous drug registered in the Russian Federation for more than 20 years and impossibility to perform its bioequivalence study:

State duty	Creation of registration Dossier	Pre-Clinical studies	Clinical study	Samples, Reference materials, Columns, & their import
30,000 rubles	400,000 rubles	15,000-450,00 rubles	Not required	50,000-100,000 rubles

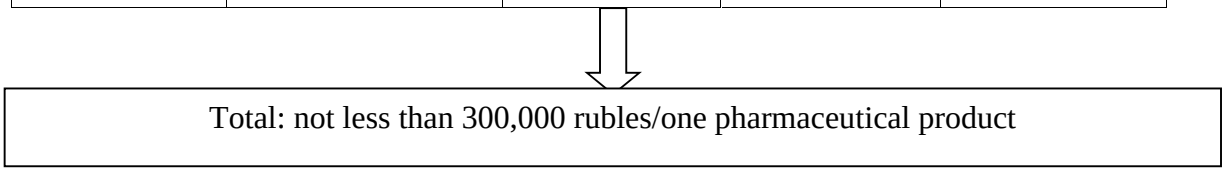


Fig 7: Fees for Registration in Russian Federation

9. Regulations and Registration of medicinal product in Turkmenistan

9.1 Registration Regulations

Medicines are approved for use in Turkmenistan only after their state registration, except as provided in the Law of Turkmenistan on pharmaceuticals and drug supply. Feature of the registration system of medicines in Turkmenistan is the proximity to the registration requirements and rules that is in the most CIS countries.

Medicines are approved for use in Turkmenistan only after their state registration, except as provided in the Law of Turkmenistan on pharmaceuticals and drug supply[17].

State registration of medicines is provided by the Ministry of Health and Medical Industry of Turkmenistan or its authorized body.

Medicines which are registered in Turkmenistan will be included to the State register of medicines the list of medicines permitted for use in Turkmenistan. Maintaining and edition of the State register of medicines is made by the Ministry of Health and Medical Industry of Turkmenistan.

9.2 The following medicinal product (MP) categories are subject to state registration:

1) Original pharmaceutical products;
2) Generic pharmaceutical products;
3) New combinations of earlier registered pharmaceutical products

9.3 The procedure of state registration.

1. State registration of medicines is performed on the basis of written application to the Ministry of Health and Medical Industry of Turkmenistan or its authorized body. To written application for registration of the medicine in appropriate cases are attached:

- ✓ Samples of medicinal product in the proposed packaging, its name, trade name;
- ✓ The name and address of the medicine manufacturer
- ✓ Manufacturing license of the medicine;
- ✓ Name of the active substance (synonyms)
- ✓ Release form, conditions of release;
- ✓ The composition of the medicine;
- ✓ Methods of application, indications and contraindications;
- ✓ Terms and conditions of storage;
- ✓ Data on the registration of the medicine in other countries;
- ✓ Materials of pre-clinical and clinical studies;

- ✓ Normative documents of the medicinal product;
- ✓ Quality certificate;
- ✓ Document confirming the payment of the registration fee.

Registration fees are determined by the Ministry of Health and Medical Industry of Turkmenistan as agreed with the Ministry of Economy and Finance of Turkmenistan

2. Upon results of evaluation of materials the Ministry of Health and Medical Industry of Turkmenistan or its authorized body in the three-month period will make decision to register or to refuse in registration of the medicine.

3. The medicines which are registered will be assigned registration number and the applicant will be issued a certificate which indicates duration, during which the medicine is permitted for use in Turkmenistan. The decision on registration is approved also the normative documentation for the medicine.

4. Medicinal product can be used in Turkmenistan for five years from the date of its registration. At the request of the applicant for registration of medicinal product, the prescribed period, during which it is permitted to be used on the territory of Turkmenistan, under the decision of the registering authority may be reduced

5. Upon the expiration period within which the registered medicinal product was authorized for use in Turkmenistan, the medicine may be used again only after re-registration.

6. In case of revealing inconsistencies in medicinal product requirements to normative documentation Ministry of Health and Medical Industry of Turkmenistan or its authorized body may decide to fully or temporary decline its usage

7. Medicines manufactured in pharmacies by prescription and ordered by medical institutions authorized for use of active substances and excipients are not subjected for state registration.

8. Submitted for registration documents, expert conclusions, copies of registration certificates and other relevant documents will be stored in the registration authority.

9.4 Documents required for the state registration

Table 8: List of required documents for registration of medicines (substances) in Turkmenistan

S.No	Contents
1	Application for state registration in the approved form. Summary (generic) certificate preparation containing briefly summarized information on each of the following items.
2	Certificate for pharmaceutical product as recommended by the WHO, if not available Certificate (Registration Certificate) of registration in the country of origin and in other countries (notarized).
3	Certificate confirming manufacturing of the medicine in conditions of GMP (notarized).
4	State license for pharmaceutical activity (notarized).
5	Summary of product characteristics (SPC) in English and Russian languages.
6	Draft Instruction for medical use in Russian language.
7	Color models of packaging and labels in paper form.
8	Qualitative and quantitative composition of the medicinal product.
9	Document confirming the quality of the finished product of 1 series (certificate of analysis).
10	Approved standard technical documents for quality control and safety of medicinal product in Russian language.
11	The results of stability testing
12	The data on bioavailability, bioequivalence.
13	Data on clinical pharmacology. Results of clinical trials, scientific publications and reports.
14	Periodic safety update reports (reregistration).
15	Samples of medicinal product in the package in an amount sufficient for the three-fold analysis.
16	Standard samples in an amount necessary for the three-fold analysis.

9.5 Registration fees

Registration fees are determined by the Ministry of Health and Medical Industry of Turkmenistan as agreed with the Ministry of Economy and Finance of Turkmen.

Registration terms depending on the type of products range from 4 to 6 months.

10. Regulations and Registration of medicinal product in Uzbekistan

10.1 Registration Regulations

Registration, re-registration and variations to the registration dossier of medicinal products in the Republic of Uzbekistan is regulated by Instruction "Order of examination, clinical trials, registration and re-registration of drugs and substances of foreign countries and CIS countries" from 3rd August,1998.

This Instruction defines the organization and conduction of examination, clinical trials, registration and re-registration of drugs and foreign substances (active substances) in the Republic of Uzbekistan.

Before exporting a pharmaceutical product to Uzbekistan it has to be registered at the Ministry of Health of Uzbekistan. In fact, it is the Department for registration of pharmaceuticals which is accountable for the registration procedure[18].

Uzbekistan still has its own, unique regulatory system which does not correspond to U.S. or EU practices. Not only do cultural and language barriers often become a challenge to foreign companies attempting to register pharmaceuticals by themselves; it is also the registration procedure which is quite complicated and the documents tend to be modified due to constant changes in the regulatory requirements[19].

10.2 Following Pharmaceuticals subject to the State Marketing Authorization

- Treatment and prophylactic medicines, diagnostic tools, health food and parapharmaceuticals ;
- Pharmaceutical substances and biologically active additives used in drug manufacturing;
- New combinations of authorized drugs;
- Drugs in new doses, dosage forms and compositions or innovative technology medicines;
- Generics;
- Health Care products.

Medicines produced in the pharmacies (own-name preparations) do not require authorization.

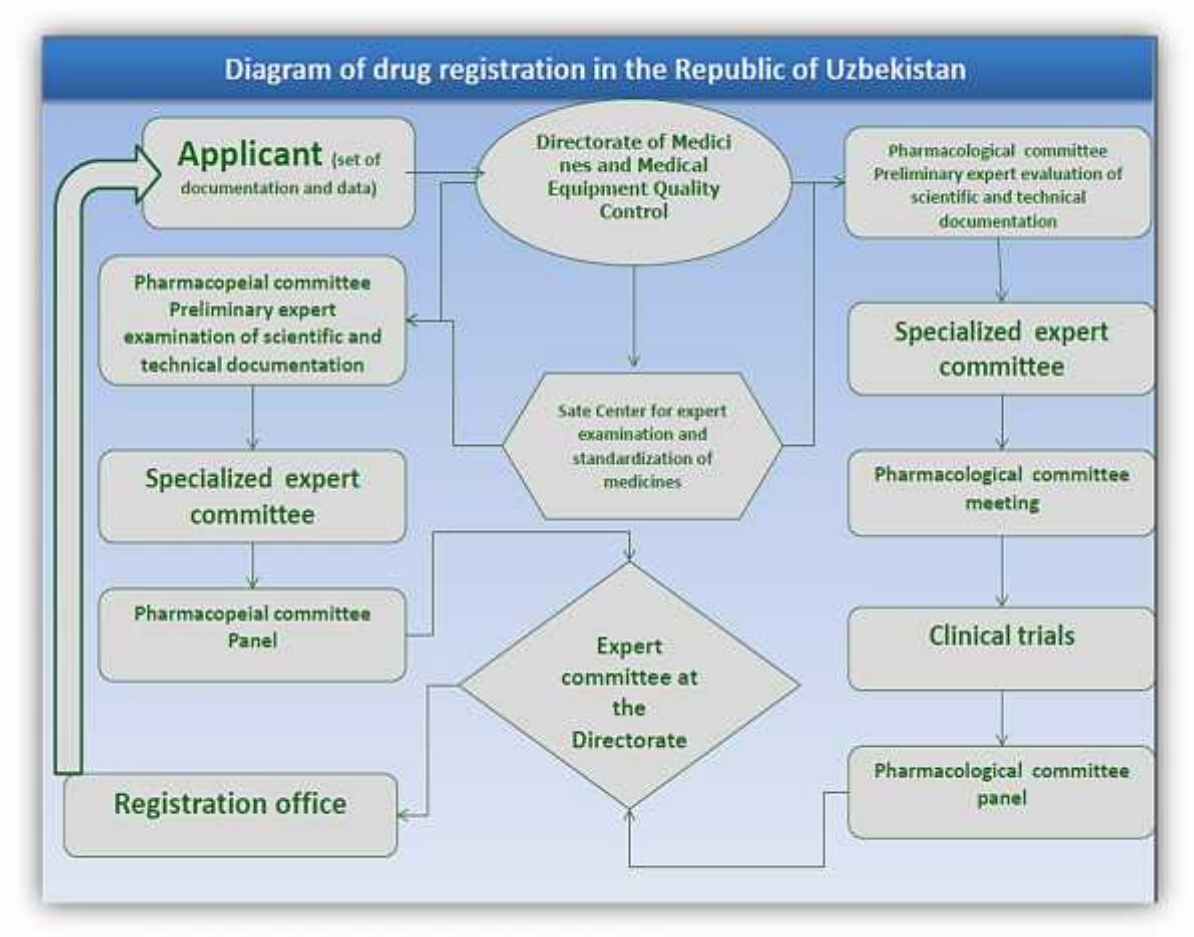
Instruction is mandatory for organizations engaged in examination, clinical testing, registration and re-registration of drugs and foreign substances.

10.3 Registration Procedure

In accordance with the legislation of the Republic of Uzbekistan all drugs (substance) can be purchased for the purpose of medical use, before they have to be registered in the prescribed manner by the Ministry of Health of the Republic of Uzbekistan.

1. Foreign manufacturers wishing to register drug (substance) in Uzbekistan, sends the letter of presentation in 2 copies and the documents for the drug (substance) to the General Directorate for the quality control of medicines and medical equipment (hereinafter GDQC).
2. Depending on the drug the applicant company has to submit the documents and samples in accordance with respected regulations
3. Re-registration of the drug (substance) is due to the expiration of the registration period (5 years).
4. For re-registration of the drug (substance) the applicant company will submit the documents till the expiration date. In case of change in the name of the drug, country of origin, company or normative analytical documentation (NAD) documents provided.
5. After receiving the documents and samples of drug (substance), declared for registration (re-registration) the contract is made between the applicant and the National Center for examination and standardization of drugs (the NCES) for payment of registration (re-registration), which is signed by the head of departments.
6. The beginning of the registration starts after the receipt of payment the registration fee in accordance with the signed agreement.
7. In case of refusal for registration (re-registration) based on the results of the examination the fee to the applicant company is not returned. If the company within 60 days does not pay, the contract will canceled.

Fig 9: Drug registration in the Republic of Uzbekistan[18]



State registration of drugs is to be performed within no more than six months after the application to the registration authority[20].

9. The General Directorate for the quality control of medicines and medical equipment (GDQC) directs to:
   - ✓ The Pharmacological Committee - Pharmacological study document reports in 1 copy, and 3 packages of the drug;
   - ✓ The Pharmacopoeia Committee - documents according to the application in 1 copy and 1 package of the drug;
   - ✓ The Committee on Drug Control Documents in the case of control means;
   - ✓ In the NCES the documents in 1 copy and the number of samples of the drug required for conduction of the 3-time analysis
   - ✓ The Bureau for Registration of medical, preventive, diagnostic and medical equipment (the Bureau of registration)- documents 1 copy.

10. In the Pharmacological Committee the experts (three, one of whom is a member of the Presidium of the Pharmacological Committee) conduct an examination of the documents within 10 days from receipt of materials.
11. Expert conclusion is considered in the Presidium of the Pharmacological Committee and on the basis of experts' conclusion and decision of the Presidium the drugs are determined that can be registered without clinical trials and the medicines for which clinical trials or tests for bioequivalence are required and clinical bases are appointed.
12. Presidiums decision is registered in the protocol within 15 days after the meeting, signed by the chairman of the committee and approved by the chief scientific secretary of the Office.
13. The decision to conduct clinical trials or tests for bioequivalence of the drug will be reported to applicant - company, which will, within 30 days after receipt of the decision submit to the Pharmacological Committee the Clinical Trial Protocol - 4 copies in Russian and samples of the drug (s) sufficient for testing on 90 patients and in the case of test for bioequivalence - samples of the drug and the reference drug (s) sufficient to test for 12 patients of each drug. If the company - applicant do not submit samples of the drug for clinical trials within 6 months after receipt of the decision to conduct the clinical trial, the Committee may suspend the registration. In this case, the documents and payment will not be returned.
14. In the case of first-controlled medicines the documents are reviewed by the Committee on Drugs and the conclusion of the feasibility of registration are passed the Pharmacological Committee.
15. All clinical trials of foreign drugs are conducted on a contract basis, in accordance with the approved calculation. Calculation for clinical trials is approved by the Presidium of the Pharmacological Committee.
16. Mandatory conduction of clinical trials and bioequivalence testing for new pharmacological treatments and medicines produced under license and not registered in the Republic of Uzbekistan, by the licensee, as well as herbal medicines and natural origin that were not used previously in the Republic of Uzbekistan.
17. Without clinical trials (based on examination of the documentation and analysis of samples) may be registered:

- Medicines (used in medical practice for at least 5 years), registered in several countries, as well as mandatory in the manufacturer country (with a certificate of quality and the evidence of clinical effectiveness and safety of the proposed drug);
- Medicines produced under license and that are registered in the Republic of Uzbekistan by the licensee (with a letter of guarantee from the licensor about the drug safety).
- Generics, approved for medical use in the country of origin, as well as manufactured and registered in one or more countries (with bioequivalence studies).

18. Reports on the results of clinical trials are presented only in the Pharmacological Committee without the right to transfer it to the company prior before the decision made by the Pharmacological Committee.
19. Decision on the recommendation for medical use and registration of the foreign drug is taken at the meeting of the Pharmacological Committee or its Presidium on the basis of Experts' conclusion, the results of clinical trials and the analysis of samples and will be made as the protocol within 15 days after the meeting.
20. The protocol is signed by the chairman of the Pharmacological Committee and Scientific Secretary and after approval is transferred to the administration.
21. Excerpts from the protocol are signed by the Chairman of the Pharmacological Committee and Scientific Secretary and forwarded to the Administration within 5 days after approval.
22. Examination of normative - technical documents for the drug (substance) is conducted by Pharmacopoeia Committee within 30 days in the presence of the drug protocol analysis.
23. The decision about the possibility of assessing the quality of the medicine according and the recommendations provided by the NAD for the registration is accepted by the Presidium of Pharmacopoeia Committee and is registered in the protocol.
24. The protocol is signed by the chairman of Pharmacopoeia Committee and Scientific Secretary and is approved by the Head of Administration.
25. Excerpts from the protocol are signed by the chairman of Pharmacopoeia Committee and Scientific Secretary and is forwarded to the Administration and to the Pharmacological Committee within five days after the approval of the protocol.
26. Pharmacopoeia Committee prepares NAD for approval of the medicine for follow-up control within 6 months.
27. The Center conducts the quality control and testing of samples of NAD within three months of all drugs (substances), submitted for registration in the Republic of Uzbekistan.

28. Conclusion on the results of quality control of samples, signed by the Head of laboratory and approved by the Director of the Centre are transferred to the Pharmacological and Pharmacopoeia committees.
29. The Administration has the right to suspend the registration of the drug (substance), if the company - applicant within 90 days does not answer on the requests of the Administration, as well as in case of the no conformity results of analyzes to requirements of NAD. Documents and the registration fee are not refundable.
30. The decision on registration of the drug (substance) is accepted by the Expert Council of the Administration on the basis of recommendations of the Pharmacological and Pharmacopoeia Committees and the conclusion of the Centre.
31. The decision on re-registration (as well as the permission for one-time use of drugs received as humanitarian aid) is taken at the meeting of the Commission on the advice of Pharmacopoeia Committee for re-registration of the drug and is approved by the Head of Administration.
32. The Registration Bureau under the authority of the Administration within 10 days executes official registration certificate and proof of re-registration and transmits it to the signature of the Head of the Administration.
33. The Registration Bureau sends registration certificate, proof of re-registration to the applicant company.
34. The validation period of the registration certificate is 5 years with a possible subsequent re-registration.
35. Pharmacopoeia Committee sends a copy of the approved NAD to the Centre within 10 days, other organizations responsible for monitoring of the drugs quality (substances), within 6 months after registration.
36. For variations and amendments in NAD the company applicant will send to the Administration an application indicating the motive of making changes and additions and documents proving the necessity of their introduction - 2 copies in Russian, and 2 copies of the English language.
37. The Administration sends the documents to:
    - The Pharmacological Committee - 1 copy;
    - The Pharmacopoeia Committee - 1 copy;

38. Pharmacological and Pharmacopoeia Committees within two months in the prescribed manner by the Presidium will decide whether to make changes and additions and report it to the Administration.
39. The Administration informs the Registration Bureau and the company - applicant about made decision.

10.4 For the registration procedure a company has to submit the following documents:

1. General documents:

- Application for the State registration of a pharmaceutical which includes the name of the pharmaceutical preparation, the name and the contact information of the manufacturer
- Name of the pharmaceutical preparation, including international non-proprietary name, scientific name in Latin, trade name and main synonyms
- List of active ingredients and components
- Recommended dosage, instruction for use
- Description of the drug and its packaging, shelf life and storage conditions
- Power of Attorney issued by the manufacturer to the authorized company for carrying out registration procedure (notarized original with apostil)

2. Certificates:

- Copy of Free Sales Certificate (must be notarized and apostilled)
- Copy of the license of pharmaceutical manufacture (must be notarized and apostilled)
- Copy of GMP certificate (must be notarized and apostilled)
- Copy of Certificate of manufacturer registration in their own country (must be notarized and apostilled)
- Original of Certificate of analysis of the drug and its active substance (must be signed and stamped by manufacturer)
- Copy of Certificate of trade mark (must be signed and stamped by the manufacturer)
- Information of registration of the drug in the country of the manufacture and in other countries

3. Information and test reports:

- Summary of the method of the drug manufacturing (must be signed and stamped by manufacturer)
- Complete description of the quantitative and qualitative control methods with references to the pharmacopoeia and specification (must be signed and stamped by manufacturer)
- Stability data of three drug batches – by date
- Patterns of the spectrums and chromatograms of the drug
- Report of the pharmacological (specific) activity study substantiated the indications for use which are formed and described in the instruction
- Test report of the drug toxicity (acute, sub-acute, sub chronic, chronic toxicity)
- Test report of the specific influences (cancerogenity, mutagenic and teratogen effects, embryo toxicity, allergic and local-irritative effects)
- Clinical trial report of the medicine usage in clinic (the information which concerns only the drug that is produced by this manufacturer)
- Copies of publications of the medicine usage in clinics after its registration in the country of origin (the information which concerns only the drug that is produced by this manufacturer)
- Report of pharmacokinetics of the pharmaceutical study and its bioequivalence to the original drug
- Summary information of the side effects, in comparison with other analogous medicines, used at the same indications
- Instruction for use (must be signed and stamped by the manufacturer)

4. Samples and package:

- Information of the material used for package: Certificates of the packaging materials (must be signed and stamped by the manufacturer)
- Color design of internal and external packages (Original and Russian version)
- Standard samples of the active substance for quality control
- Standard and referenced samples of the drug for the binding examination of quality (should be in the standard package)

The documents necessary for the registration include a certificate of analysis of the drug in the country of origin of the manufacturer, GMP certificate and information on registration

of the drug in the foreign country. The Ministry of Health determines whether these approvals are sufficient for an exemption of the drug from clinical and other testing in Uzbekistan before issuing a registration certificate.

Table 9: Content of the dossier for drug product registration in Uzbekistan:

S.No	Contents
1	Petition letter
2	Application form
3	Manufacturing license (notarized copy)
4	Certificate of registration of the product in the country of manufacturer (notarized copy)
5	GMP certificate (notarized copy)
6	Free sale certificate (notarized copy)
7	Certificates of registration in other countries (notarized copy)
8	Leaflet (instruction for use
9	Unit composition of the product
10	Master formula
11	Manufacturing process
12	Flow chart of manufacturing process
13	Certificates of Analysis of finished product (for 3 batches)
14	Certificates of Analysis of raw material of active ingredients
15	Certificates of Analysis of raw material of inactive ingredients
16	Notarized documents confirming source of gelatin, lactose, magnesium stearate. In case of animal origin, notarized documents confirming absence of BSE/TSE, and other infectious agents (brucellosis, tuberculosis, anthrax, foot-and-mouth disease, prionic diseases) in used material
17	Specification and methods of analysis of raw material of active ingredients
18	Specification and methods of analysis of raw material of inactive ingredients
19	Specification and methods of analysis of finished product
20	Packaging instructions
21	Specifications of packing materials
22	Certificates of analysis of Packaging Materials

23	Artworks of the strip, package and leaflet
24	Stability data
25	Pharmacology, toxicology, etc.
26	Clinical data
27	Reports of Clinical Studies of the product.
28	Samples enough for triple analysis
29	Working Standards enough for triple analysis

10.5 Registration Fees

According to the Law on Medicines, a fee in form of a state duty is to be paid for state registration and the registration should take no longer than 9 months. Registration fee is four thousand USD Dollars and 20% VAT for one product (one dosage form).

Regulations and Registration of medicinal product CIS (CTD)

Countries

1. Kazakhstan
2. Moldova
3. Ukraine

11. Regulations and Registration of medicinal product in Kazakhstan

11.1 Registration Regulations

Kazakh traditions enactment is truly created and to an expansive degree taking into account the standards of World Customs Organization. Since January 2010, Kazakhstan is an individual from the Customs Union with Russia and Belarus; therefore, the nation was obliged to fit its more liberal exchange terms with Russia's more prohibitive tenets. Access to the Union has not yet influenced the pharmaceutical market as Customs charges for imported pharmaceuticals from CU part nations and third nations will be still zero. Then again, starting 2014, traditions expenses for pharmaceutical imports from third nations will be expanded first to 5% and after that in 2015 to 10%.

Republican State Enterprise "National Center for Drug Expertise, restorative gadgets and medicinal hardware" (the National Center) is an administration master association in the medication market. It was created by the Government of the Republic of Kazakhstan on October 2, 2002 № 1081 by transmuting the State Enterprise "Center of drugs "Dari-dermek" formed by the Government of the Republic of Kazakhstan on November 17, 1997 № 1591.

11.2 Categories of medicinal products which are subject to state registration:

- New (original) and generic drugs
- Other doses, dosage forms and new indications drugs
- New combinations of drugs

11.3 Registration of generics in Kazakh

State enrollment, re-enlistment and varieties to the enlistment dossier will be directed by the state power in the field of medications, medicinal devices.

Examination of prescriptions is directed by the State Expert Organization in the field of medications, medicinal supplies and restorative gear that is not specifically included in the advancement and production of the prescription with an agreement with the candidate.

Registration process consist of Following Stages

1. Initial evaluation;

2. Analytical expertise;
3. Specialized pharmaceutical expertise;
4. Specialized pharmacological expertise;
5. Conclusions about the safety, effectiveness and quality.

Every ensuing phase of the examination of the medication is hung on the premise of the positive finish of the past phase of examination.

In the event that there are remarks (missing material), the candidate has 30 days to give an answer (asked for materials) or other composed support for the timing of their records planning, however not over sixty days. In the event of inability to present a reaction the master council stops the aptitude and gives the choices to the general population powers and the candidate inside ten schedule days from the date of the choice.

The state power settles on choice on state enrollment, re-enlistment, and varieties to the enlistment dossier, or refusal on the premise of master association finish of wellbeing, viability and nature of medications.

Initial expertise of drugs

As per appropriate law the receipt of approaching reports and materials for aptitude and the issuance of sanction archives is in light of the rule of "one window".

Beginning examination of the reports and materials will be held inside 10 days for re-enlistment of prescriptions and alterations to the enrollment dossier, 20 days - for medication enrollment from the date of cash receipt on record NCEM. Toward the end of stage the finish of introductory assessment is exchanged to the candidate.

Before seeking examination of medications the candidate signs the agreement with NCEM on examination of medications for state enrollment, re-enlistment and varieties to the enrollment dossier.

The methodology of fare of pharmaceutical items to the Republic of Kazakhstan incorporate compulsory enrollment of the items at Ministry of Health (Committee of Pharmaceutical Control).

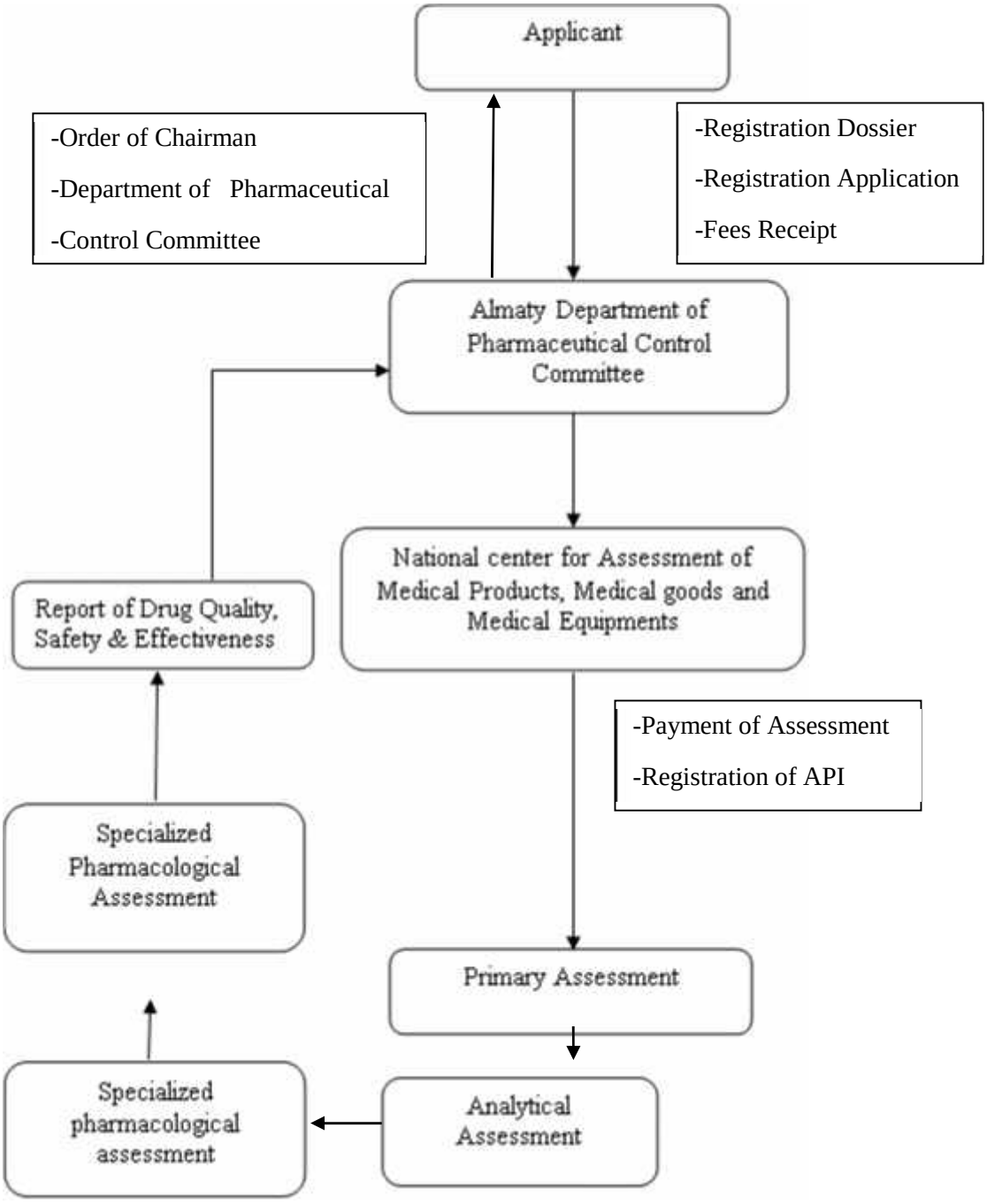
The procedures to get the state registration are following:

1. Submission of the Application on registration of pharmaceutical products with enclosed confirmation of payment of state registration fee to the Committee of Pharmaceutical Control. The Application initialed by the head of the Department of the Committee of Pharmaceutical Control transfers to the department of experts' work of National Center

of Expertise of the Ministry of Health of RK (NCE).

2. The Applicant concludes the contract with NCE for carrying out expert examination.
3. The specialist of expert department accepts the Application for state registration, checks the availability of contract for expert examination, than issue the referral for payment. The referral for payment initials by specialist and head of department and goes to the account department. The account department prepare invoice within 5 working days.
4. After check the registration dossier, samples and standards of pharmaceutical products validity of samples, standards and storage mode all these goes to small achieve. The certificates of analyze is require for the given standards and samples. (In case of failure to submit the all necessary document within 30 day the company must inform in written form about the term to NCE, otherwise the given pharmaceutical product will get a refusal in state registration.
5. Primary expertise of documents and materials carry out within 20 days for registration of pharmaceutical product and 10 days in case of re-registration from the day of money in payment to the account of NCE. In case of positive finding of primary expertise the product sends for analytic expertise.
6. Analytic expertise conducts out within 50 days, immune biological products - 70 days.
7. Special pharmaceutical expertise conducts by Pharmacopoeia Center (including expertise of technological normative document on control of quality and security, 40 days) within 90 days.
8. Special pharmacological expertise conducts by Pharmacological Center within 90 days after getting the positive decision of pharmaceutical expertise.
9. After passing of complete cycle of expert's work the conclusion on safety, efficiency and quality of pharmaceutical product prepares within 20 days if registration, 10 days if re-registration On the bases of the order of Chairman of Committee of Pharmaceutical Control the registration card issues.

Fig 11: Registration Process in Kazakhstan



11.4 Dossier Requirements in Kazakhstan

- Dossier in CTD format (as per EU CTD)
- Labeling in Russian/English
- Annex 1 for application form and Annex 4 stating list of documents
- Notarized COPP
- Related Substance data from 3 batches
- Product Development report
- Quality overall summary (QOS)
- Clinical and Non Clinical summaries and overview
- Full shelf life stability data
- Specification compliance with EP or State Pharmacopoeia

12. Regulations and Registration of medicinal product in Ukraine

12.1 Registration Regulations

The Ministry of Health of Ukraine ensures state registration and control of manufacturing, storage, sale and quality of drugs and stipulates unified qualifying requirements for persons exercising pharmaceutical activity. The State Service of Ukraine for Medicinal Products; the State Expert Centre of the Ministry of Health of Ukraine; and the State Price Control Inspectorate are also entrusted with enforcing the regulatory framework for the marketing, authorization and pricing of medicinal products in Ukraine[21].

State registration of medical products is carried out on basis of application and respective document package submitted to the State Drug Inspectorate by the applicant liable for manufacturing, safety and efficacy of medical products.

In order to conduct necessary expert examinations and testing of medical products the State Drug Inspectorate shall engage expert institutions and give the applicant respective referrals.

The applicant shall choose expert institutions taking into account profile of the expert institution and the list comprised and approved by the State Drug Inspectorate. Results of the expert examination conducted by the expert institution shall be stated in a protocol (report, conclusion) which shall be sent to the State Drug Inspectorate or handed over directly to the applicant.

The certificate is valid for up to 5 years, after expiration of its term import to Ukraine, sale and use of medicinal products is possible only after its re-registration.

Medicinal products shall be allowed for use in Ukraine after their state registration. The state registration of medicinal products shall be performed pursuant to the application submitted to the Ministry of Health of Ukraine or to its authorised body.

Based on the results of examination of the aforementioned materials, the Ministry of Health of Ukraine or the body authorised by it shall take the decision to approve or reject the application for registration of the medicinal product within the period of one month.

If the medicinal product has been registered in Ukraine it is prohibited to use the registration information for submission of the application for state registration of another medicinal product during five years of the day of such registration (regardless of the validity period of any patent related to the medicinal product) except for cases when the right to refer to or use such information has been obtained in accordance with the acting legal procedure.

Persons being at fault for disclosure, illegal use of registration information shall be brought to disciplinary, administrative, civil and/or criminal liability according to the Ukrainian laws.

For state registration of medicinal products based on or related to the intellectual property with the patent issued according to the Ukrainian legislation the applicant shall submit a copy of the patent or manufacturing and selling license for the registered medicinal product. Applicants shall submit a letter indicating that the rights of third parties being patent-protected are not violated because of the registration of the medicinal product.

The applicant shall be given a Certificate for the registered medicinal product, specifying the period of validity within which it shall be permitted for use in Ukraine.

12.2 Categories of medicinal products which are subject to state registration:

According to the Law of Azerbaijan Republic "About medicinal products" the following medicinal products are to be registered:

- Original medicinal products;
- Analogues (generics) of medicinal products;
- New combinations of early registered medicinal products;
- Medicinal products with the expired period of state registration pharmaceutical substances used as active ingredients in the medicinal products manufacturing

12.3 Registration Procedure

Materials that are submitted for state registration for a medicinal product are examined under the following stages:

- Primary examination.
- Preliminary examination.
- Specialized examination.

The period of examination must not exceed 210 calendar days following the official date of receipt of a full and independent application for medicinal product registration. The period of examination must not exceed 90 calendar days from the official date of receipt of the application for other types of, such as, for example, application on similar biological medicinal product, active substances. The period of examination does not include the time taken by applicants to update materials or the time taken for additional examinations (tests).

Cooperation scheme

↓

Confidentiality agreement

↓

You send us dossier for preliminary expertise and analysis

↓

As a result of the expertise we send you list of missing documents

↓

Filling the Application and "micro-dossier", translation of documentation, development of AND, package insert and package mock-ups

↓

Contracting of state authorities, submission of Application and receipt of Invoices for state fees

↓

Submission of the dossier, start of state expertise

↓

Deficiency letters, mutual efforts for fast responding

↓

Import of the samples for laboratory analysis

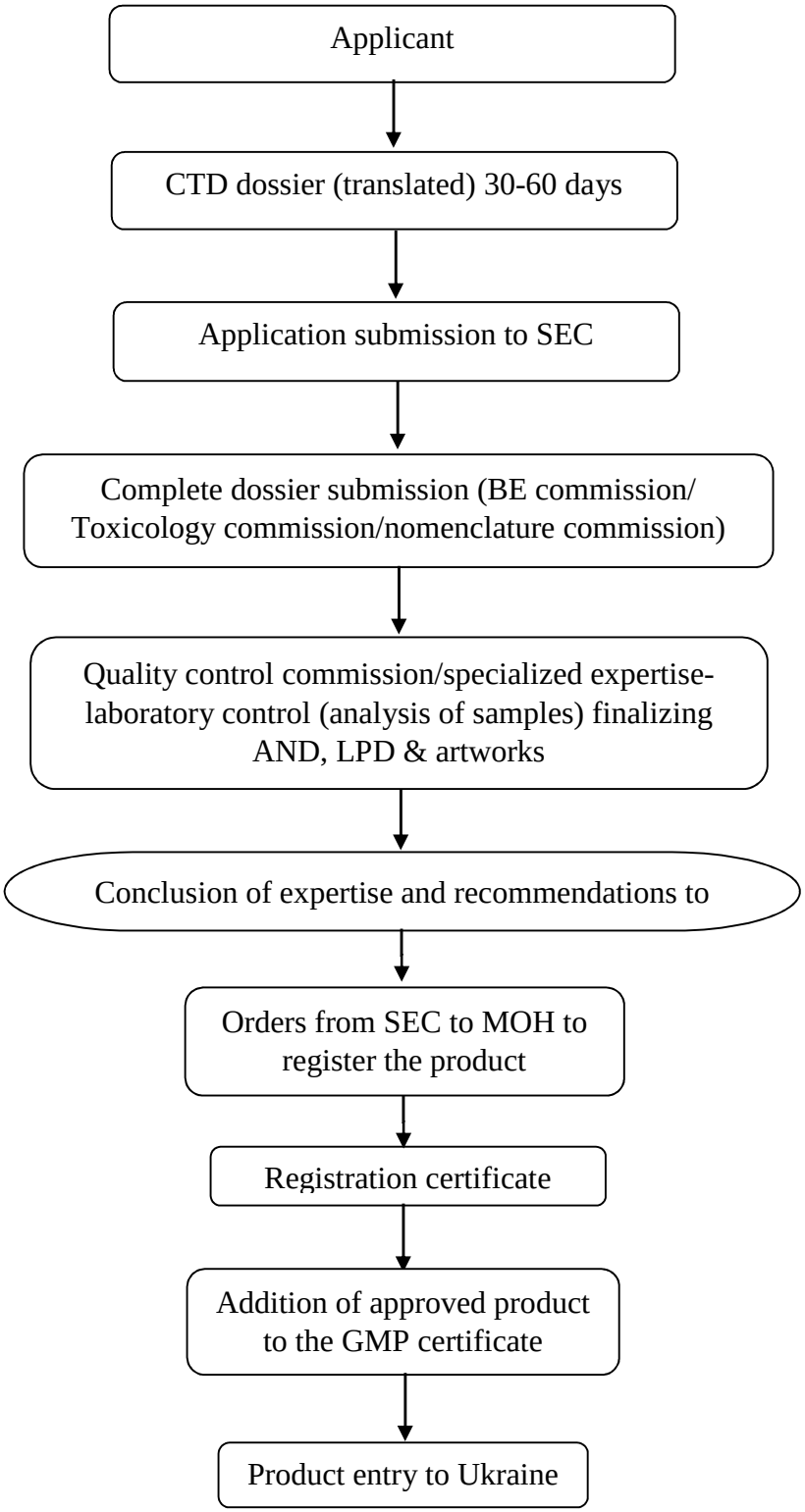
↓

Product's approval for registration in Ukraine

↓

Issue of original certificate of marketing authorization

Fig 11: Registration Procedure of generic medicinal product in Ukraine



12.4 Denial of State Registration in Ukraine

The registration of medicinal products is rejected if the following is available:

- A negative conclusion of the expertise.
- Alerts on the medicinal product received from international specialized sources
- The medicinal product contains adulterations
- The submitted documents are false or fabricated

12.5 General requirements for manufacture of medicinal products

Active ingredients, excipients, and packaging materials permitted for use by the Ministry of Health of Ukraine or by the body authorized by it may be used in the manufacture of medicinal products.

The manufacture of medicinal products shall be performed pursuant to the technological requirements, the pharmacopoeial monographs and other state standards and technical conditions, taking into consideration the international standards on manufacture of the medicinal products. Should the active substance or excipient be changed, the manufacturer of the medicinal product shall apply for registration of the medicinal product.

Labelling of medicinal products

Medicinal products intended for clinical study shall carry the text 'For clinical research'.

Each medicinal product sold shall be accompanied by instructions for use of the medicinal product comprising information as follows:

- Name of the medicinal product;
- General description (chemical name, main physical and chemical properties, composition);
- Pharmacological data;
- Indications for use;
- Contraindications;
- Interactions with other medicinal products;
- Method of use and dosage;
- Adverse effects;
- Precautionary measures;
- Pharmaceutical forms;
- Storage conditions and shelf-life;

- Dispensing conditions.

12.6 Fees required for registration of medicinal product in Ukraine

Table 10: Registration fees of generic (analogue) medicinal product

Fees	CTD format	Simple format
State fee to the Treasury of Ukraine	100 EURO	100 EURO
Expertise by State Pharmacological Center	2900 EURO	2100 EURO
Quality assurance in State laboratory (+/- 25%)	1200 EURO	1200 EURO

12.7 heck List for Product Registration in Ukraine and Kazakhstan[22]

Module 1: Administrative documentation

1.1 Table of contents.

1.2. Application with micro dossier. Micro dossier consists from following parts:

- ✓ Document that confirms rights of the person to represent Application (Power of Attorney, Letter of Authorization etc.)
- ✓ Copy of manufacturing license
- ✓ GMP certificate
- ✓ Certificate of the Pharmaceutical Product (CPP)
- ✓ Copy of registration certificate from manufacturer's country (can be replaced with CPP) and list of countries where the product is registered
- ✓ Written consent of the Marketing Authorization Holder (if different from Applicant) of the registration certificate from manufacturer's country (or from CPP) to register product's on behalf of Applicant
- ✓ CV of the person responsible for pharmacovigilance in Ukraine
- ✓ CV of the person responsible for quality of medicinal product (batch recall purposes etc.) in Ukraine
- ✓ Brief scheme of manufacturing process with mentioned manufacturing sites
- ✓ Copies of conclusions/reports of the Authority that performed inspection of the manufacturing site
- ✓ Copies of trademark protection certificate, registered brand name, patent
- ✓ Guarantee letter that intellectual rights of the third party are not infringed
- ✓ Guarantee letter that pharmacological vigilance system in Ukraine will be established and maintained.

1.3. Summary of product characteristics (SmPC), labelling and instructions for medical use:

1.4. Information about the independent experts:

1.5 Specific requirements for different types of applications.

- ✓ Annex to Module 1. Environmental risk assessment

Module 2: CTD summary (As per EU CTD)

Module 3: Quality (As per EU CTD)

3.2.S. Active substance(s)

3.2.P. Finished medicinal product

Module 4: Preclinical studies reports (As per EU CTD)

Module 5: Clinical studies reports (As per EU CTD)

Table 11: Structure and content of Registration Dossier for Ukraine and Kazakhstan

Module 1. Administrative information:	
	• Application form;
	• Comprehensive table of contents;
	• Suggested summary of product characteristics;
	• Labelling;
	• Package leaflet/insert;
	1.3.4 Summary of product characteristics approved in manufacturer/ applicant country
	1.4.1. Information on quality expert
	1.4.2. Information on pre-clinical expert
	1.4.3. Information on clinical expert
	• Certificates: - GMP certificate; - Manufacturing license; - Certificate of pharmaceutical product - Certificate of registration in manufacturer's country; • Overseas regulatory status: - List of countries where the product is registered (or submitted for registration) with mentioned date of first registration - Copies of the registration certificate from mentioned countries; Comment: preferable, but not necessary; • Environmental risk;
Module 2. Summary of CTD	
	2.1. Table of contents of modules 2.3.4.5
	2.2 Introduction to CTD
	2.3 General summary on quality
	2.4 Review of preclinical data

	2.5 Review of clinical data
	2.6 Summary of pre-clinical data 2.6.1. Summary of pharmacological data in text format 2.6.2. Summary of pharmacological data in tabular format 2.6.3. Summary of pharmacokinetics data in text format 2.6.4. Summary of pharmacokinetics data in tabular format 2.6.5. Summary of toxicological data in text format 2.6.6. Summary of toxicological data in tabular format
	2.7. Summary of clinical data 2.7.1. Summary of biopharmaceutical studies and related analytical methods 2.7.2. Summary of clinical pharmacology studies 2.7.3. Summary of clinical efficacy 2.7.4. Summary of clinical safety 2.7.5. Copies of used literature sources 2.7.6. Short reviews of individual trials
Module 3. Quality	
	3.1. Table of contents
	3.2. Relevant data
3.2.S	**Medicinal substance**
	3.2.S. Medicinal substance (for medicinal products containing more than one medicinal substance an information should be given in full with respect to each of them) 3.2.S.1.1. Name 3.2.S.1.2. Structure 3.2.S.1.3. General properties
	3.2.S.2. Manufacture 3.2.S.2.1. Manufacturer 3.2.S.2.2. Description of manufacturing process and its control 3.2.S.2.3. Control of materials 3.2.S.2.4. Control of critical stages and intermediate products 3.2.S.2.5. Process validation and/or its assessment

	3.2.S. 2.6. Development of manufacturing process
	3.2.S.3. Characteristics 3.2.S.3.1. Demonstration of structure and other characteristics 3.2.S.3.2. Impurities
	3.2.S.4. Control of medicinal substance 3.2.S.4.1. Specification 3.2.S.4.2. Analytical methods 3.2.S.4.3. Validation of analytical methods 3.2.S.4.4. Batch analysis 3.2.S.4.5. Substantiation of specification
	3.2.S.5. Standard samples or substances
	3.2.S.6. Container/closure system
	3.2.S.7. Stability 3.2.S.7.1. Summary on stability and conclusions 3.2.S.7.2. Report on post-registration stability study and stability associated obligations 3.2.S.7.3 Stability data
3.2.P	**3.2.P. Medicinal product**
	3.2.P.1. Description and composition of the medicinal product
	3.2.P.2. Development pharmaceutics 3.2.P.2.1. Constituents of the medicinal product 3.2.P.2.1.1. Medicinal substance 3.2.P.2.1.2. Excipients
	3.2.P.2.2. Medicinal product 3.2.P.2.2.1. Development of composition 3.2.P.2.2.2. Overages 3.2.P.2.2.3. Physical and chemical, and biological properties
	3.2.P.2.3. Development of manufacturing process
	3.2.P.2.4. Container/closure system
	3.2.P.2.5. Microbiological characteristics
	3.2.P.2.6. Compatibility
	3.2.P.3. Manufacture

	3.2.P.3.1. Manufacturer (-s) 3.2.P.3.2. Composition for batch 3.2.P.3.3. Description of manufacturing process and process control 3.2.P.3.4. Control of critical stages and intermediate products 3.2.P.3.5. Process validation and/or its assessment
	3.2.P.4.Control of excipients 3.2.P.4.1. Specifications 3.2.P.4.2. Analytical methods 3.2.P.4.3. Validation of analytical methods 3.2.P.4.4. Substantiation of specifications 3.2.P.4.5. Excipients of human and animal origin 3.2.P.4.6. New excipients
	3.2.P.5. Control of medicinal product 3.2.P.5.1. Specification (-s) 3.2.P.5.2. Analytical methods 3.2.P.5.3. Validation of analytical methods 3.2.P.5.4. Batch analysis 3.2.P.5.5. Characteristics of impurities 3.2.P.5.6. Substantiation of specification (-s)
	3.2.P.6. Standard samples and substances
	3.2.P.7. Container/closure system
	3.2.P.8. Stability 3.2.P.8.1. Summary and conclusions on stability 3.2.P.8.2. Report on post-registration stability study and stability associated obligations 3.2.P.8.3. Stability data
3.2.A.	**3.2.A. Amendments**
	3.2.A. Amendments 3.2.A.1. Technical devices and facilities 3.2.A.2. Safety assessment of foreign microorganisms 3.2.A.3. New excipients
3.2.R	**3.2.R. Regional information**

	3.3. Copies of used literature sources
Module 4. Reports on preclinical trials	
	4.1. Table of contents
	4.2.1. Pharmacology 4.2.1.1. Primary pharmacodynamics 4.2.1.2. Secondary pharmacodynamics 4.2.1.3. Safety pharmacology 4.2.1.4. Pharmacodynamic drug interactions
	4.2.2. Pharmacokinetics 4.2.2.1. Analytical methods and their validation report 4.2.2.2. Absorption 4.2.2.3. Distribution 4.2.2.4. Metabolism 4.2.2.5. Excretion 4.2.2.6. Pharmacokinetic drug interactions (pre-clinical) 4.2.2.7. Other pharmacokinetic studies
	4.2.3. Toxicology 4.2.3.1. Toxicity after a single dose administration 4.2.3.2. Toxicity after repeated administration 4.2.3.3. Genotoxicity 4.2.3.4. Carcinogenicity • Reproductive and ontogenetic toxicity • Local tolerance • Other toxicity studies • Copies of used literature sources
Module 5. Report on clinical trials	
	5.1. Table of contents
	5.2. List of all clinical trials in tables
	5.3. Report of clinical trials 5.3.1. Reports on biopharmaceutical studies 5.3.2. Reports on studies related to pharmacokinetics studies with use of human biomaterials

	5.3.3. Reports on pharmacokinetic studies in human beings 5.3.4. Reports on pharmacodynamic studies in human beings 5.3.5. Reports on efficacy and safety studies 5.3.6.Reports on post-registration experience 5.3.7. Samples of individual registration forms and individual lists of patients.
	5.4. Copies of used literature sources

13. Sample dossier for Turkmenistan

Registration Dossier of Cefuroxetil (Cefuroxime Axetil Tablets 250 mg) In Turkmenistan

Table 12: Table of Contents

S. No.	Content
1	Application for registration of drug in Turkmenistan
2	Certificates on the drug registration in the manufacturer countries and other countries
3	GMP certificates
4	Instruction for use
5	Certificates of analysis for the sample provided
6	Detailed methods of quality surveillance and analytical methods for the finished drug product
7	The data on pharmacokinetics and bioavailability
8	Preclinical and clinical data
9	Standard package
10	Summary of product characteristics
11	Free-sale Certificate
12	The sanction (license) for production

Application

for registration of medicinal product in Turkmenistan

Application

for registration of medicinal product in Turkmenistan

1. Trade name of product : CEFUROXETIL BP 250 mg
2. International non patented name : Cefuroxime Axetil
3. Synonyms of the drug : Cefuroxime 1-Acetoxyethyl Ester
4. Pharmaceutical form of the drug : Uncoated capsule shape tablets
5. Composition of the product

Composition of Cefuroxime Axetil Tablets

Intragranular

Cefuroxime axetil Amorphous

Cellulose microcrystalline

Croscarmelose sodium

Sodium lauryl sulfate

Silica, colloidal anhydrous

Hydrogenated vegetable oil

Extragranular

Croscarmelose sodium

Silica, colloidal anhydrous

Hydrogenated vegetable oil

6. Presence of change in composition of a drug : None
7. Route of administration : Oral
8. Name and Address of Manufacturer

Name _____

Business address _____

Postal address _____

_____

Telephone number_____

9. Main indication for use of the drug :
10. Standard Pack size : 1 X 10 Tablets Aluminum Blister
11. Shelf-life : 36 months
12. Storage Conditions : Store below 30º C.

The signature

1. **Certificates on the Drug Registration In The manufacturer Countries and Other Countries**
2. **GMP Certificates**
3. **Instruction for Use**

5. Certificates of Analysis for the Sample Provided

Cefuroxime Axetil is manufactured by ABC Pharma India. The manufacturer is the holder of certificate of suitability ABC-XYZ for Cefuroxime Axetil, Certifying that the quality of Cefuroxime Axetil manufactured is suitably controlled by the current version of the monograph of the European Pharmacopoeia.

Table 13: Certificates of Analysis for the Sample of Cefuroxetil

SUBJECT	CERTIFICATEOF ANALYSIS (Finished Product)	A. R. No.	
		BATCH. No.	
DEPARTMENT	QUALITY CONTROL	BATCH SIZE	
		MFG. DATE	
PRODUCT NAME	Cefuroxetil 250 mg	EXP. DATE	
		SPEC. No.	
PRODUCT CODE	_____	Revision No.	
GENERIC NAME	Cefuroxime Axetil BP 250 mg	PAGE No.	

Specification of Cefuroxime Axetil	Specification No. _____

S. No.	Tests	Limits	Method Reference
1	**Description**	A white or almost white powder.	Visual
2	**Solubility**	Slightly soluble in water, Soluble in acetone, in ethyl acetate and in methanol, slightly soluble in alcohol	Physical Ph.Eur.general Chapter
3	**Identification**		
	a) By IR	The IR spectrum must exhibit maxima at the same wave numbers as the Cefuroxime axetil amorphous working slandered spectrum	Spectrophotometric Ph.Eur. method 2.2.24 (method-I)
	b) By HPLC	In Assay chromatograms the retention time and the size of the principle peaks obtained with the test solution should be same as those of the peaks due to Diastereoisomers-A and B of Cefuroxime Axetil	Liquid Chromatography, In-house

		chromatogram obtained with reference solution'd'.	
4	**Diasterioisomer Ratio** (By HPLC)	Between 0.48 and 0.55	Liquid Chromatography Ph.Eur. Monograoh
5	**Related substance** (By HPLC, % w/w)		
	E- isomer (impurity B)	Not more than 1.0	Liquid Chromatography In-house
	Δ^{3-}isomer(impurity A)	Not more than 1.5	
	Cefuroxime acid (Impurity D)	Not more than 0.5	
	Di-α-cefuroxime ethyl ether (Diastereoisomer-1)	Not more than 0.15	
	Other detectable impurity	Not more than 0.10	
	Any unknown related compound	Not more than 0.10	
	Total related substance	Not more than 3.0	
6	**Acetone** (By GC, % w/w)	Not more than 1.1	Gas Chromatography, In-house
7	Water (% w/w, by KF)	Not more than 1.5	Wet chemical Ph.Eur. Method 2.5.12
8	**Assay** (By HPLC, %w/w, As Diasteroisomer of Cefuroxime axetil, on anhydrous and acetone free basis)	Not less than 96.0 and Not more than 102.0	Liquid Chromatography Ph.Eur. Monograph
	Additional tests		
9	**Residual Solvents** (By GC, ppm) Ethyl acetate Cyclohexene	 Not more than 2000 Not more than 1000	Gas Chromatography, In-house
10	**Microbiological Quality** Bacteria Fungi E. Coli	 Not more than 1000 Not more than 100 Must be absent	Microbiological Ph.Eur. methods 2.6.12 & 2.6.13

***Storage**: Store in a well-closed Container, at controlled room temperature*

	PREPARED BY	**CHECKED BY**	**APPROVED BY**
NAME	_____	_____	_____
SIGNATURE	_____	_____	_____

DATE	_____	_____	_____

Table 14: Drug Product Manufacturer's specification for Cefuroxime Axetil Ph.Eur

S. No.	Tests	Specifications/Limits
1	**Description**	A white or almost white powder.
2	**Solubility**	Slightly soluble in water, Soluble in acetone, in ethyl acetate and in methanol, slightly soluble in alcohol
3	**Identification**	
	a) By IR	The transmission minima or absorption maxima in the spectrum obtained with the sample recorded, as KBr pellet should correspond in position and relative size to those in spectrum obtained with Cefuroxime Axetil amorphous working standard
	b) By HPLC	The retention time and size of the principle peaks for the Cefuroxime Axetil distereoisomer A & B in the chromatogram of sample solution should correspond to that the sample peaks in the chromatogram of standard solution as obtained in the "Assay"
4	**Diasterioisomer Ratio** (By HPLC)	Between __ and __
5	**Related substance** (By HPLC, % w/w)	
	Methoxyiminofurylacetic acid	Not more than __
	E- isomer (impurity B)	Not more than __
	Δ^{3-}isomer(impurity A)	Not more than __
	Cefuroxime acid (Impurity D)	Not more than __
	Di-α-cefuroxime ethyl ether (Diastereoisomer-1)	Not more than __

	Di-α-cefuroxime ethyl ether (Diastereoisomer-2)	Not more than __
	Di-α-cefuroxime ethyl ether (Diastereoisomer-3)	Not more than __
	Any unknown related compound	Not more than __
	Total related substance	Not more than __
6	**Acetone** (By GC, % w/w)	Not more than __
7	**Water** (% w/w, by KF)	Not more than __
8	**Assay** (By HPLC, %w/w, As Diasteroisomer of Cefuroxime axetil, on anhydrous and acetone free basis)	Not more than __
Additional in house tests		
9	Residual solvents (by Gc, ppm)	
	Ethyl acetate	Not more than__
10	**Crystallinity** (By microscopy)	Should be amorphous
11	**Color absorbance** (AU, 10% w/v Solution in acetone at 410nm, 1 cm cell)	Not more than__
12	**Practical size** (µm By Malvern Particle size analyzer)	
	90% particles	Not more than__
	50% particles	Not more than__
	10% particles	Not more than__
13	**Bulk density** (g/ml)	
	Untapped	Not more than__
	Tapped (500 taps)	Not more than__
14	**Microbiological contamination**	
	Total aerobic microbial count [TAMC]	Not more than__

	(cfu/g)	
	Total combined yeast/moulds count [TYMC] (cfu/g)	Not more than__
	Specified micro-organisms	Not more than__
	Escehrichia coli	Must be absent

**** Test for residual and microbial contamination are non-routine tests and will be carried out only in the first three batches and thereafter on every 10th batch or one batch per year whichever is earlier.***

	PREPARED BY	**CHECKED BY**	**APPROVED BY**
NAME	_____	_____	_____
SIGNATURE	_____	_____	_____
DATE	_____	_____	_____

Specifications

Table 15: Proposed release & shelf life specifications of Cefuroxime axetil 250mg

Sr. NO	**TEST**	**SPECIFICATION**	
		RELEASE	**SHELF-LIFE**
1	**Description**	A white or almost white powder.	
2	**Solubility**	Slightly soluble in water, Soluble in acetone, in ethyl acetate and in methanol, slightly soluble in alcohol	
3	**Identification**		
	a) By IR	The transmission minima or absorption maxima in the spectrum obtained with the sample recorded, as KBr pellet should correspond in position and relative size to those in spectrum obtained with Cefuroxime Axetil amorphous working standard	
	b) By HPLC	The retention time and size of the principle peaks for the Cefuroxime Axetil distereoisomer A & B in the chromatogram of sample solution should correspond to that the sample peaks in the chromatogram of standard solution as obtained in the "Assay"	
4	**Diasterioisomer Ratio** (By HPLC)	Between __ and __	
5	**Average weight** (in mg)	----------	
	Uniformity of Dosage Units (by weight variation) in %	Not more than __	
6	**Related substance** (By HPLC, % w/w)		
	Methoxyiminofurylacetic acid	Not more than __	
	E- isomer (impurity B)	Not more than __	

	Δ^3 ⁻isomer(impurity A)	Not more than __
	Cefuroxime acid (Impurity D)	Not more than __
	Di-α-cefuroxime ethyl ether (Diastereoisomer-1)	Not more than __
	Di-α-cefuroxime ethyl ether (Diastereoisomer-2)	Not more than __
	Di-α-cefuroxime ethyl ether (Diastereoisomer-3)	Not more than __
	Any unknown related compound	Not more than __
	Total related substance	Not more than __
7	**Assay** (By HPLC) Each uncoated tablet contains Cefuroxime axetil equivalent to Cefuroxime	
	In mg	_____
	% Labeled amount	----------
	Additional In-House tests	
8	**Water** (%m/m, By KF)	Not more than__
9	**Microbial Contamination***	
	Total aerobic microbial count [TAMC](cfu/g)	Not more than__
	Total combined yeast/moulds count [TYMC](cfu/g)	Not more than__
	Specified micro-organisms	Not more than__
	Escherichia coli	Must be absent

**** Test for residual and microbial contamination are non-routine tests and will be carried out only in the first three batches and thereafter on every 10th batch or one batch per year whichever is earlier.***

	PREPARED BY	**CHECKED BY**	**APPROVED BY**
NAME	**_____**	**_____**	**_____**

SIGNATURE	_____	_____	_____
DATE	_____	_____	_____

6. Detailed Methods of Quality Survellance and Analytical Methods for the Finished Drug Product

The analytical test procedures and Quality surveillance for testing Cefuroxime axetil Tablets are presented in this section. The test for the determination of assay and related substances in Cefuroxime Axetil Tablets are stability indicating and have been used in testing the drug product, both during release and stability.

The references for the test procedures used in the testing of Cefuroxime Axetil Tablets are given in Table below-

S. NO.	**Tests**	**Reference**
Pharmacopoeial tests		
1	Description	By visual examination
2	Identification	BP
3	Average Weight (by mass)	BP
4	Uniformity of dosage units (by weight Variation)	BP
5	Dissolution	BP
6	Related substance	USP
Additional in-house tests		
7	Water by KF	IHS
8	Microbial limits	Ph.Eur.

Table 16: Analytical methods for testing of Cefuroxime Axetil

BP - British Pharmacopoeia

USP - United States Pharmacopoeia

IHS - IN-House Specification

Ph.Eur. – European Pharmacopoeia

Analytical Test Procedures of Cefuroxime Axetil Tablets

01. DESCRIPTION

Spread the tablets over a clean and dry petridish, Note the color, shape and debossing details of the tablets

02. IDENTIFICATION

A. By IR

Instrumentation:

a. Perkin Elmer FT-IR, model Spectrum One or equivalent

b. Hydraulic pellet press, Agate mortar and pestle, 13mm die and pellet holder

Procedure:

Standard Preparation

Weigh and transfer about 120 mg of Cefuroxime axetil amorphous working standard into a Stoppard test tube and add 5ml Dichlomethane and dissolve. Filter through whatmann 41 filter paper and evaporate the filtrate to dryness on a water bath.

Sample preparation

Weigh and transfer tablet powder equivalent to about 100 mg of Cefuroxime into a Stoppard test tube and add about 5 ml 5ml Dichlomethane and sonicate for 10 min. Filter through whatmann 41 filter paper and evaporate the filtrate to dryness on a water bath.

Procedure:

Triturate about 2 to 3 mg of the residue in 200 to 300 mg of previously dried Potassium bromide (at 250ºc for 1 hour). Make a pellet and record the IR spectrum between 400 and 2000 cm. Carryout the background correction by using a Potassium bromide pellet.

03. Average weight (mass):

Take individual weights of 20 tablets and find out the average weight of 20 tablets.

04. Uniformity of dosage units (by weight variation);

Determine the weight of 10 tablets individually.

From the result of the Assay, calculate the content of Cefuroxime axetil in each of 10 tablets

05. Dissolution (by uv);

06. Dissolution parameters:

1. Medium : 0.1 M Hydrochloric acid, 900 ml
2. Apparatus : Paddle
3. RPM : 50
4. Temp : 37.0˚± 0.5˚C
5. Time : 45 minutes

Preparation of 0.1 M Hydrochloric Acid

Dilute 85ml of Hydrochloric acid with water to 10 liters.

Preparation of Diluent:

Use dilution medium as diluent

Preparation of Solution

Standard Solution:

Weigh and transfer accurately 60 mg of Cefuroxime axetil working standard to a 100 ml volumetric flask, add about 5ml of methanol and sonicate to dissolve . add about 50 ml of diluent sonicate for 2 minutes, then dilute to a volume with diluent and mix. Dilute 3ml of this solution to a 100 ml with diluent and mix

Sample Solution:

Set the parameters of Dissolution apparatus as mentioned above. Place one tablet into each of the six dissolution vessels and start the dissolution test. At the specified tie interval, withdraw about 10 ml of the sample solution from each vessel and filter.

For 250 mg tablet

Dilute 3ml of the filtrate to 50 ml with diluent.

Note: Sample solutions is stable for at least 6 hours at room temperature

Procedure:

Measure the absorbance of standard and sample solutions in 1 cm cell on suitable UV spectrophotometer at 278 nm, using the diluent as blank, Record the absorbance and calculate the percentage labeled amount of Cefuroxime dissolved in dissolution media

RELATED SUBSTANCES: (BY HPLC)

Reagents

Ammonium dihydrogen orthophosphate	: AR grade
Orthophosphoric acid	: AR grade
Methanol	: HPLC grade
Water	: Milli-Q grade

Chromatographic conditions:

Column	: Zorbax TMS, 5 µ(250mm X 4.6mm)
Pump Mode	: Gradiet
Flow rate	: 1.2 ml/min
Detection	: UV 278 nm
Injection	: 20 µl
Column oven temperature	: 30ºC
Data acquisition time	: 45 minutes

Preparation of Solutions

Standard solutions

Weigh and transfer accurately 30 mg of Cefuroxime axetil working standard into a 50 ml clean, dry volumetric flask, add 30 ml of methanol and sonicate to dissolve. Make up to the volume with methanol and mix. Dilute 5ml of this solution to 50 ml diluent. Further dilute 5 ml of this solution to 50 ml with diluent. Filter through 0.45 µ membrane filter

Sample Solution:

Transfer 10 tablets or equivalent amount of blend into 250 ml clean, dry volumetric flask, add about 50ml of ammonium dihydrogen orthophosphate buffer pH 2.4, and sonicate to

disperse the tablets. Then add 150 ml methanol, shake by mechanical means for 20 minutes. Make up the volume with methanol and mix. Dilute 5 ml of the solution to 100ml with diluent. Filter through 0.45 µ membrane filter.

Placebo Solutions:

Weigh and transfer placebo powder equivalent to 250 mg of Cefuroxime axetil into a 100 ml clean , dry, volumetric flask, add about 5 ml of ammonium dihydrogen orthophosphate buffer pH 2.4 and 50 ml of methanol and mix. Dilute 10 ml of this solution to 50 ml with diluent. Filter through 0.45 µ membrane filter.

Evaluation of system suitability:

Inject 20 µl of system suitability solution before and after the analysis into the chromatograph and record the chromatograms.

Procedure:

Inject 20 µl each of diluent and placebo solution into the chromatograph and record the chromatogram.

Inject 20 µl sample solution into the chromatograph and record the chromatogram.

Examine the diluent and placebo chromatograms for any extraneous peaks and disregard corresponding peaks observed in the chromatogram of the sample solution.

Disregard any unknown peak with an area less than 0.05% in the chromatogram of sample solution. Retention time of Cefuroxime axetil distereoisomers are calculated

Elution order:

S. No.	Name	RRT	LOQ* (% m/m)
1	Methoxyiminofurylacetic acid		
2	Cefuroxime acid		
3	Cefuroxim lactose		
4	Cefuroxime acid (Distereoisomer –B)		
5	Cefuroxime Axetil (Distereoisomer –A)		

6	Cefuroxime Axetil Δ^{3-} isomers		
7	Cefuroxime Axetil Anti isomer (Distereoisomer –B)		
8	Cefuroxime Axetil Anti isomer (Distereoisomer –A)		
9	Di-α-cefuroxime ethyl ether (Diastereoisomer-1)		
10	Di-α-cefuroxime ethyl ether (Diastereoisomer-2)		
11	Di-α-cefuroxime ethyl ether (Diastereoisomer-3)		

Table 17: Elution order of Cefuroxime axetil distereoisomers

LOQ = Limit of Quantification

8. Additional IN-House Tests:

WATER: (By KF)

Apparatus : K.F. Titrator

Reagents : Methanol, Karl-Fischer reagent

Procedure:

Transfer 35 to 40 ml methanol into the titration vessel, and titrate with Karl-Fischer reagent to the electrometric end point to consume any moisture that may be present . Transfer immediately about 0.3 g of sample accurately weighed, mix, and again titrate with the reagent to the electromeric end point. Calculate the water content of the sample using K.F. factor

Perform the test in duplicate.

09. Microbial Limits:

Perform the test for “Microbial Contamination” as per Ph.Eur Method

7. The Data on Pharmacokinetics and Bioavailability

8. Preclinical and Clinical Data

10. SUMMARY OF PRODUCT CHARACTERISTICS

The brief characteristic of a product

1. **NAME OF A MEDICINAL PRODUCT**

   Cefuroxetil 250mg uncoated tablets

2. **ACTIVE INGREDIENTS**

   Each uncoated tablet contains 250mg Cefuroxime axetil

3. **MEDICINAL FORM**

   White to off-white, uncoated, capsule shaped tablet

4. **CLINICAL DATA**

   4.1 Therapeutic Indications

   4.2 Posology

   4.3 Contraindication

   4.4 Interactions with pharmaceutical products

   4.5 Pregnancy and lactation

   4.6 Undesirable effects

   4.7 Overdose and toxic effects

5. **PHARMACOLOGICAL DATA**

   5.1 Pharmacotherapeutic group

   5.2 mechanism of action

   5.3 Pharmacokinetic properties

6. **Pharmaceutical Data**

   6.1 Qualitative and Quantitative Composition of product

Ingredients	**mg/tablet**	**Function of Ingredient**
Intragranular	**250 mg**	
Cefuroxime axetil Amorphous Ph.Eur		Active ingredient
Cellulose microcrystalline Ph.Eur		Diluent
Croscarmellose sodium Ph.Eur		Disintegrant
Sodium lauryl sulfate Ph.Eur		Surfactant
Silica, colloidal anhydrous Ph.Eur		Glident
Hydrogenated vegetable oil BP		Lubricant
Extragranular		
Croscarmelose sodium Ph.Eur		Disintegrant

Silica, colloidal anhydrous Ph.Eur		Glident
Hydrogenated vegetable oil Bp	5.00	Lubricant
Total tablet weight (mg)	500.00	

Table 18: Qualitative and Quantitative Composition of Cefuroxetil

Ph.Eur - - - European Pharmacopoeia
BP - - - - - British Pharmacopoeia

6.2 Incompatibilities

6.3 Shelf-life

6.4 Storage condition

6.5 Packaging material

6.6 Instruction for use

7. Name and Address of Manufacturer

Name _____

Business address _____

_____

Postal address _____

_____

Telephone number _____

Fax number _____

E-mail address _____

8. The countries where the product is registered

Name of countries Date of registration

a._____ _____

b._____ _____

c._____ _____

9. Date of first authorization/ renewal of the authorization

DD/MM/YYYY

11. FREE-SALE CERTIFICATE

12. THE SANCTION (LICENSE) FOR PRODUCTION

Conclusion

In the unindustrialized markets like CIS countries the registration process is different from other countries even though there is an incessant progression of harmonization fascinating all around the world, still we understand vast challenge, which is yet to be dazed by the Pharmaceutical manufacturer in case of generic drug market expansion and filing.

To come upon these challenges, a lot of deliberate arrangement is essential before filing of any generic medicinal product into the market.

The CIS market is vast, fast growing and clearly offers massive opportunities for pharmaceutical firms. Though, this is a multifarious market, with huge scale and very different pharma-economies. Basically two types of filling processes are seen in the CIS nations. The major difference between these two processes is because of regulatory diversions among the CIS territory.

The CIS is a complex market, with huge scale and very different pharma-economies Although there is a continuous process of harmonization taking place all around the world, still we see a huge challenge, which is yet to be overcome by the Pharmaceutical industry in case of generic drug development and filing in such non harmonized countries To meet these challenges, a lot of strategic planning is required before the development of any generic drug product.

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