WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 13, 993-1004. Review Article ISSN 2277– 7105

REGULATIONS AND REGISTRATION PROCESS OF MEDICINAL PRODUCTS AND MEDICAL DEVICES IN CIS COUNTRIES

Shaik Ayesha BI*, M. V. Nagabhushanam, G. Ramakrishna, P. V. Sivakrishna, Brahmaiah Bonthagarala

Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

Article Received on
10 Sept. 2021,

Revised on 30 Sept. 2021,
Accepted on 21 October 2021

DOI: 10.20959/wjpr202113-22161

***Corresponding Author**
Shaik Ayesha BI
Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

ABSTRACT

The CIS region has a potential market for India. The registration of the drug products in CIS regions is a challenging task because these countries have no harmonized regulatory organization. The CIS region includes 12 countries such as Russia, Kyrgyzstan, Ukraine, Uzbekistan, Kazakhstan, Tajikistan, Turkmenistan, Armenia, Azerbaijan, Belarus, Georgia and Moldova, which require different regulatory guidelines for medicinal product registration as per their FDA guidelines. The different guidelines for the same region become a challenging task for the manufacturer and exporter. The registration of the same product for different countries of CIS is not possible with the same dossier due to the lack of their regulatory harmonization. These countries obey their country-specific dossier format, so to target these market manufacturers and exporters needs to submit different dossier documents for different countries. But Ukraine and Kazakhstan have harmonization and it varies in Uzbekistan and Tajikistan. Ukraine and Kazakhstan are also imposing strict rules and expecting USFDA level documents for approval. The overall conclusion is that harmonization in CIS is highly imbalanced, which affects both time and cost for product registration. Harmonization is the need of the era for easy product registration, and it will be beneficial for the manufacturer, regulator, importer, exporter, and to access medicines of high public health value.

KEYWORDS: CIS region, drug product, guidelines, harmonization, regulatory, registration.

1. INTRODUCTION[1,2]

In several countries the process of registration (marketing authorization) is simplified, e.g. due to small quantity of national manufacturers, or aiming at creation of maximum effective price setting in the healthcare system. For example, Georgia conducts simplified registration policy for products, which was approved by the countries with high regulatory requirements (the EU, the USA and others), the parallel importing is permitted.

Other countries have chosen the way of creating of the Eurasian economic union (EAEU), which includes Armenia, Belarus, Kazakhstan, Kyrgyzia and Russia. Participation of a country in the Customs Union influences regulatory policy of a state and so far allows realizing both national and "centralized" registration.

- Regulatory planning and preliminary consulting;
- Patent search;
- Check of the registration dossier for compliance with legislative requirements;
- Preliminary consulting with the competent authorities;
- Confirmation of the status and/or type of the Application;
- Translation of scientific, medical, technical and legal documentation;
- Legal analysis and preparation of administrative documentation;
- Preparation of specific national documents, including instructions for use (leaflet), labeling and mock-ups;
- Preparation and execution of the registration dossier;
- Submission of documentation, support
- Development and maintenance of the pharmacovigilance system;
- Development and maintenance of a quality assurance system;
- Management of all payments;
- Examination process support, communication with competent authorities;
- Analysis of remarks, preparation of recommendations for responding to remarks;
- Obtaining permission to import samples and standards for intra-registration quality control;
- Import (customs clearance) of samples and standards;
- Deadlines control at all stages of the examination;
- Verification of the registration certificate and its annexes drafts;

2. Registration Process of Medicinal Products in Cis Countries[3-10]

2.1. Armenia

The registration procedure of the medicinal product in Armenia can be briefly described by the following stages:

1. State fee payment.
2. Submission of the Application for registration, of the registration dossier, samples of the medicinal product and standards for laboratory control.
3. Preliminary examination (preliminary materials observation).
4. Obtaining an opinion on the preliminary examination and invoice on the cost of expert works.
5. Expert work payment, receipt of payment confirmation.
6. Specialized documents examination (quality, safety, efficacy assessment, risk/benefit ratio, manufacturing conditions observation, documentation on quality assurance of raw materials and finished product, shelf life and stability studies reports, labeling, instructions for use, etc.), during which questions on submitted documents may be asked or additional documents may be requested.
7. Answers to the remarks of the specialized expertise.
8. Laboratory examination (quality approbation of medicinal product samples), issuance of a Conclusion on laboratory examination.
9. Providing of the examination conclusion to the Pharmacological Board.
10. Issue of the registration conclusion.
11. Receipt of the registration conclusion notification.
12. Issuance of the registration certificate, disposition of artworks, instructions and general characteristics of the medicinal product on the site.

2.2. Azerbaijan

registration procedure of medicinal products consists of several stages and includes primary and specialized examination. Specialized examination includes laboratory analysis, assessment of normative and technical documentation and assessment of results of pharmaco-toxical and clinical studies.

During examination process the Center may request outstanding documents or information, an Applicant is required to provide requested data within set timelines. Time needed for preparation of replies to the Center requests is not included into examination time frame.

Inspection of manufacturing site during registration of medicinal product is not required.

Duration of registration process is not more than 180 calendar days starting from the date of examination fee payment by an Applicant.

Registration certificate (Marketing Authorization certificate) valid for f 5 years is issued as a result of registration, and data about registered medicinal product are included in State Registry of medicinal products. Together with Registration certificate an Applicant gets approved Instruction for medical use (Package Leaflet), package artworks and normative document which includes analytical methods of control, specification, certificates of analysis for finished product and description of medicinal product in Azerbaijani language.

Azerbaijan's legislative requirements for importation and marketing of medical devices and medical equipment are quite simple. In order to import the products it is necessary to obtain a confirmation letter regarding medical device type (classification) and then to obtain a hygiene certificate from the Republican Center of Hygiene and Epidemiology of the Republic of Azerbaijan.

2.3. Belarus

Stages of registration procedure may be presented as follows:

1. Preparation of registration dossier and payment of the fee for primary examination.
2. Filing of the dossier and conducting of the primary examination.
3. Obtaining conclusion on results of primary examination, obtaining invoice and payment of the fee for specialized examination.
4. Conducting of specialized examination of registration materials of medicinal product, providing replies to expert observations, if necessary.
5. Conducting of laboratory analysis of registration samples according to draft of Normative document for compliance with the requirements stated in finished product specification; providing replies to expert observations, if necessary.
6. Conduction of inspection at manufacturing site on compliance to GMP requirements, if necessary.
7. Conducting of clinical trials in certain cases if necessary.
8. Obtaining the conclusion on results of specialized examination and making decision decision on recommending medicinal product for registration at meeting of Academic Council of the Unitary Enterprise “Center for Examinations and Tests in Health Service”.

9. Drafting and issuing of Registration Certificate.

Medical devices and medical equipment of foreign manufacture may be imported and marketed in the territory of the Republic of Belarus after state registration. Currently Application form for registration may be submitted both under "national" Belarusian and under "unified" procedure of EAEU.

2.4. Georgia

Registration is carried out on behalf of an Applicant (Marketing Authorization Holder). Both resident and non-resident legal entity including the manufacturing site itself may apply as Applicant in the country. Applicant is responsible for quality, safety and efficacy of medicinal products. The company "Cratia" may represent interests of Applicants based on power of attorney.

Registration of medicinal products is carried out by the Ministry of Labor, Health and Social Affairs of Georgia, and the competent authority that performs examination of registration materials is the State Regulation Agency for Medical Activities of Georgia (website: moh.gov.ge).

Documents for examination should be submitted to the Agency in national format along with samples of finished product and reference standards in quantity for two laboratory analysis. CTD format is not accepted.

During examination process the competent authority may provide queries and observations which should be replied by Applicant within 2-months period. If Applicant fails to reply to queries within set timelines, registration process for medicinal product may be withdrawn.

Inspection of manufacturing site is not foreseen in the legislation.

Registration of medical devices is not required in Georgia, however medical devices are certified for importation. Prior importation it is recommended to obtain a letter from the Ministry of Labor, Health and Social Affairs of Georgia confirming that the imported product ation is not a medicinal product and does not require registration.

2.5. Kazakhstan

The registration procedure may be presented by the following stages:

- Making contract with the National Center for expert examination.
- Obtaining and payment of invoice for the expert examination.
- Obtaining permission to import samples of medicinal product and required standards.
- Filing of registration dossier and samples to the National Center for Expert Evaluation.
- Expert examination:
  - Primary expert examination.
  - Analytical expert examination.
  - Specialized expert examination.
- Inspection at manufacturing site if necessary.
- Reconciliation of final documents.
- Obtaining a conclusion on safety, efficacy and quality of medicinal product.
- Submission of Application form for registration of medicinal product to the Ministry of Health.
- Payment of state fee for registration.
- Issuing an order of Ministry of Health, obtaining a Registration Certificate.

Medical devices and medical equipment of foreign production may be imported and sold in the territory of the Republic of Kazakhstan after state registration. At present Application form for state registration may be submitted both under the "national" Kazakh and under the "unified" procedure of the EAEU.

Registration is performed based on the national legislation: Order of the Minister of Health of the Republic of Kazakhstan No. 735 dated 18 November 2009, Order of the Minister of Health of the Republic of Kazakhstan No. 736 dated 18 November 2009, etc.

2.6. Kyrgyzstan

The registration expert evaluation of finished medicinal products is performed by the Department of Pharmaceutical Supply and Medical Equipment of the Ministry of Health of the Kyrgyz Republic (website: http://www.pharm.kg/).

Stages of the registration procedure in brief are as following:

1. Preparation of registration dossier.
2. Submission of the dossier and registration samples to the state authority.

3. Obtaining of invoice for conducting expert examination and payment providing.
4. Expert examination (primary and secondary) of the materials provided.
5. Replying to the expert queries, amendments and reconciliation of the text of instruction for medical use, normative document and package labelling.
6. Laboratory analysis of the samples.
7. Obtaining the positive conclusion of examination.
8. Issue of the order on state registration of the medicinal product.
9. Obtaining the Registration Certificate.

Medical devices and medical equipment of foreign production may be imported and sold in the territory of the Kyrgyz Republic after their state registration. Currently application form for registration may be submitted both according to "national" Kyrgyz and "unified" procedure of the EAEU.

2.7. Moldova

Main legislative acts regulating processes of registration and marketing of medicinal products in Moldova are as follows:

- Law of the Republic of Moldova No. 1456-XII "On Pharmaceutical Activities" dated 25 May 1993.
- Law of the Republic of Moldova No. 1409-XIII "On Medicinal Products" dated 17 December 1997.
- Order of the Ministry of Health of the Republic of Moldova No. 739 "On Authorization of Medicinal Products for Human Use and Approval of Post-Marketing Changes" dated 23 July 2012.

Registration of medicinal products is coordinated by Ministry of Health of the Republic of Moldova; examination of registration materials is performed by Medicines and Medical Devices Agency (http://amed.md/).

Medical devices not marketed in EU should be submitted for passing conformity assessment procedure in accordance with regulatory requirements of Moldova. Then data on authorized medical devices are entered in the State Register of Medical Devices. For authorization of such medical devices the following activities should be provided:

1. To appoint the authorized representative in Moldova, for which purpose the manufacturer must transfer the necessary rights to the resident legal entity of Moldova by means of the power of attorney or contract.
2. To comply with the necessary legislative requirements for package labeling and instruction for use (user manual).
3. Depending on the class of medical device:

a. For class I (non-sterile, without measurement functions) to compile technical file and issue declaration of conformity to the requirements of Regulations on setting conditions for placing medical devices on market.

b. For products of other classes to choose procedure for assessing conformity (for one batch, with inspection, etc.), to submit Application form and required technical documents to designated conformity assessment authority, to perform prescribed activities and obtain certificate of conformity.

2.8. Tajikistan

The state registration of medicines in the Republic of Tajikistan is carried out by the Ministry of Health and Social Protection, and the documentation examination is performed by the State Service for Control of Healthcare and Social Protection of the Republic of Tajikistan.

The registration procedure begins with the submission of the Application and the registration dossier to the State Service for Control of Healthcare and Social Protection of the Republic of Tajikistan. Payment of the state fee is carried out after the completion of the examination of registration documents. Tariff reductions are provided for manufacturers from the CIS countries.

Medical products, which include healthcare products, medical devices and patient care products are subject to mandatory state certification.

Registration is carried out in the name of the Applicant company (registrant). The Applicant can be a resident or non-resident legal entity of the Republic of Tajikistan. The company “Cratia” may represent the interests of the Applicant by proxy.

Registration is carried out based on the submitted Application and the package of documents, samples may also be required. The registration dossier is submitted in Russian.

The registration certificate of medical products is valid for 5 years.

2.9. Turkmenistan

The main legislative act regulating the registration and circulation of medicinal products is the Law of Turkmenistan "On Drug Provision".

The competent authority responsible for the registration of medicinal products is the Ministry of Health and Medical Industry (website www.saglykhm.gov.tm). The authorized body that performs the examination of the documentation for the medicinal products is the State Registration Center for Medicinal Products of the Ministry of Health and Medical Industry of Turkmenistan.

To register a medicinal product, the manufacturer shall appoint a representative in Turkmenistan. Data on the representative shall be indicated in the Application for registration.

The registration procedure of the medicinal product in Turkmenistan may be described by the following stages:

1. Submission of the Manufacturer's letter of reference, the application for registration, the registration dossier, samples and standards.
2. State fee payment.
3. Examination of documents.
4. Checking the reproducibility of the Drug master file methods for the medicinal product.
5. Inclusion of the medicinal product into the State Register of medicinal products authorized for manufacture in Turkmenistan or importation into Turkmenistan.
6. Issuance of registration certificate.

The main legislative act regulating the registration and circulation of medical devices is the Law of Turkmenistan "On Drug Provision".

The competent authority responsible for the registration of medical devices is the Ministry of Health and Medical Industry (website www.saglykhm.gov.tm). The authorized body performing the examination of the documents for medical devices is the State Center for Registration of Medicinal Products and State Quality Control under the Ministry of Health and the Ministry of Manufacturing Industry of Turkmenistan

2.10. Uzbekistan

The applicant (owner) of the registration can be a legal entity, both resident and non-resident of Uzbekistan. The name of such legal entity, in whose name the registration certificate is issued, is indicated in the certificate form.

The Applicant is not required to establish a representative office or company in Uzbekistan, but the Applicant shall develop and maintain a local pharmacovigilance system.

Instructions for medical use state the name and address of the organization accepting claims (proposals) on the quality of medicinal products in the territory of the Republic of Uzbekistan.

The registration procedure of a medical device in Uzbekistan can be briefly described in the following stages:

1. Submission of the Application for registration, copies of the certificate of state registration of the applying company, registration dossier, and a sample of the medical device, if necessary.
2. Primary (preliminary) examination.
3. Signing of the Agreement between the Applicant and the State Center for Expertise and Standardization of Medicinal Products.
4. Receipt and payment of examination bills.
5. After payment is confirmed, registration materials and samples are sent for specialized expertise to the structural units of the State Center for Expertise and Standardization of Medicinal Products:

a. laboratories;
b. New medical equipment committee;
c. Pharmaceutical inspection (if verification of manufacturing conditions is required).

6. During examinations and tests, questions and/or remarks may arise which the Applicant shall respond to in due time.
7. Produced positive conclusions are based on examinations and tests.
8. At the meeting of the Expert Council a decision to register the medical device and to use it in the medical practice is made.

3. CONCLUSION

CIS is an area where there is an enormous growth potential for India. Out of the major trading partners, Belarus, Kyrgyzstan, Kazakhstan, Russia, Ukraine, and Uzbekistan account for over 90 percent of India's total bilateral trade with CIS. The study of the registration requirements and registration procedure for various CIS countries has been carried out to evaluate the variation in document requirements and registration procedures of various countries. The lack of harmonization between these countries can lead to needless duplication of work and waste of valuable resources, and ultimately to increase drug lag. Harmonization makes it easy to enter more than one country in a single target and more effectively. Companies need to create only one dataset for all regions, thus reducing the number of human and animal experiments. The costs of developing regulatory documents for both new and generic drugs would also result in reduced costs. The public can rapidly access medicines of high value to health. Many Regional Harmonization Initiatives (RHIs) have been created where the geographical group of countries come together to coordinate technical and scientific requirements, and in some cases coordinating the Member States. These groups are invited to nominate permanent representatives to the Global Cooperation Group (GCG). Total exports from India of pharmaceutical formulations increased from US $ 631.90 million in 2016-17 to US $ 788.27 million in 2018-19. There is enormous potential, in the future, for drug exports of pharmaceuticals to CIS countries.

4. REFERENCES

1. Regulatory Affairs. (2019). *Pharmaguideline*,https://www.pharmaguideline.com/2012/12/regulatory-affairs.html[December 29, 2019.]. Website:
2. Regulatory Affairs. (2019). *EUPATI (2016),* https://www.eupati.eu/glossary/regulatory- affairs/[December 29, 2019.]. Website:
3. Praneeth, P. (2016). Regulatory Affairs and its Role in Pharmaceutical Industry. *SSRG-IJPBE, 3*(1), 1-2. http://dx.doi.org/10.14445/23942576/IJPBE-V3I1P101
4. Regulatory Affairs, 2019. *Gratisol Website,* http://gratisol.com/index.php/life-sciences- training/regulatory-affairs[December 29, 2019.].
5. Commonwealth of Independent States. (2019). *Cisstat.,* http://www.cisstat.com/eng/cis.html[December 30, 2019.].
6. *List of Globally identified Websites of Medicines Regulato- ry Authorities. World Health Organization (2012).* https://www.who.int/medicines/areas/quality_safety/

regulation_legislation/list_mra_websites_nov2012.pdf Website:

7. *List of Authority Websites – Tarius – Global Regulatory Requirements*.http://www.tarius.com/?page_id=612
8. *The Essential List of Regulatory Authorities in Asia*, https://www.raps.org/regulatory-focus/news- articles/2015/4/the-essential-list-of-regulatory-authorities- in-asia[December 31, 2019.].
9. *ICH CTD*, https://www.ich.org/page/ctd[December 30, 2019.]. Website:
10. Common Technical Document-Pharma Dossiers-CTD Format *Perfectdossier.*, http://www.perfectdossier.com/ctd- dossiers.html[December 30, 2019.]. Website: