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The registration process in the Republic of Kazakhstan is regulated by the order No. 735 dated November 18, 2009.

The registration term is 12 months. The marketing authorization is issued for a period of 5 years.

The organizational structure of the health care system in the examination of the registration of medical equipment and medical devices consists of the following:

1. Ministry of Health and Social Development of the Republic of Kazakhstan;
2. Pharmacy Committee;
3. RSE National Center for Expertise of Medicines and Medical Devices.

The main examination process in terms of registration of a medicinal product during the state registration and re-registration includes:

1) primary examination;
2) analytical examination;
3) specialized pharmaceutical examination
4) specialized pharmacological examination;
5) formation of an opinion on safety, efficiency and quality.

The primary examination of the registration dossier of a medicinal product includes:

1) assessment of the completeness, accuracy and satisfactory form of submitted documents of the registration dossier;

3) assessment of the composition of the medicinal product for the presence of prohibited dyes and other excipients, substances derived from human tissues and products of the animal origin, and, if available, a document confirming the safety of active substances of protein origin used in the manufacture of medicinal products (prion safety) ;

4) assessment of the composition of the medicinal product for the content of narcotic drugs, psychotropic substances and precursors;

5) examination of the name subject to the absence in it:

- graphic similarities with previously registered medicinal products and words with inconsistent expressions;
- ability to mislead regarding the true composition and action of the drug;
- advertising information regarding the use of the medicinal product and its presentation as unique, effective, safe and exceptional in the absence of side effects;
- similarities with previously registered medicinal products and words with inconsistent expressions;

6) examination for the presence of the identical name of the medicinal product (hereinafter - MP) in the state register, with a different composition of active substances;

7) examination of the regulatory document on quality control and safety of the medicinal product to the established requirements;

8) check for the presence of an indication concerning the order of delivery from pharmacies (on prescription or over the counter);

9) assessment of labeling the samples of packing layouts, labels, stickers for the compliance with legal requirements;

Analytical examination of the medicinal product includes:

1) physical, chemical, physicochemical and biological tests of samples for the compliance with the requirements of the regulatory document on medicinal product quality and safety control;

2) assessment of the regulatory document on medicinal product quality and safety control subject to the reproducibility of analysis methods and compliance of registration samples with the regulatory document on quality and safety control.

Specialized pharmaceutical examination of a medicinal product includes an assessment of:

1) chemical safety and quality of the medicinal product, impact of the changes made to the registration dossier on the safety and quality of the medicinal product;

2) composition of the medicinal product and opinion on its rationality (pharmaceutical development), quality of medicinal substances and excipients;

3) production of a medicinal product (production formula, production technology, control in the production process, validation of production processes);

4) finished product (compliance of the parameters specified in the quality certificate for finished products to the described quality control methods in the regulatory document on medicinal product quality and safety control, testing laboratory report analysis, assessment of the possibility of reproduction and objectivity of quality control methods, adequacy of the composition of the medicinal product and methods of the quality control);

5) conformity of quality indicators specified in the regulatory document on medicinal product quality and safety control of the manufacturing organization, the State Pharmacopoeia of the Republic of Kazakhstan and pharmacopoeias recognized as operating in the Republic of Kazakhstan;

6) stability of the medicinal product, validity of the specified conditions and shelf life, period of use after the first opening of the packing or dissolution;

7) data on chemical, pharmaceutical equivalence of the medicinal product;

8) labeling and packaging subject to their sufficiency to ensure the preservation of quality of the medicinal product during the storage and transportation;

9) name subject to the absence in it:

- similarities with previously registered medicinal products and words with inconsistent expressions;
- ability to mislead regarding the true composition and action of the medicinal product;
- advertising information regarding the use of the medicinal product and its presentation as unique, effective, safe and exceptional in the absence of side effects;
- similarities of INN and (or) similar names of medicinal product having the different chemical composition or action;

10) text of the instruction on the medical use of medicinal product, packing layouts, labels subject to the compliance with information on the conditions of storage, transportation, shelf life, period of use after the first opening of the packing or dissolution, and presence of the necessary warning labels;

11) composition of the medicinal product subject to the belonging to narcotic drugs, psychotropic substances and precursors, possibility or impossibility of extracting the controlled substances in an easily accessible way, in quantities sufficient for the abuse in order to exclude some control measures;

12) calculation of samples of the medicinal product, medicinal substances, standard samples of medicinal substances and their impurities, consumables (in exceptional cases and on conditions of return) for sending to analytical examination.

Specialized pharmacological examination includes:

1) analysis of the reliability of the qualitative and quantitative composition of the active substances and excipients specified in instructions for the medical use, in comparison with the composition declared in the statement, analytical regulatory document and packing layout;

2) assessment of the pharmacological compatibility of components, including excipients; in the case of registration of a generic or biosimilar, a comparison is made with the composition of the original preparation;

3) assessment of the pharmacokinetic and/or pharmacodynamic interactions for the compliance with the List of non-rational combinations of medicinal products in terms of pharmacokinetic and (or) pharmacodynamic interactions in accordance with the Annex 9-1 to this order;

4) scientifically based definition of the degree of risk of abuse: the high risk of abuse, or the risk of abuse is absent or insignificant; determination of the maximum allowable content of narcotic drugs, psychotropic substances and precursors in medicinal products;

5) analysis of the documentation on preclinical testing - assessment of the results of studies for the toxicity, effects on the reproductive function, embryotoxicity, teratogenicity, mutagenicity, carcinogenicity, pharmacodynamics, pharmacokinetics, correctness of the choice of objects and methods of the study, methods of administration and doses of the test substance, compliance of the study with provisions of the good laboratory practice;

6) analysis of the documentation of clinical studies - assessment of the report of clinical studies based on the protocol, studied contingent of subjects and their number, method of distribution of subjects into treatment groups, doses, treatment methods, levels and methods of blind test conduction, type of control, methods of statistical analysis of the obtained data, compliance of the study with requirements of the good clinical practice;

7) assessment of the safety and efficacy of the drug in view of the results of clinical studies based on an analysis of the observed complications, side effects, measures to eliminate them, doses of the medicinal product, concentration and their relationship with the safety and efficacy of the medicinal product;

8) analysis of the data of equivalence studies (in case of the state registration of generic) - assessment of a report on bioequivalence studies based on the protocol, assessment of the correctness of choice of the medicinal product for the comparison, study conditions, methods for determining the concentration of the medicinal product, plotting, calculation of parameters, justification of conclusions regarding the bioequivalence; in case of a generic application for the biowaiver procedure, the assessment of feasibility of the biowaiver procedure based on the in-vitro study documentation provided;

9) assessment of the similarity of the biosimilar with the original preparation based on the analysis of data from comparative trials of preclinical and clinical studies, immunogenicity;

10) check of the compliance of a text of instructions for the medical use subject to the reliability of the information about indications and contraindications to use, doses, methods of administration (injection), side effects, precautionary measures, first aid in case of overdose, shelf life, storage conditions, order of delivery from pharmacies (general characteristics of the medicinal product or approved instructions for the medical use for manufacturers of CIS countries; information on the websites of the regulatory authorities of the manufacturer’s country, EMA, FDA) and the compliance of the modern reference information; analysis of the compliance of indications for the use, contraindications, side effects, medicinal product interactions, special instructions for the generic and biosimilar with regard to the original medicinal product;

11) assessment of the correctness of assignment of an anatomic-therapeutic-chemical classification code depending on the pharmacological properties and indications for the use;

12) check of the adequacy of specified doses according to pharmacokinetic parameters - analysis of recommended doses, dosage regimen taking into account the pharmacokinetic properties (half-life, degree of binding with plasma proteins, effect on liver enzyme activity, time of bacteriostatic (bactericidal) concentration in case of antibacterial medicinal product), paying special attention to the doses recommended for children, elderly, patients with impaired renal, liver function;

13) analysis of the correctness of the specified shelf-life – conduction of the comparison of shelf-life specified: in the application, in the brief description of the medicinal product, in the instructions for the medical use, in the packing layout, and compliance with its shelf life specified in the regulatory document;

- name subject to the absence in it:
- similarities with previously registered medicinal products and words with inconsistent expressions;
- ability to mislead regarding the true composition and action of the medicinal product;
- advertising information regarding the use of the medicinal product and its presentation as unique, effective, safe and exceptional in the absence of side effects;

14) similarities of INN and (or) similar names of medicinal product having the different chemical composition or action;

15) determination of the delivery order (on prescription, over-the-counter) taking into account the pharmacological action, side effect profile, risk of overdose, dependence and abuse;

16) assessment of the source of origin (blood, organs, tissues of humans and animals) and specific activity for immunobiological preparations;

17) assessment of the proposed changes to the registration dossier, and, if necessary, minimization of known or potential risks when using the medicinal product, the marketing authorization holder shall provide a risk management plan for the medicinal product;

18) assessment of the pharmacovigilance system of the marketing authorization holder;

19) assessment of the risk management plan: analysis of all problematic issues identified during the evaluation of the medicinal product dossier that may affect the risk management plan (such issues include preclinical safety results, deficiencies in clinical pharmacology data, potential safety signals coming from clinical studies, etc.); whether the risk management plan takes into account important identified risks, important potential risks, important missing information;

20) assessment of the safety and efficacy of the medicinal product based on data from periodically updated safety reports - analysis of the safety profile, introduction of new side effects, contraindications to the brief description of the medicinal product and instructions for the medical use or refusal to reregister the medicinal product, changes in the registration status of the medicinal product in other countries, updated data on measures taken by the regulatory authority or the manufacturer for safety reasons, changes in the medicinal product safety information, sales, number of patients who received the medicinal product during the reporting period, study of the description of individual cases and a list of side effects and summary tables, individual cases of manifestations of side effects identified by the marketing authorization holder, nature and number of serious side effects not previously registered by the company; general safety assessment based on the data from periodically updated safety reports and an opinion on maintaining or changing the safety profile, introducing the new side effects, contraindications to instructions for the medical use or refusing to reregister the medicinal product;

21) recommendation for the state registration and (or) re-registration or introduction of declared changes to the registration dossier for the period of validity of the marketing authorization or justification of the necessity to submit additional materials; or reasoned recommendation in the refusal of the state registration and (or) making the specified changes in the registration dossier.

Opinion on the safety and quality.

- According to the results of the primary, specialized examination, an opinion is drawn up regarding the safety, efficacy and quality of the medicinal product under the form.
- In order to increase the transparency, objectivity, independence and consistency of the results of the examination of medicinal product, the state expert organization creates the collegial expert council (hereinafter referred to as the council) for its further consideration.
- The council board includes experts in various fields of medicine and pharmacy, with the experience and qualifications in the field of conduction of the examination for the assessment of

effectiveness, safety and quality of MD, as well as the representatives of non-governmental organizations subject to agreement.

- The council considers the differences arising in results of the examination, the grounds (reasons) for issuing negative opinions on the effectiveness, safety and quality.

Terms for the conduction of examination of each stage:

1) primary examination - not more than thirty five calendar days, including confirmation of the authenticity of translation of the labeling for primary and secondary packing, labels, stickers (not more than two working days);

2) analytical examination - not more than seventy five calendar days;

3) specialized pharmaceutical examination - not more than eighty calendar days (with the specialized pharmaceutical examination of aqueous solutions of generic products and the introduction of transfer of industrial and technological processes - not more than 40 calendar days), including confirmation of the authenticity of translation of the labeling for packing, labels, stickers (not more than two working days);

4) specialized pharmacological examination - not more than eighty calendar days (with the specialized pharmacological examination of aqueous solutions of generic products and the introduction of transfer of industrial and technological processes - not more than 40 calendar days), including verification of the authenticity of translation of instructions for the medical use (not more than fifteen calendar days);

5) formation of an opinion on the safety, efficacy and quality of a medicinal product, drafts of final documents for the examination of medicinal products - not more than twenty calendar days.