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BRINGING THE REGISTRATION DOSSIER FOR A MEDICINAL PRODUCT TO CONFORMITY WITH THE REQUIREMENTS OF THE EURASIAN ECONOMIC UNION

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At the moment, the pharmaceutical market is gradually moving from the circulation of medicines according to national requirements to the common market of the Eurasian Economic Union (EEU). Until December 31, 2020, the applicant can register a medicinal product according to both national requirements and the rules of the EEU. All registration dossiers (RD) for the medical products must be brought to conformity with the requirements of the EEU by December 31, 2025. The article analyzes the registration procedures and regulatory documents that explain the requirements for the design and content of the RD, which will facilitate the process of bringing the RD to conformity with the requirements of the EEU for Market Authorization Holders (MAH). Thus, during the analysis, the documents necessary for adding to the registration dossier (RD) were identified when it is brought to conformity with the EEU rules in modules 1–5 of the Common Technical Document (CTD).

Keywords: medicinal product, medicine, marketing authorization, Eurasian Economic Union, general pharmaceutical market, registration dossier, common technical document, Market Authorization Holder

One of the functions that form the basis of state regulation of medicines is marketing authorization. Marketing authorization of a medicinal product is the process of obtaining a permit for medical use of a medicinal product, carried out in accordance with current legislation. "For the state registration of a medicinal product, the applicant shall submit to the appropriate Authorized Federal Executive body carrying out state registration of medicinal products, the marketing authorization application for a medicinal product and in accordance with the corresponding procedure of the Authorized Federal Executive body, the necessary documents which form the registration dossier for the medicinal product" [1]. In accordance with Art. 18, p. 3 [1], the registration dossier (RD) for medicinal products for medical use is provided in the form of a Common Technical Document (CTD). The principle of documentation is specified in all good practices. Documenting is a great way of self-reflection. Comprehensive documentation is always required for audit and inspection control. Unlike inspection purposes, for marketing authorization and examination purposes the comprehensive documentation is not required. The registration dossier (RD) does not include all documents that are required by the rules of good practice, called GxP.

One of the main provisions of the Agreement on common principles and rules for the circulation of medicines within the EEU dated December 23, 2014 is the smooth transition of marketing authorization of medicines from national requirements to supranational requirements of the EEU. To solve this problem, the Council of the Eurasian Economic Commission made Decision No. 78 dated 03.11.2016 "On the rules for marketing authorization and examination of medicines for medical use" [4], which will become mandatory for all states-members of the EEU from January 1, 2021. Until December 31, 2020, you can register a medicinal product according to both national requirements and the rules of the EEU. From January 1, 2021 the marketing authorization shall be provided only under the legislation of the EEU, but medical products previously registered under national rules will circulate until the expiration of the marketing authorization certificate (but no later than December 31, 2025) on the territory of the country under rules of which they are registered. Accordingly, all RDs for medicinal products that are registered before December 31, 2020, must be brought conformity with the requirements of the EEU by December 31, 2025. There are two registration procedures within the European Economic Union for new medicinal products that are not registered in the EEU. One of them is the procedure of mutual recognition, when the medicinal product is successively submitted for registration in several states, first to the reference state, and then to the member states concerned (if desired, it can be registered only in the reference state). Another procedure is a decentralized registration procedure, when there is a simultaneous filing of RD for the medicinal product in several countries with selection of the reference state.

For medicines that are registered in the EEU States according to national requirements, there is a procedure for bringing the RD documents to conformity with the requirements of the EEU, making amendments to the RD and confirming registration. In this regard, a number of problems arise, including such as the purchase or creation of software XML to create an electronic common technical document (eCTD) [5,6], re-provide clinical and preclinical studies, for which there is a need for the development and making of organizational and managerial decisions both at the level of various departments (e.g. Registration Department) and senior management of the company.

For Russian pharmaceutical companies, this transition of registration is complicated by new regulations that will allow the circulation of medicines. The search for inconsistencies and differences between the EEU and the Russian Federation takes a sufficient amount of time, because it is necessary not only to identify differences in the rules of the EEU, but also to apply the rules and eliminate inconsistencies in your company.

The purpose of this study is to review the documents of regulatory authorities to resolve the problems that may arise in the Market Authorization Holder (MAH) in the process of bringing the RD for registered medicinal products to conformity with the rules of the EEU.

MATERIALS AND METHODS OF THE STUDY

The main method used in this study is a comparative analysis of registration procedures between the Russian Federation, the Eurasian Economic Union, and the European Union (EU). In the course of this analysis, both the main differences and certain similarities in the procedures were identified, which served as a starting point in searching for problems that may arise for pharmaceutical manufacturers in the process of mandatory re-registration under the requirements of the EEU.

RESULTS AND DISCUSSION

The Market Authorization Holder (MAH) must perform work until December 31, 2025 to provide the RD in the format of a common technical document (CTD) of the EEU to the authorized bodies of the EEU member-states. When bringing the documents to conformity with the requirements of the Union, the applicant can simultaneously amend the registration dossier. The duration of this procedure is no more than 100 calendar days. The applicant independently selects the reference state, then in the Member State concerned brings the registration dossier to confirmity with the type of mutual recognition. Required documents [4]: application in hard copy and (or) in the form of an electronic document in accordance with Annex 2; state fees in accordance with the procedure specified in the reference state and the Member State concerned; RD (modules 1–3) in electronic form. Module 1 is provided on paper, if the medicine is intended for circulation in the territory of the member-state in which it was registered, and modules 4–5 (without necessarily bringing them to conformity with the requirements of the Union for preparation of reports on preclinical studies and clinical trials). The risk management plan, the main dossier (master file) of the production site (s) and the pharmacovigilance master file are also provided in electronic form. When conducting an examination of the registration dossier as part of its harmonization with the requirements of the Union, the "benefit – risk" ratio is not re-evaluated [4]. An exception can only be made if the medicinal product is in the future applied for registration under the mutual recognition procedure in member -states where it was not registered before the entry into force of the Agreement, or before December 31, 2020 after bringing its registration dossier to conformity with the requirements of the Union.

In addition to significant changes in the authorisation procedure and quality evaluation, significant changes also affected the structure of the RD. The requirements for the execution of the dossier and its content have expanded. The contents of the CTD of the Russian Federation and the EEU differ significantly. For example, the administrative part of the EEU dossier does not belong to the CTD, unlike the Russian Federation. Also, the CTD of the Russian Federation does not include the content and introduction to the CTD, reviews and summaries of preclinical and clinical studies. The differences in the authorisation procedures for medicinal products in the Russian Federation, the European Union and the Eurasian Economic Union are due to the fact that the Russian Federation is a separate state that has its own authorized bodies, each of which fulfils a certain role in the authorisation process. As for the EU and the EEU, they are unions of several countries, so the authorisation process differs depending on the chosen procedure. Thus, it follows that in a decentralized procedure or under the procedure of mutual recognition in both the EU and the EEU, the authorized registration body is the national agency (in the EU) or the authorized body of the member state (in the EEU). In addition, the EU has a centralized procedure, unlike the EEU. The duration of the authorisation procedure for a medicinal product in the Russian Federation is 160 working days. But in the EU and the EEU the durations of the authorisation are the same and in the decentralized procedure the duration is 210 working days, and in the mutual recognition procedure it is 90 days. In case of authorization according to the rules of the EEU and the EU it is necessary to be more careful with post-marketing studies of the medicinl product, than in Russia, as they can not in every case issue a perpetual license upon the expiration of five-year period of validity of marketing authorisation.

The range of subjects of circulation of medicines involved in obtaining of marketing authorization has expanded. Subjects of circulation of medicines participating in obtaining of marketing authorization within the EEU are the Eurasian

Economic Commission; authorized (regulatory) bodies of the EEU member-states, including the Ministry of Health of the Russian Federation; expert institutions of the member-states, in particular NC ESMP of the Ministry of Health of the Russian Federation.

Marketing authorization application forms also differ between the Russian Federation and the EEU: the Russian Federation form is the same regardless of the type of a medicinal product, and the EEU form contains different information depending on the type of a medicinal product. In the Russian Federation, the application includes the minimum required amount of information that allows you to subsequently form a marketing authorization and release the medicinal product into circulation, and in the Eurasian economic Union, the application contains a significant amount of additional administrative information that is responsible for the safety of the medicine in circulation in all member-states.

For example, according to the rules of the EEU [4], only module 1 (administrative information) of the registration dossier for a medicinal product is provided on paper. The main file, modules 2–5 are available only in electronic format in accordance with the requirements of [4] to the structure of electronic folder, that for the Russian Federation is an innovation, because in Russia dossier is submitted entirely in electronic and in paper forms [1]. This fact may be a failure for applicants who have only one attempt to correct errors within the framework of an additional request, whereas in Russia the number of additional requests was unlimited. And the EEU procedure provides for only one request at the stage of evaluating the completeness and reliability (validation) of the registration dossier for a medicinal product, and one additional request during the examination process. At the same time, the applicant is limited to 90 calendar days for providing a response. If the response is not provided or is incorrect, the application will be rejected in accordance with the established procedure during the dossier validation stage. There is no legal restriction on the refiling of RD to the regulatory authority. In case of refusal to review the documents, the state fee is not returned, and if you re-submit the documents, you will need to pay it again.

According to [4], it is possible to submit a simplified RD for certain types of medicines. For herbal and homeopathic medicines, it is possible to submit a simplified type of dossier. There are also special requirements for medicines with well-studied medical applications [4].

Differences in the structure of the registration dossier (RD) are shown in the diagram. According to the diagram, the content of the Russian CTD has 4 sections, while the EU and EEU CTDs have 5 modules each, which are similar to each other in content and name, because the structure of the EEU CTD was based on Directive 2001/83/EC [7]. In the CTD structure in the Russian Federation there are only 4 sections and 58 sub-sections, whereas in the EEU, the CTD has 5 modules, which contain 91 subsections that requires thorough study of composition of the dossier for the EEU in order to correctly complement the CTD with missing documents to bring the medicine to conformity with the rules of the Union. Module 1 of the EEU RD is similar to section 1 of the Russian dossier, but contains more items. Significant changes are associated with the introduction of new module 2 "Summary of the Common technical document" in the EEU, which includes brief information on preclinical and clinical studies, as well as on quality. The information should reflect the summary actual data of modules 3–5. Module 3 of the EEU CTD is similar to section 2 of the Russian dossier, but contains more documentation. Modules 4–5 of the Union dossier include the results of preclinical and clinical studies confirming the effectiveness and safety of human use of the medicine.

In the Russian Federation, the presence of preclinical and clinical studies of the medicinal product is mandatory when submitting the RD

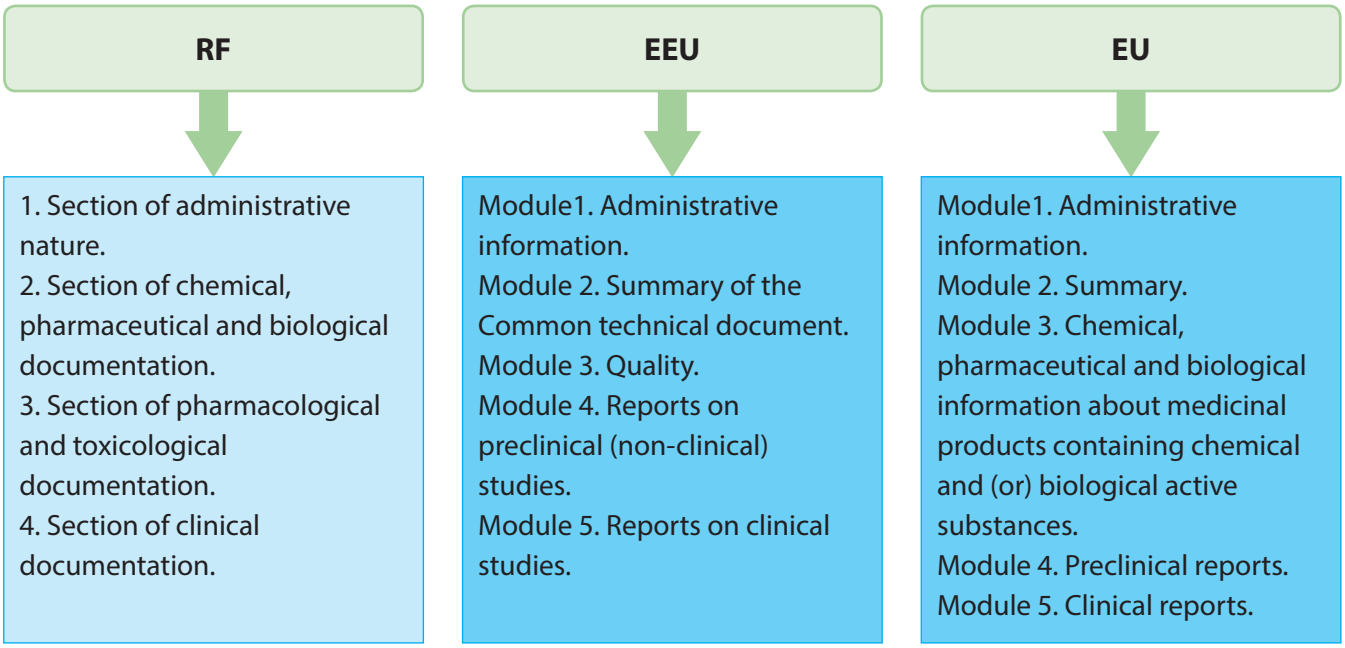

DIAGRAM. *Structure of the registration dossier (CTD) for medicines in the RF, EEU and EU countries*

[8]. However, for generics (other than biological ones) that have been on the market for more than twenty years, the manufacturer can apply reviews of scientific papers, as well as experience of their post-authorization use, instead of reports on preclinical and clinical studies. In addition, when authorizating the generics, it is allowed to apply instead of medicine manufacturers' reports on clinical studies, the reviews of scientific works based on the reference standard, and instead of reports on clinical studies, bioequivalence studies [1]. However, this report is not required to be attached in accordance with article 18 of Federal law No. 6-FZ [1] if the certain conditions are met.

In the EEU, pre-clinical and clinical studies are also required when authorizating a medicinal product. Just like in the Russian Federation, the EEU has a simplified version of submitting a package of documents for clinical trials, for example, bioequivalence studies are not required for certain medications [7]. For the rest of medicinal products, preclinical studies must comply with the GLP (Good laboratories practice) of the EEU, and clinical studies must comply with GCP (Good clinical practice) of the EEU. Preclinical and clinical studies of medicinal products that have been conducted in non-EU countries are considered in the course of medicine examination, if these studies were conducted and described in the report on preclinical and clinical studies in accordance with the requirements of GLP and GCP, as well as the requirements of the EEU (or not lower) [4]. In the RD for homeopathic medicines, modules 4 and 5 are missing, and modules 1–3 must be attached, but not in full.

So, during analysis the following documents which are required for adding to the RD were identified in accordance with the EEU rules.

Module 1. Administrative information

- draft general characteristic of the medicinal product;
- letter of a holder of the Master-file for active pharmaceutical ingredients (API) with obligation to inform on any changes both the medicine manufacturer and authorized body of member-state before introduction of any significant amendments;
- GMP-certificate issued under the EEU rules;
- letter of an quality authorized person on compliance of conditions of production of the

medicinal product presented for authorisation with the requirements of the EEU Guidelines of Good Manufacturing Practice;
- information about claims regarding the quality of themedicinal products for the last 3 years;
- consent of the applicant to conduct the pharmaceutical inspection for compliance with the requirements of the EEU Guidelines of Good Manufacturing Practice (GMP);
- a copy of the Site Master File;
- diagram of production stages with indication of all production sites involved in the process of production and quality control of medicinal products;
- a brief summary of the professionals who prepared a summary on the quality, preclinical and clinical data;
- a letter stating that the Market Authorization Holder (MAH) is a qualified person responsible for pharmacovigilance on the territory of a member-state of the EEU;
- risk management plan for the medicine in accordance with the requirements of the EEU Guidelines of good practice of pharmacovigilance.

Module 2. Summary of the Common technical document

Seven subsections that must be attached in accordance with Appendices 1 and 5 [4] are completely absent in the Russian Federation.

Module 3. Quality

- specifications and their justifications related to the medicine;
- summary of stability studies and conclusion;
- post-authorisation stability studies program and stability commitment;
- production facilities and equipment;
- evaluation of safety regarding extraneous agents;
- regional information;
- copies of the literature sources used.
- In this module, it is necessary to finalize the following documents:
- description of pharmaceutical development of the medicine.

Module 4. Reports on preclinical (non-clinical) studies

- copies of the literature sources.

Module 5. Reports on clinical studies

- list of all clinical studies in the form of a table;
- biopharmaceutical study reports;
- post-authorisation use experience reports;
- case record forms and patient lists;
- copies of the literature sources.

After bringing the registration dossier documents to conformity with the requirements of the EEU, if the medicinal product has been authorised in three states for 5 years or more, a perpetual marketing authorisation certificate is issued. If the medicinal product has been authorised in three countries for less than 5 years, a marketing authorisation certificate is issued for 5 years, and then the re-authorisation procedure must be carried out.

CONCLUSION:

Due to the transition of the medicine market from national requirements to supranational ones, the Market Authorization Holder (MAH) has the opportunity of circulation of medicinal products in the common market of the EEU. When bringing the RD to conformity with the requirements of the EEU the Market Authorization Holder must take into account the following:

1. The need to update documentation according to the requirements of the EEU.

2. Inability to submit the RD on paper, except for the 1st module.

3. Possibility of a simplified RD for a medicine when submitting it for authorisation/re-authorisation.

4. Possibility of scientific advice from the authorized body of the EEU member -state.

5. Expertise on the "benefit-risk" ratio is not required when bringing the RD to conformity with the requirements of the EEU.

6. Possibility of making changes to the RD before submitting it to the authorized body of the reference state

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