

Arranging Introduction of Changes in Registration Dossier for a Registered Drug in Russia

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Abstract.

The article considers specifics of arranging introduction of changes in the registration dossier for a registered drug. The authors used the system method to develop and propose charts for the formation of a set of documents in order to introduce changes in the registration dossier for a registered drug in Russia. These charts are compiled with due regard for Russian law and clearly show how to properly compile a set of documents for making the most common changes in the registration dossier.

Key words. Drugs registration, registration dossier for a drug, charts, registered drug.

INTRODUCTION

Drugs can be introduced into civil circulation on the territory of the Russian Federation if they are registered by the appropriate authorized federal executive body.

The authorized federal executive body regulating the drugs' registration is the Ministry of Health of the Russian Federation. The Department of State Regulation of Drugs Circulation under the Ministry of Health of the Russian Federation is engaged in registration of new drugs and circulation of already registered drugs.

For the purposes of state registration of a drug, a registration dossier is formed as a general technical document representing a set of documents and materials consisting of several sections: administrative documentation, chemical, pharmaceutical and biological documentation, pharmacological, toxicological documentation, and clinical documentation. The registration dossier contains exhaustive information about a particular drug [1].

In cases of changes in information contained in the documents of the registration dossier for a registered drug at the time of its registration, it becomes necessary to make changes to the registration dossier.

METHODS

Based on the system method of the study, charts were developed and proposed for the formation of a set of documents in order to introduce changes in the registration dossier for a registered drug.

RESULTS

Currently, the regulatory framework governing the arrangement of changes in the registration dossier for a registered drug in Russia is made up of the Federal Law [2], the Tax Code [3], the Decree of the Government of the Russian Federation [4], and the Orders [5,6,7,8,9,10] of the Ministry of Health of the Russian Federation.

Besides, since early 2017, the Federal Law has been amended [2], and the Ministry of Health of the Russian Federation has approved the classification of

changes introduced in the documents contained in the registration dossier for a registered drug [6].

The following are the changes made to the documents contained in the registration dossier for a registered drug that do not require execution of an examination of the proposed methods for drug quality control, the quality of the submitted drug samples using these methods and/or examination of the ratio of the expected benefit to the possible risk of drug use:

- change in the name, form of legal entity's incorporation, address, contact information of the holder or owner of the registration certificate;
- change in the name, form of legal entity's incorporation, contact information of the drug manufacturer, not related to the change in the place of production of the drug and/or the pharmaceutical substance included in the drug;
- exclusion of one or more participants in the drug production process;
- replacement or addition of one or more participants in the drug production process who carry out the drug quality control and its packaging in the secondary (consumer) packaging;
- change in the name and/or address of the organization authorized by the holder or owner of the drug registration certificate to accept claims from consumers;
- changes aimed at correcting misprints and misspellings;
- changes in the design of the drug labeling;
- change in the name and/or address of the manufacturer or supplier of any source material, reagent or intermediate matter of the pharmaceutical substance, not related to the change in the place of their production;
- change in the characteristics and properties of packaging materials and means of sealing that are not in contact with the drug;

- change in the pharmacovigilance system of the holder or owner of the drug registration certificate;
- exclusion of the primary packaging of the drug, which has no impact on the dosing regimen [6].

The following are the changes that require execution of an examination of the proposed methods for drug quality control and the quality of the submitted drug samples using these methods and/or examination of the ratio of the expected benefit to the possible risk of drug use:

- change in the drug trade name;
- change in the international unpatented, chemical name of the drug or pharmaceutical substance;
- changes related to the change in the drug name or code under the Anatomical Therapeutic Chemical Classification System recommended by the World Health Organization;
- change in the drug dosage form without changes in the qualitative composition and/or quantitative composition of active ingredients and/or qualitative composition of the drug additive agents;
- change in the description of the finished dosage form caused by the addition, modification or removal of engravings, thickenings or other markings that have no impact on the drug dosage, as well as changes in the shape of pills, capsules, suppositories;
- change in the information about the drug pharmacodynamics and pharmacokinetics (except for pharmacokinetics of homeopathic and herbal drugs);
- change and/or additions of indications, contraindications for the drug use;
- addition of new precautions for the drug use;
- change in the indication of the possibility and specifics of the drug use by pregnant women, breastfeeding women, children and adults with chronic diseases;
- change in the dosage regimen, method of administration and use, time of the drug administration (if necessary), duration of treatment, including in children younger and older than one year;
- change and/or additions of information on possible side effects and undesirable reactions during the drug use;
- change and/or additions of information on symptoms of overdose, measures to assist in drug overdose;
- about interaction with other drugs and/or food products;
- about the specifics of the drug effect at its first administration or withdrawal;
- change in information about the possible drug effect on the ability to drive vehicles and mechanisms;
- change in the conditions for drug dispensing;
- change in the forms of the drug presentation, addition or replacement of the measuring device for single-dose preparation;
- change in the drug shelf life and storage conditions;
- change in the information contained in the instruction for the drug medical use or a brief drug description approved in the producer country;
- change and/or addition, and/or deletion of quality indicators, methods for determining the quality

indicators and/or addition and/or deletion of an alternative method for determining, changes for the purpose of carrying out drug regulatory documentation in accordance with the requirements of the state pharmacopoeia;

- exclusion of the drug dosage;
- change in the risk management plan for biological drugs;
- change or addition of one or more participants in the process of the drug production related to the change in the places of the drug production;
- change in the production process and/or technology, and/or change in the control methods at one or several stages of the drug production, subject to no changes in the drug specification, changes in the specification for the pharmaceutical substance;
- change in the process of production of a herbal drug, related to the change in the geographical source, method of production or manufacture of that herbal drug;
- change in the analytical methods used in the drug quality control, change in the standard samples or substances used in the drug quality control;
- change in the characteristics and properties of packaging materials and means of sealing the primary packaging of pharmaceutical substances, change in the data on the drug stability;
- change in the shelf life of the pharmaceutical substance, change in the drug microbiological characteristics;
- change in the description and/or composition of the excipients contained in the drug;
- change in the drug primary packaging in terms of including additional primary packaging;
- change in the information on the drug toxicological properties;
- change in the information on the drug bioavailability and bioequivalence, data on the drug clinical efficacy and safety, data on the practical post-marketing study of the drug [6].

To compile a set of documents for the purpose of introducing changes in the registration dossier for a registered drug for medical use, the holder or owner of the registration certificate of the drug or another legal entity authorized by them (hereinafter referred to as the applicant) compiles a set of documents, which includes:

- application for changes in due form [9];
- copies of documents evidencing the payment of the state fee for introducing changes in the documents contained in the registration dossier for a registered drug for medical use that require execution of an expert examination in the amount of 1,000 Euros, changes that do not require execution of an expert examination of the drug in the amount of 70 Euros [3];
- changes in the above documents;
- documents confirming the need to introduce changes;

– if the changes are to be introduced in the documents from the registration dossier for a registered drug that require execution of an expert examination of the drug quality and/or expert examination of the ratio of the expected benefit to the possible risk of using the drug for medical use:

a) if the drug is produced in the Russian Federation, then a copy of the license for the drugs production is required, or a copy of the conclusion [12] on the conformity of the drugs producer to the requirements of the rules [14] of the due manufacturing practices issued by the authorized federal executive body;

b) if the drug is produced outside the Russian Federation, then a copy of the license issued by the authorized body of the producer's country for the drug production and its translation into Russian, certified in accordance with the established procedure [12], as well as a copy of the conclusion [12] on the conformity of the drugs producer to the requirements of the rules [14] of the due manufacturing practices issued by the authorized federal executive body are required [2].

Changes in the registration dossier are compiled based on the declared type of the expert examination, with observance of general recommendations for all types of expert examinations. The set of documents and data are presented in folders with the following information on the cover: the drug trade name, the international unpatented name, the dosage form, the dosage, the name of the applicant's organization [1]. All documents must be submitted in Russian or have a duly certified translation into Russian.

A letter of justification of the need to introduce changes in the documents contained in the registration dossier is made, reflecting the information on the changes introduced with the justification of reasons. A power of attorney for the submission of documents or its copy, and a copy of the valid registration certificate for the drug are attached to the set of documents for introducing changes to the registration dossier.

The drafts of statements of changes to regulatory documents, instructions for the drug medical use [11], the draft models of primary and secondary packaging are presented in at least 2 copies, signed by an authorized person and certified by their seal.

The applicant also attaches the set of documents for introducing changes in the registration dossier for a registered drug to the application electronically on the website of the Ministry of Health of the Russian Federation.

The application for introducing changes to the documents contained in the registration dossier for the registered drug [9], submitted to the Ministry of Health of the Russian Federation, and the documents are accepted as per checklist and registered on the day they are received. A copy of the application with a note of the date of receipt of the above application and documents is sent (handed) to the applicant [5].

Having studied out the specifics of compiling a set of documents to introduce changes in the registration dossier for a registered drug, it is worth noting that there is

no clear list of documents confirming the need to introduce changes in the registration dossier for a registered drug at the moment, which respectively complicates the work. Besides, since January 1, 2017, if changes are needed in the registration dossier documents for a registered drug that require execution of the expert examination, in case of production outside Russia for each participant in the production process, the applicant has to provide a copy of the certificate of the drug producer compliance with GMP requirements issued by the Ministry of Industry and Trade of Russia, and in case of the drug production in Russia for each participant in the production process, the applicant has to provide a copy of the license for drug production or a copy of the certificate of the drug producer compliance with GMP requirements issued by the Ministry of Industry and Trade of Russia.

The authors have developed and proposed charts that describe compiling of a set of documents with a view to introducing changes in the registration dossier for a registered drug in Russia. These charts (charts 1-3) are designed with due regard for Russian law and clearly reflect how to correctly compile a set of documents for introducing the most common changes in the registration dossier.

As such, the presented charts 1,2 and 3 clearly reflect how to correctly compile a set of documents for introducing the most common changes in the documents contained in the registration dossier for a registered drug.

DISCUSSION

The regulatory framework that regulates the arrangement of changes in the registration dossier for a registered drug in Russia was significantly amended in 2016. Amendments were made to Article 30 of the Federal Law No. 61-FZ "On drugs circulation" and came into force on 01.01.2017. The administrative policy of the Ministry of Health of the Russian Federation for the provision of a state service for the state registration of drugs for medical use was approved, along with a classification of changes introduced in the documents contained in the registration dossier for a registered drug for medical use.

The adoption of this classification of changes indicated the need for evaluation of the need for examination of changes in the documents contained in the registration dossier for a registered drug.

The applicant's work on introducing changes in the registration dossier for a registered drug primarily consists in compiling a set of documents with a view to introducing changes in the registration dossier.

The completeness and reliability of the information contained in the materials submitted by the applicant during the introduction of changes in the registration dossier for the registered drug are evaluated by checking the availability of the mandatory list of documents and verifying the authenticity of the information contained in those documents. At this stage, difficulties occur in the interpretation of documents confirming the introduction of changes, as well as with designing drafts of changes to regulatory documents, instructions for medical use, and draft packaging models.

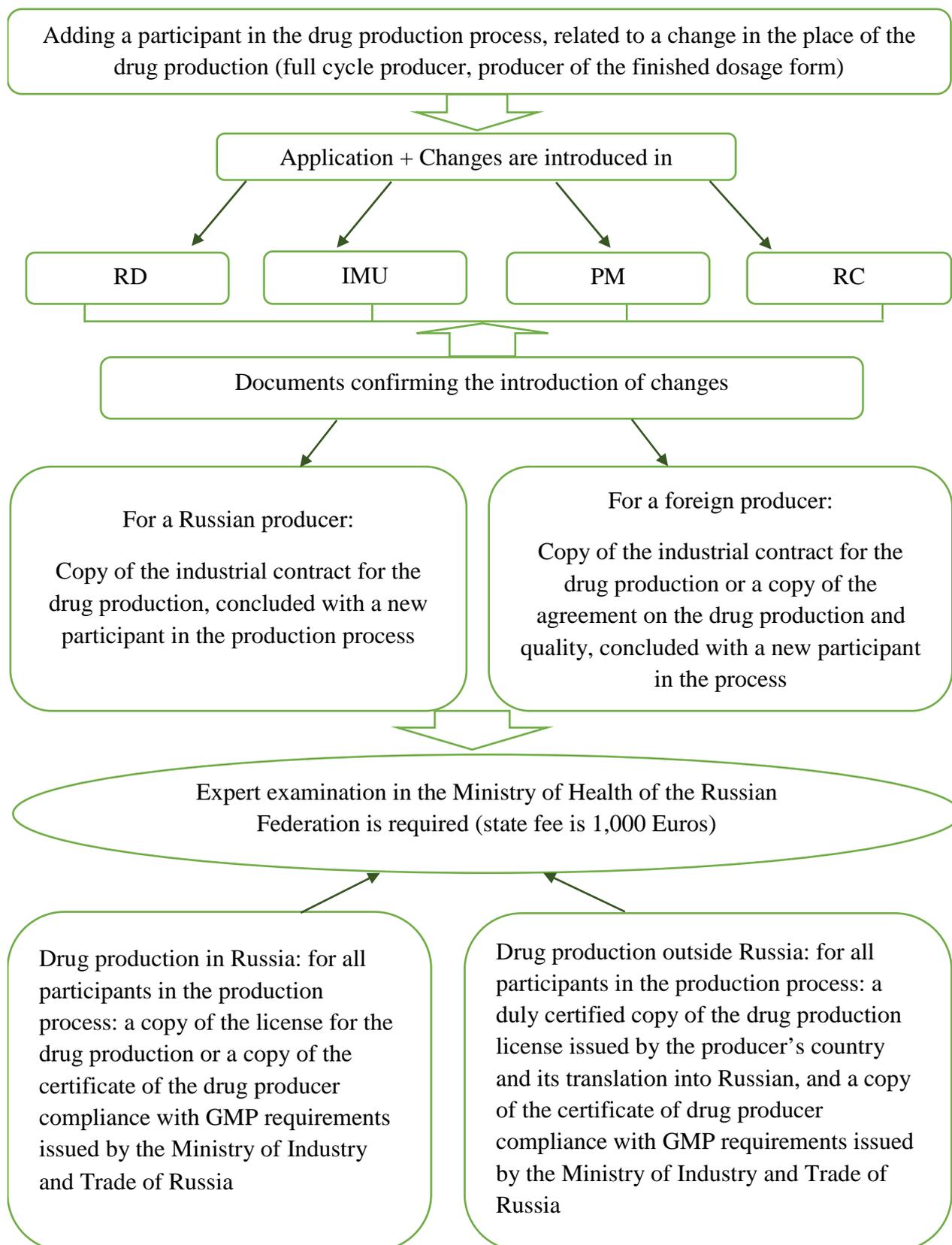


Chart 1. Compiling a set of documents for introducing changes in the registration dossier for a registered drug in Russia in case of adding a participant in the production process: RD – regulatory document, IMU – instruction for medical use, PM – packaging model, RC –

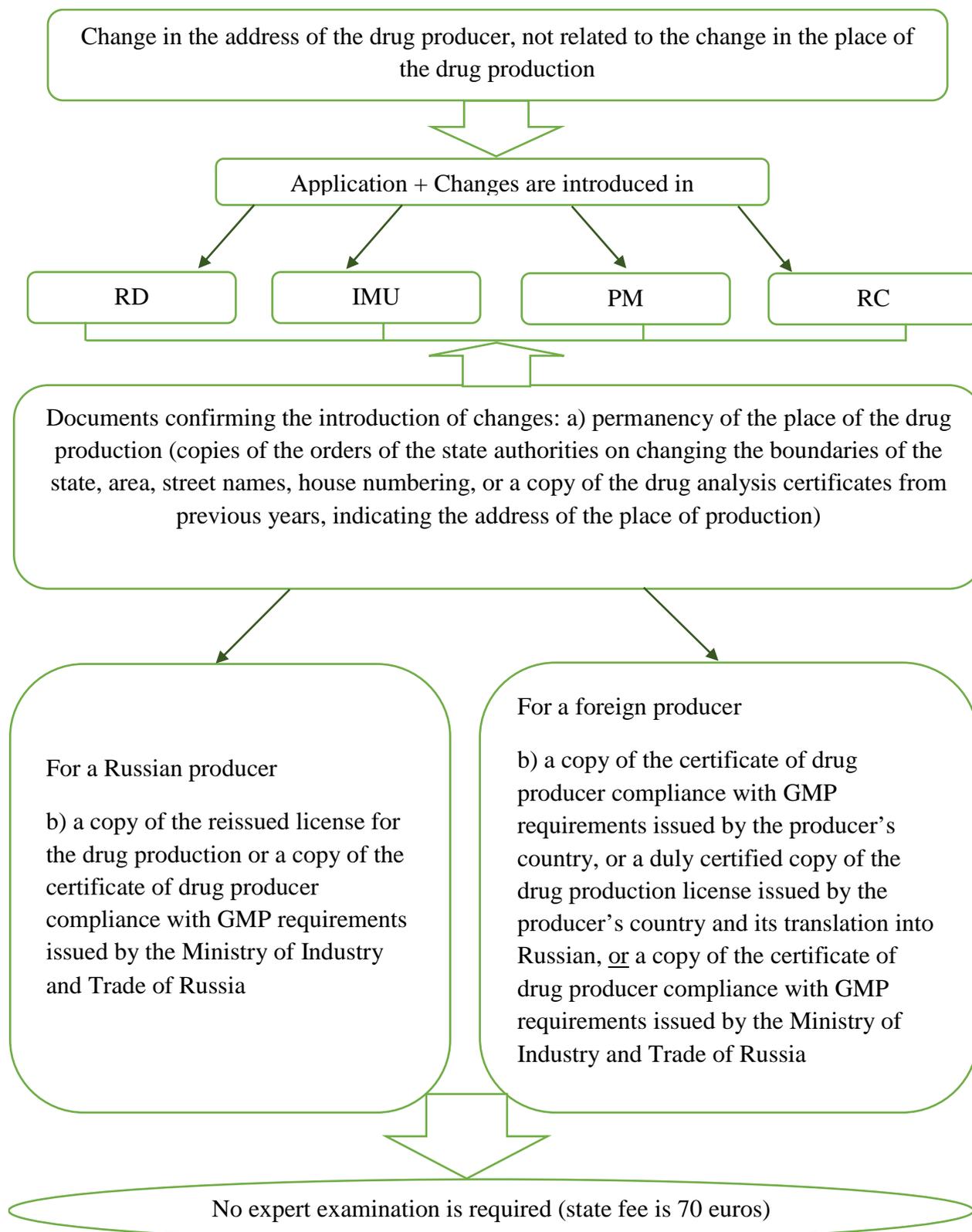


Chart 2. Compiling a set of documents for introducing changes in the registration dossier for a registered drug in Russia in case of the change in the address of the drug producer: RD – regulatory document, IMU – instruction for medical use, PM – packaging model, RC – registration certificate

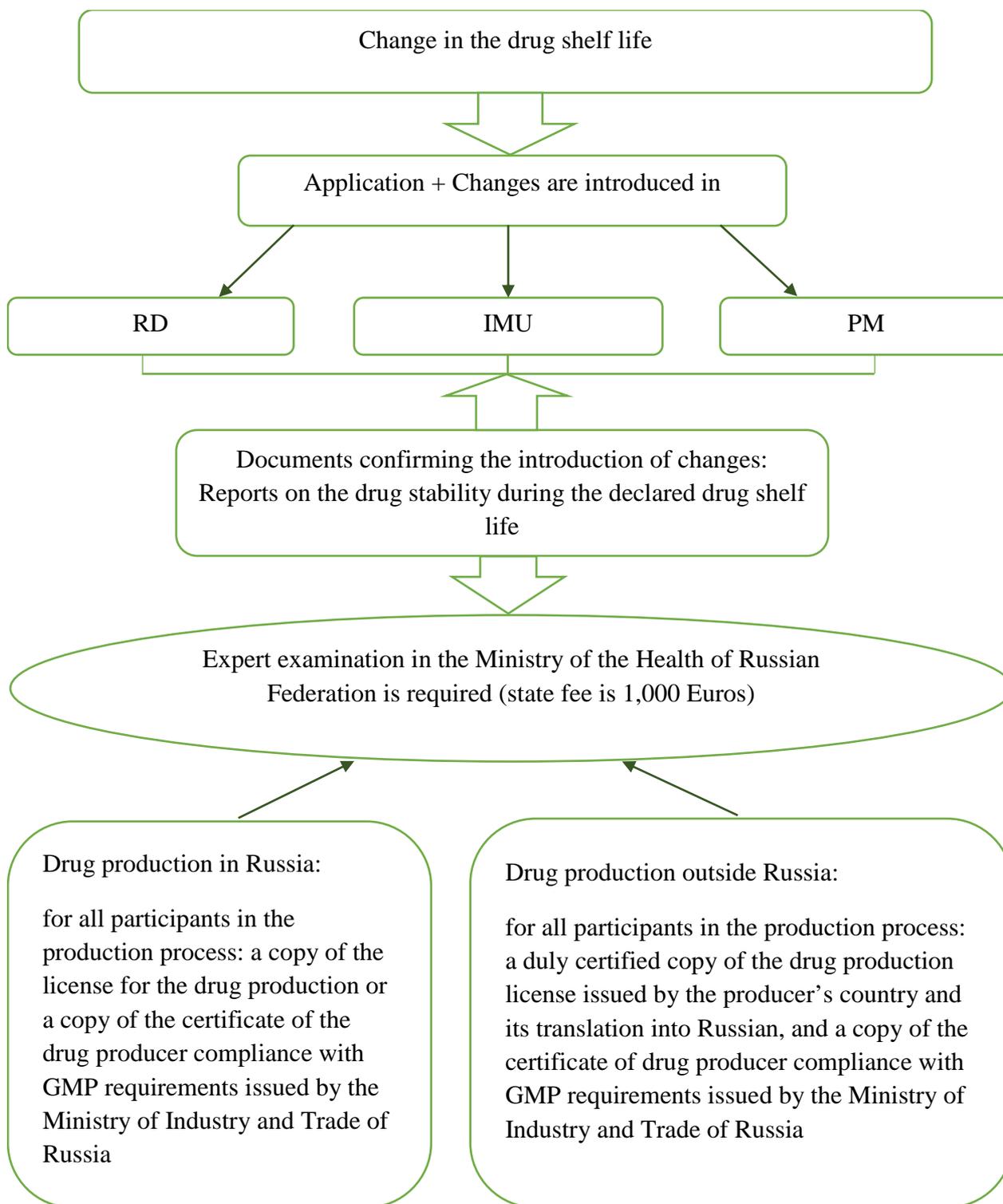


Chart 3. Compiling a set of documents for introducing changes in the registration dossier for a registered drug in Russia in case of change in the drug shelf life: RD – regulatory document, IMU – instruction for medical use, PM – packaging model, RC – registration certificate

CONCLUSION

The presented charts were developed within the regulatory framework of the Russian Federation, in view of the changes that require and do not require an expert examination. Besides, the charts show how to properly compile a set of documents to introduce the most common changes in the registration dossier for a registered drug.

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