Dear colleagues,

In this digest you can find the most important news on issues of registration, safety management, and quality of **medicinal products** in post-Soviet countries: Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Mongolia, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan **for the first half of 2018**.

The highest activity has been observed in the **Eurasian Economic Union (EAEU)**: medicinal products registration under the Unified Rules was formally started as of March 1. The new procedure allows submission of Application forms for registration in five participating countries according to the "sequential" and "parallel" registration procedure. Since the beginning of this year, related legislative acts have been approved and come into effect: the accelerated procedure for registration of vaccines has been introduced and quality requirements for various dosage forms, stability studies, validation, etc. have been approved.

In **Kazakhstan**, in addition to the start of work under the EAEU Unified Rules, new format of Application forms for registration procedures have been approved since the beginning of this year, the new procedure for submission of registration dossiers has been introduced and some legal aspects have been specified.

In **Kyrgyzstan**, the Law "On Circulation of Medicinal Products" came into effect in February. This law contains a number of changes aimed at harmonization of the national legislation with the EAEU Unified Rules, and also introduces the accelerated registration for medicinal products imported from the countries with strict regulatory requirements, changes the procedure and timelines of registration, and introduces unlimited Marketing Authorization.
In August, the relevant authority published the information letter with requirements for providing information on the QPPV (Qualified Person Responsible for Pharmacovigilance) in Kyrgyzstan, and also specified the procedure for change of QPPV.

In **Ukraine**, in April, the changes have been introduced to the procedure for expert examination concerning the requirements for biotechnological medicinal products. In April, the new edition of the Guide on Good Pharmacovigilance Practices (GVP) also came into effect.
In June, minor changes in the authenticity procedure for the medicinal products authorized with the purpose of procurement by specialized organizations have been approved.
Since the beginning of the summer, the relevant Associations, the Ministry of Health and the pharmaceutical community have been actively discussing ways out of the current situation with the introduction of requirements for labeling of medicinal products using SI units as of January 1, 2019.

In **Uzbekistan**, the new Regulation on the state registration of medicinal products has been approved in March, and the expert examination function has been delegated to the State Center for Expertise and Standardization of Medicinal Products, Medical Devices and Medical Equipment of the Agency for the Development of the Pharmaceutical Industry under the Ministry of Health. The timelines of the specialized expert examination were reduced depending on the type of Application from 180 to 50-155 days.
In April, the new Regulation on the procedure for informing on adverse reactions has been approved, timing of informing has been defined and the local Notification Form has been introduced.
It is planned to introduce the simplified procedure for registration of medicinal products by recognizing authorization in countries having high regulatory requirements.

For more detailed information, please refer to the following pages of the digest or contact us by e-mail info@cratia.ua or by phone +38 044 332-42-94.

Eurasian Economic Union (EAEU):

1. Since March 2018, in the EAEU countries (Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia), the relevant authorities have started accepting Application forms for registration of medicinal products under the Unified Rules approved by Decision No. 78 of the Council of the Eurasian Economic Commission dated November 3, 2016, "On Registration and Expert Examination Rules for Medicinal Products for Medical Use".

The Unified Rules allow submission of Application forms for registration of medicinal products according to the "sequential" (mutual recognition) and "parallel" (decentralized) registration procedure. The registration dossier is submitted in CTD-format with a partial translation into Russian.

In each individual EAEU member state the national legislation also remains effective. The abolition of national procedures and full transition to the registration under the EAEU Unified Rules should take place in January 2021. However, all medicinal products registered under the national procedures should be brought into compliance with the EAEU requirements until the end of 2025.

The new EAEU legislation also extends to the issues of safety (pharmacovigilance) and quality of medicinal products.

Currently Kazakhstan is a leading country in EAEU by number of accepted and examined Application forms.

2. Decision No. 69 of the Board of the Eurasian Economic Commission (EEC) dated May 10, 2018, "On Approval of the Requirements for Stability Study for Medicinal Products and Pharmaceutical Substances" comes into effect on November 14, 2018.
This Decision describes the requirements for evaluation of the stability of active substances and finished medicinal products intended for use in planning and conducting studies of pharmaceutical substances and medicinal products formulated on their basis as well as in the preparation of a registration dossier.

3. Decision No. 55 of the Council of the EEC dated June 14, 2018, "On Amendments to Decision No. 78 of the Council of EEC dated November 3, 2016" introduced a number of changes in the Rules for Registration and Expert Examination of Medicinal Products in the EAEU:

1. The accelerated procedure of introducing changes for vaccines related to changes in the influenza strains has been introduced. Duration of the procedure for introducing these changes to the registration dossier should not not exceed 40 calendar days.
2. The deadline for submission of documents confirming the compliance of manufacture with the GMP requirements and granted to the medicinal product manufacturer by the authorized body of the country-member of the Union is extended for two years. The new deadline for submission of these documents is December 31, 2020.

This decision comes into effect as of January 20, 2019.

4. Decision No. 113 of the Board of the EEC dated July 17, 2018, "On Approval of the Guidelines on Validation of Analytical Methods for Medicinal Products Testing" determines the rules for validation of analytical methods for conducting medicinal products testing as well as the list of characteristics to be evaluated when validating these methods and including them into registration dossiers which are submitted to the authorized bodies of the EAEU member states.
This decision comes into effect as of January 20, 2019.

5. Decision No. 149 of the Board of the EEC dated September 7, 2018, "On the List of Steps (Stages) of Medicinal Product Manufacturing process", according to which the list of steps (stages) of medicinal product manufacturing has been approved, i.e.: release quality control, quality control of the medicinal product, quality control of the bulk product; several stages relating to the manufacturing site, primary and secondary packaging sites. Each stage corresponds to a specific code identifier.

The list is included into the EAEU unified system of normative and reference information. The use of the code identifiers of the list is mandatory at implementation of global processes in the sphere of medicinal products circulation.
This decision comes into effect as of January 20, 2019.

6. Decision No. 150 of the Board of the EEC dated September 7, 2018, "On the Classifier of Measuring Units for Strength and Concentration of Active Substances in the Medicinal Product Compositions" approves the classifier included into the EAEU unified system of normative and reference information.
The use of the code identifiers of the classifier is mandatory at implementation of global processes in the sphere of medicinal products circulation. The classifier will be used for electronic interaction between the authorized bodies of the Union countries including compiling, maintenance and use of the unified electronic register of medicinal products authorized in the EAEU, as well as for the preparation of an application form for registration of medicinal products.
This decision comes into effect as of January 20, 2019.

7. Decision No. 151 of the Board of the EEC dated September 7, 2018, "On Approval of the Guidelines for Preparation of Normative Document on the Medicinal Product Quality" establishes requirements for medicinal product quality control based on the expert examination performed. The document is approved by the authorized body of the Union member state upon registration of the medicinal product and intended for post-marketing quality monitoring. The document should contain in particular specification and description of test methods or references to them, acceptability criteria for the quality parameters etc.
There are unified guidelines for compiling the full number of quality specifications for the medicinal product, including specifications for the active pharmaceutical substance, intermediate products and finished medicinal products.
This decision comes into effect as of March 12, 2019.

8. Recommendation No. 6 of the Board of the EEC dated May 10, 2018, "On the Guidelines for the Quality of Herbal Medicinal Preparations" describes harmonized requirements for pharmaceutical development, conducting studies and registration of herbal preparations.

9. Recommendation No. 11 of the Board of the EEC dated July 17, 2018, "On the Guidelines for General Issues of Clinical Studies" describes the harmonized requirements for conducting clinical studies within the territory of the EAEU member states and set forth in the attached "Guide on General Issues of Clinical Studies".

10. Recommendation No. 2 of the Board of the EEC dated January 16, 2018, "On Guidelines for the Quality of Modified Released Oral Medicinal Products" describes the harmonized requirements for quality assurance when introducing changes into the registration dossier and evaluating the equivalence of medicinal products with modified release.

11. Recommendation No. 17 of the Board of the EEC dated September 7, 2018, "On Guidelines for the Quality of Inhalation and Nasal Medicinal Products" defines the requirements applied to the conduct of research studies for the development of dosage forms, the compiling of registration dossiers for the inhalation and nasal medicinal products, the expert examination of the relevant documents as well as to registration and introduction of variations to registration dossiers.
This decision comes into effect as of March 12, 2019.

Kazakhstan:

1. As of August 28, 2018, Order No. 374 of the Minister of Health of the Republic of Kazakhstan dated June 15, 2018, "On Amendments to Order No. 736 of the Minister of Health of the Republic of Kazakhstan dated November 18, 2009, "On Approval of the Rules for Expert Examination of Medicinal Products, Medical Devices and Medical Equipment" introducing significant changes into the procedure of state registration has come into effect. The most significant are the following:

- Registration procedures are maximally converted into electronic document flow: Application and registration dossier are prepared in the information system of the relevant authority and submitted electronically. The procedure of expert examination is automated and integrated with the unified "Drug Supply Management System" database of the Unified Health Information System;
- Harmonization of the national legislation with the EAEU Unified Rules has been gradually started: the national rules for the expert examination refer to the Decisions of the Council of the Eurasian Economic Commission;
- Foreign manufacturer's registration dossier is submitted on an electronic medium only in CTD-format (format of common technical document consisting of 5 modules);
- Registration process for a medicinal product consists of:
    - Initial expert examination (30 days + 60 days clock stop);
    - Specialized expert examination (90 days + 60 days clock stop);
    - Laboratory testing (70 days + 90 days clock stop);
    - Preparing conclusions on safety, efficacy and quality (20 days);
- Stricter deadlines have been introduced for the expert examination of documentation for medicinal products manufactured in Kazakhstan and in the countries of the ICH region;
- Conducting the laboratory testing is not required in the following cases:
    - Expert examination of medicinal products manufactured in the countries of the ICH region;
    - Expert examination of medicinal products prequalified by WHO;
    - Renewal of medicinal products manufactured by domestic manufacturers;
- Opportunity has been introduced to provide the laboratory control by the manufacturer's laboratory in the presence of representatives of the expert organization (if required);
- Updated requirements have been introduced variations to the registration dossiers and lists of necessary documentation similar to the requirements which are effective in the EU.

2. Order No. 533 of the Ministry of Health of the Republic of Kazakhstan dated July 17, 2017, "On Introduction of Changes and Additions to Order No. 293 of the Minister of Health and Social Development of the Republic of Kazakhstan dated April 28, 2015, "On Approval of Standards of Public Services in the Sphere of Pharmaceutical Business". This legislative act made changes into the sphere of regulatory activity, including:

- New format of Application forms for registration, renewals and variations in the medicinal product registration dossier been approved;
- A new procedure for submission of registration dossiers for registration, renewal and variations procedures has been implemented;
- Certain legal points have been identified with regard to registration procedures, including the need in making a contract with the Expert Center for every separate registration procedure.

Kyrgyzstan:

1. As of February 2018 in Kyrgyzstan, Law No. 165 dated August 2, 2017, “On Circulation of Medicinal Products” has come into effect. This legislative act contains the following changes into the sphere of regulatory activity:

- The unified terminology has been introduced taking into consideration the EAEU requirements;
- New requirements have been implemented in the sphere of registration and circulation of medicinal products;
- State fees for the registration of orphan drugs and humanitarian aid drugs have been abolished;
- Accelerated registration for certain groups of medicinal products has been implemented;
- New requirements have been introduced for the validity period of Marketing Authorization and its cancellation.

By-laws to above-mentioned Law No. 165 "On Circulation of Medicinal Products” have been adopted but not yet in force. Prior to their implementation the previous requirements for registration of medicinal products according to the Technical Regulations remain in force.

2. The Department of Medicines Provision and Medical Equipment of the Ministry of Health of the Kyrgyz Republic published information letter No. 4391/3 dated August 15, 2018 which specifies the requirements for the provision of information on the QPPV in Kyrgyzstan to the regulatory body. It is required to submit CV of the Qualified Person, order on his/her appointment with specified functional responsibilities, contact phone number and e-mail address.
Information on changes of the QPPV or his/her contact details should be submitted to the relevant authority within 3 days. These changes are considered as variations procedure.

3. On August 28, 2018, Resolution of the Government of the Kyrgyz Republic “On Some Issues Related to the Registration in the Sphere of Medicinal Product Circulation” has been adopted (it comes into effect as of March 4, 2019). This legislative act significantly changes the national registration procedure and partially harmonizes it with the EAEU Unified Rules. It contains references to the Decisions of the Council of the Eurasian Economic Commission.

Thus the registration dossier of a foreign manufacturer is compiled in the CTD-format in accordance with the Rules for Registration and Expert Examination of Medicinal Products for Medical Use approved by Decision No. 78 of the Council of EEC dated November 3, 2016, and the labelling is developed in accordance with the EAEU requirements.
An accelerated registration for medicinal products prequalified by WHO as well as approved in the US, EU, Japan, Switzerland and the United Kingdom is being introduced. State fees for registration of orphan products and humanitarian aid drugs have been abolished.

The timelines and stages of registration have been significantly changed:

- The initial expert examination is carried out within 14 days plus one clock stop of 90 days for the Applicant to respond to the remarks and deficiencies;
- The relevant authority shall issue an invoice for payment of expert examination services within 14 days plus 45-day clock stop for payment;
- Conducting specialized expert examination including laboratory testing may take 130 days plus two clock stops of 90 days;
- The conclusion on the results of expert examination is prepared within 5 business days;
- The Marketing Authorization and a package of approved documentation is issued within 5 business days.

Total duration of a new drug registration may take up to 16 months.

Laboratory analysis of sample quality is not required in of the following cases:

- Availability of a GMP certificate for a manufacturing site issued by the regulatory authorities of the countries of the ICH region,
- Availability of a certificate/protocol of analysis/testing for the last 6 months carried out by a laboratory accredited under ISO 17025 and located within the EAEU territory,

- Accelerated registration,
- Renewal (repeated registration).

Possibility to carry out laboratory control by the manufacturer's laboratory in the presence of representatives of the expert organization (in case of inaccessibility, high cost of samples including orphan medicines, narcotic drugs, psychotropic drugs, etc.) has been introduced.

The decree establishes the new validity period of the Marketing Authorization: **5 years** at initial registration, **unlimited** after renewal (repeated registration). Duration of renewal (repeated registration) is up to 10 months.

Ukraine:

1. Order No. 711 of the Ministry of Health of Ukraine dated April 13, 2018, introduced a number of changes to the "Procedure for the Expert Examination of Registration Materials for Medicinal Products Submitted for State Registration (Renewal), as well as Expert Examination of Materials on Variations in Registration Materials During the Validity Period of Marketing Authorization" approved by Order No. 426 of the Ministry of Health. The most significant changes are the following:

- The requirement for providing confirmation of registration in countries with strict regulatory standards at registration of biosimilars has been excluded;
- The submission of the Application form can be done both in paper form and electronically;
- The Procedure is amended with the definition of a "non-comparable biotechnological product" and with the provision on requirements for the registration of such type of medicines;
- The registration procedure and the requirements for the registration dossier for medicinal products for the treatment of viral hepatitis prequalified by WHO have been changed.

2. Order No. 620 of the Ministry of Health of Ukraine dated April 5, 2018, approved the new revision of the Guideline "Medicinal Products. Good Pharmacovigilance Practice". This Guideline applies to medicinal products authorized and marketed in Ukraine and covers development and maintenance of a pharmacovigilance system, audits and inspections, development of an updated risk management system, exchange of safety data, analysis of post-marketing safety data, etc.

3. Order No. 721 of the Ministry of Health of Ukraine dated November 3, 2015, "On Approval of the Procedure for Expert Examination of the Authenticity of Registration Materials for Medicinal Product Submitted for State Registration for the Purpose of Their Procurement by Specialized Organization" has been amended in June. The changes detailed the requirements for the assessment report of medicinal product. These changes are made to simplify the requirements for the package of documents submitted for registration of the medicinal product by authenticity procedure.

4. Since the beginning of the summer, the relevant Associations, the Ministry of Health and the pharmaceutical community have been actively discussing ways out of the current situation with the implementation of requirements for labelling of medicinal products using SI units as of January 1, 2019.
Thus, Order No. 914 of the Ministry of Economic Development dated August 4, 2015, set forth mandatory requirements for the use of SI units in the labeling of products entered a market from January 1, 2019, including medicinal products. The requirements of Order No. 914 contradict the requirements of the relevant legislative acts on registration of medicinal products, and there are no explanations regarding the ways of implementing the use of SI units in labelling, the needs in changes and their type

Uzbekistan:

1. Decree No. 213 of the Cabinet of Ministers dated March 23, 2018, approved “Regulation on Procedure of the State Registration of Medicinal Products, Medical Devices and Medical Equipment and Issuance of Marketing Authorizations”. The previous version of the document has lost its effect. The most significant changes are the following:

- The function of conducting registration (renewal, variations) of medicinal products has been delegated to the State Center for Expert Examination and Standardization of Medicinal Products, Medical Devices and Medical Equipment of the Agency for the Development of the Pharmaceutical Industry under the Ministry of Health of Uzbekistan;
- The requirements to the registration dossier have been changed: the national format is almost completely repeats Modules 1, 3, 4 and 5 of the ICH CTD format (Module 2 is not required);
- The timelinesfor examination the Application forms and registration dossier have been reduced and differentiated. So, the timelines for a new registration depending on the type of product and type of Application are the following:
    - 50 days for active pharmaceutical substances (APIs)
    - 120 days for medicinal products in the form of bulk and packaged pharmacopoeial herbal medicinal raw materials;
    - 155 days for other medicinal products.

2. Order No. 3000 of the Ministry of Health dated April 16, 2018, approved “Provision on the Procedure for Informing on Identified Adverse Reactions at Medicinal Product Administration”. This provision specifies the reporting procedure, and introduces the local adverse reactions report form..
The following timelineshave been approved for submission of reports on spontaneous adverse drug reactions:

- 1 day for spontaneous reports on anaphylactic shock, Stevens-Johnson syndrome or death;
- 10 days for all other spontaneous adverse reactions.

3. The Decree of the President of Uzbekistan dated June 20, 2018, “On Measures to Increase the Efficacy of State Registration of Medicinal Products and Improve Their Supply to General Public" defines the system of state registration of medicinal products as too much complicated and decides the following:

- To change over fixed prices for socially important medicines to the marginal trade mark-up of a social pharmacy in the amount of 10 percent of the purchase price or of the wholesale price;
- to implement the procedure for recognition of the results of state registration (marketing authorization) provided in countries with strict regulatory requirements for medicinal products as well asactive substances (APIs)..

Based on this decree, a number of related acts are planned to be approved in the nearest future.

4. 24.09.2018 Decree of President of Republic of Uzbekistan № ПП-3948 “On additional measures in improving the procedure of state registration and circulation of medicinal products” was adopted determining list of countries and international regulatory authorities which results of registration (marketing authorization) is recognized in Uzbekistan.
Thus, the EMA results of registration (marketing authorization) as well as marketing authorizations from national regulatory authorities of Australia, Belgium, United Kingdom, Germany, Denmark, Israel, Ireland, Spain, Italy, Canada, Korea, the Netherlands, Norway, Slovenia, USA, Finland, France, Switzerland, Sweden and Japan.

Starting 01.11.2018 the decree also implements new procedure according to which Registration Certificate (Marketing Authorization) is not issued any more. Instead the Applicant can obtain by request Statement (extract) from State Register of medicinal products, medical devices and medical equipment”.

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