ANNEX

to Recommendation of the Board
of the Eurasian Economic Commission
No. _____ dated _____,
20_____

GUIDELINES
on General Considerations for Using Real-World Clinical Practice Data in Circulation of a Medicinal Product

I. General Provisions

1. These Guidelines have been developed to describe general principles and approaches to obtaining, analyzing and using real-world clinical practice data in accordance with the acts of the Eurasian Economic Union authorities in the field of circulation of medicines, as well as to optimize the conduct of research on real-world clinical practice data through general principles of applying the transformation of real-world clinical practice data into evidence derived from real-world clinical practice data to support regulatory decision-making by authorized authorities of the Eurasian Economic Union Member States (hereinafter, the Member State, the Union).

2. The principles for research on real-world clinical practice data and deriving evidence from real-world clinical practice data as set out in this Guidelines apply to any use of real-world clinical practice data and evidence derived therefrom that may be provided for in the legislation of the Member States.

3. The terms used in this document are used in the meanings defined by the Rules of Registration and Expertise of Medicinal Products for Human Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016, the Rules of Good Clinical Practice of the Eurasian Economic Union approved by Decision No. 79 of the Eurasian Economic Commission's

Council dated November 3, 2016, the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union approved by Decision No. 87 of the Eurasian Economic Commission's Council dated November 3, 2016.

II. Sources of Real-World Clinical Practice Data

4. Sources of real-world clinical practice data include:

interventional study data;

data from observational (non-interventional) studies;

registries and registry-based computerized medical databases;

data on cases of medical care provided to patients, received from medical insurance organizations and funds;

data from electronic medical records;

data from wearable devices used by patients extramurally;

data from patient-reported health status and outcome surveys (questionnaires);

social media and other sources containing patient health information.

It is acceptable to use artificial intelligence technologies to collect real-world clinical practice data

III. Suitability of Real-World Clinical Practice Data for Deriving Evidence from Real-World Clinical Practice Data

1. Data Suitability

5. Suitability of real-world clinical practice data is assessed mainly by data relevance and reliability.

Relevance

6. Relevance represents the degree to which the results of the performed data analysis are consistent with the stated scientific or clinical objective.

7. When assessing whether real-world clinical practice data is fit for purpose, the following factors shall be considered without limitation:

(a) whether real-world clinical practice data include key parameters and information that influence clinical outcomes (such as drug exposure, baseline patient demographic and clinical characteristics, significant covariates, duration of observation, etc.);

b) how unambiguously clinical outcomes are defined in the data and how clinically significant this definition is;

c) the extent to which a particular patient whose real-life clinical practice data is collected as part of the study is representative of the study population;

d) whether the sample size and duration of observation are enough to fully assess performance parameters and collect sufficient safety data (events).

Reliability

8. Reliability (reproducibility) is a characteristic of data that allows, under the necessary conditions, to obtain a stable (reliable, reproducible) result.

9. Reliability of real-world clinical practice data is assessed primarily in terms of integrity, accuracy and transparency.

10. Data integrity

When using real-world clinical practice data, it is impossible to avoid data incompleteness (omissions), including both cases of data missing entirely for a certain parameter and missing values within an indicator. Exceeding a certain amount of missing data can significantly increase the uncertainty of the conclusions derived from a study; omissions are particularly significant for key research variables as well as parameters (covariates) that influence the key variables. If a number of omissions is significant, the feasibility of using such data to derive evidence from real-world clinical practice shall be carefully evaluated.

11. Data accuracy

Data accuracy or "correctness" is a critical reliability indicator. Acceptable accuracy shall be determined in advance and estimated based on credible data sources. Accuracy shall be ensured both at the data element collection stage and at the level of any data conversion methods and algorithms. The accuracy of data is determined by its consistency and rationality. Consistency refers to the uniformity of relevant data standards, formats of their presentation and methods of calculation (transformations) in a database; rationality includes the correspondence of values of a particular variable to those expected for the indicator being studied, including an adequate (justified by the indicator nature) range of values and the nature of value distribution, as well as (for variables studied over time) the correspondence of the profile of changes in the values of the variable to the expected one.

12. Data transparency

Both the data sources themselves and the entire data collection and processing shall be transparent, understandable, and traceable; in particular, any impacts, covariates and outcome assessment variables critical to the analysis shall be unambiguously traceable to the primary data. Data transparency also includes the availability of data, the process of information sharing between databases, and the transparency of methods for protecting the privacy of participant data.

13. In order to obtain reliable real-world clinical practice data, quality assurance measures shall be observed, including but not limited to the following aspects:

a) having clear procedures and personnel qualified for data collection;

b) using unified systems for classification of elements, phenomena and events (glossaries of terms);

c) adhering to a uniform time frame for collecting information on key endpoints;

d) developing study designs, protocols and procedures for statistical analysis when collecting real-world clinical practice data;

e) adequate technical methods for collecting data elements, including:

integration of data from different sources;

a system for recording data on the use of interventions and performing laboratory tests;

incorporation of follow-up data;

reference to external sources (e.g., data from insurance companies);

data security, etc.

14. Before assessing the suitability of real-world clinical practice data, whether obtained retrospectively or prospectively, research questions shall be formulated and key indicators identified for which data will be needed to answer the questions posed with respect to the target population and target clinical setting for the medicinal product being studied.

15. The following factors are evaluated to decide whether to accept real-world clinical practice data as suitable for deriving evidence:

a) whether the criteria for assessing clinical outcomes and the condition being studied are accurate and clinically meaningful;

b) whether the data source planned to be used has the relevant indicators needed to answer the questions posed by the researcher;

c) whether the sample being analyzed is representative of the target patient populations;

d) whether the sample size and duration of follow-up are sufficient to adequately answer the research questions posed and to test the research hypothesis;

e) whether the study setting is representative of the target clinical setting for the medicinal product, whether interference with routine clinical practice is anticipated in the course of the study, and the extent and nature of that interference;

f) data integrity. When collecting real-world clinical practice data, data omissions, including missing variables and their values, cannot be ruled out. However, the proportion of missing data in a particular study shall not exceed a justified limit, especially when it comes to key study variables;

g) data correctness. Data correctness is determined by such parameters as coherence and reasonableness. Data coherence characterizes the uniformity of standards, formats and methods used to calculate and present data. Data

reasonableness is determined by the uniqueness of variable values, their distribution and dispersion, the accuracy of measurement, and the correspondence of significant variables (and their dynamics over time) to the expectations (assumptions) formulated when planning the study. The correctness of real-world clinical practice data shall be confirmed, including by comparison with data from credible sources, and any inconsistencies shall be rationalized;

h) data transparency. The sources of real-world clinical practice data and all stages of data collection and analysis shall be transparent and traceable. It is particularly important to be able to clearly define the primary data for the key indicators of the study. Data transparency also implies its availability, the possibility of obtaining information from different databases (possibility of information exchange between different databases) and reliability of methods of patients' personal data protection;

i) data quality. Quality assurance measures for real-world clinical practice data include, but are not limited to, the following:

having clear procedures and personnel qualified to collect, verify, monitor and prepare data for analysis;

having a common terminology for describing data; meeting deadlines for collecting key data elements;

guidelines for collecting real-world clinical practice data in study designs, protocols, and statistical analysis plans;

sufficient equipment for using certain methods of collecting data elements, including combining data from different sources, data on the use of medicinal products and the results of laboratory and instrumental methods of research, follow-up protocols, reference to data from medical insurance organizations, etc.;

j)data security. Security of real-world clinical practice data means protecting it from unauthorized access, alteration or deletion, as well as complying with requirements for patients' personal data protection.

16. It is recommended that the study protocol for real-world clinical practice data articulate the criteria for whether or not data can be used to derive evidence.

When creating a list of real-world clinical practice data, it is recommended to include data that allow to separate the effect of the medicinal product(s) being studied from the effects of concomitant therapy, the level of patient adherence to treatment, diagnosis, prevention and other features of routine clinical practice.

17. It is recommended that the report on studying real-world clinical practice data include a section describing:

integrity procedures;

correctness procedures;

transparency procedures;

quality assurance procedures;

procedures for ensuring the security of real-world practice data;

assumptions made in the designing and conducting the study of real-world clinical practice data and the rationale for such assumptions.

IV. Design Principles for Real-World Clinical Practice Data Studies

18. Real-world clinical practice studies can be interventional or non-interventional. Interventional studies of real-world clinical practice shall be conducted in accordance with the requirements of the Union and the legislation of the Member States for conducting and organizing clinical trials.

19. Non-interventional studies shall be conducted in accordance with Section 12 of the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union, as well as in accordance with the legislation of the Member States.

20. Independent (local) ethical committee approval shall be obtained before conducting non-interventional real-world clinical practice studies. In some cases, it is permissible to forego ethics committee approval if appropriate rationale is provided.

21. Non-interventional studies shall be scientifically justified. Any real-world clinical practice studies for marketing purposes or as part of promotional activities are not permitted.

V. Generating Evidence Derived from Real-World Clinical Practice Data

22. The main steps in generating evidence derived from real-world clinical practice data are:

a) correctness verification of the primary data of the study participants;

b) justification of the chosen methods for statistical processing of primary data;

c) statistical analysis;

d) searching for and discovering patterns;

e) making conclusions.

23. To improve the quality of derived evidence, it is recommended that a statistical analysis protocol and plan be generated prior to the statistical analysis. Since real-world clinical practice data is collected differently than data in conventional randomized clinical trials, there is a possibility of biased estimates and a threat of unreliable conclusions. As a consequence, data processing algorithms and tools in real-world clinical practice data studies are usually different from those used in conventional randomized clinical trials. Taking into account the specifics of data processing in real-world clinical practice data studies, if the results of real-world clinical practice data studies are used for regulatory decision-making, the authorized authority of a Member State is entitled to request primary patient data to verify the findings or to perform alternative statistical processing if necessary. When using complex designs and methods of statistical data processing, the applicant is entitled to request a consultation of the authorized authority (expert organization) of a Member State on the design and methods of statistical analysis to be used.

VI. Evaluating Evidence Derived from Real-World Clinical Practice Data

24. Evidence derived from real-world clinical practice data shall be evaluated using two main criteria:

a) whether evidence derived from real-world clinical practice data can be used to provide valid answers to the clinical questions being investigated; and

b) whether the necessary evidence can be obtained on the basis of available real-world clinical practice data through properly planned design of a clinical trial, its careful organization and conduct, and sound statistical analysis of its results.

25. The following aspects shall be considered when evaluating evidence derived from real-world clinical practice data:

a) ensuring that the study and data settings are as close as possible to those of routine clinical practice, such as minimizing interference with routine clinical practice, using a more representative sample, varied interventions compatible with routine clinical practice, or natural selection of interventions;

b) the application of suitable measures to ensure the study is controlled;

c) evaluating the efficacy and safety of a medicinal product based on a variety of endpoints (outcomes);

d) effective control of systematic errors

e) selection of appropriate statistical analysis methods, transparency and reproducibility of the evidence generation process;

g) validity of result interpretation;

26. The study design, all possible assumptions, specific definitions and methods needed to derive evidence from real-world clinical practice data shall be clearly defined in advance in the study protocol.

27. Before deciding whether to use evidence derived from real-world clinical practice data, the feasibility of addressing relevant clinical questions with such evidence shall be assessed. For this purpose, four aspects shall be considered, namely:

a) scientific efficiency (possibility of scientific interpretation of study results, validity of hypotheses, error control, etc.);

b) requirements of the authorized authorities of the Member States (absence of contradictions, specific requirements for certain therapeutic areas, etc.);

c) ethical aspect (minimizing the risk of ethical problems in case of refusal to use evidence derived from real-world clinical practice data, ensuring confidentiality of real-world clinical practice data);

d) ensuring adequate analysis of evidence from real-world clinical practice data (e.g., having qualified statisticians and taking steps to ensure that the statisticians are unbiased about the indicators being evaluated to avoid systematic errors).

28. The evidence, the quality of data obtained from studies using real-world clinical practice data, the methodological quality of studies using real-world clinical practice data, irrespective of the purposes for which the results of studies using real-world clinical practice data are used, shall be assessed by expert bodies of the Member States. The procedure for carrying out such an assessment shall be established by the authorized authority of a Member State.

29. If the quality of real-world clinical practice data studies is insufficient, it is not permitted to use the results of such studies to support regulatory and other decision-making.

VII. Using Evidence Derived from Real-World Clinical Practice Data

1. Evidence derived from real-world clinical practice data for pharmacovigilance purposes

30. Real-world clinical practice data may be used as an auxiliary source of information in post-authorization safety studies organized as interventional studies or observational (non-interventional) studies. A study may be initiated, controlled or financed by the holder of the registration certificate voluntarily or in accordance with an obligation imposed by the authorized authority of the Member States as a condition for issuing a registration certificate or after the issuance of the registration certificate if it is suspected that there are risks associated with the registered medicinal product that require further investigation through conducting a study. In

this case, evidence derived from real-world clinical practice data may be included in the marketing authorization application for a medicinal product.

31. In addition to the real-world clinical practice data sources listed in item 4 that may be or are used in an existing pharmacovigilance system, it is permitted to use specific data sources such as:

a) spontaneous reports on cases of insufficient therapeutic efficacy, adverse events, adverse reactions and post-vaccination complications from subjects of medicinal product circulation according to the approved notification form;

b) databases of spontaneous reports made by the Member States and internationally;

c) descriptions of cases in scientific medical publications traceable to the applicant;

d) periodic reports on the safety of medicinal products from the holders of registration certificates for medicinal products;

e) reports on safety of the medicinal product under development made by legal entities in the name of which permits to conduct clinical trials have been issued or by other legal entities authorized by them.

2. Evidence derived from real-world clinical practice data for the purposes of planning and justifying clinical trials

32. Based on the real-world clinical practice data, the applicant may plan and justify further clinical trials.

33. Data from registries and other sources of real-world clinical practice data may be used to estimate the values of the indicators being studied more accurately. In the case of planning clinical trials for the purpose of amending the instructions for human use (expansion of indications for use), real-world clinical practice data may be used to assess the medicinal product's efficacy and safety for these indications in order to calculate the sample size for clinical trial planning.

3. Evidence derived from real-world clinical practice data used for the purposes of implementing post-authorization measures

34. Chapter VII of the Rules for Marketing Authorization and Expert Examination of Medicinal Products for Human Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016 provides for the possibility of establishing supplementary requirements for applicants to obtain a new marketing authorization for a medicinal product (marketing authorization for a medicinal product with additional requirements), marketing authorization confirmation and amendments to the marketing authorization for a medicinal product. As such additional requirements, the authorized authority (expert organization) of a Member State is entitled to establish the necessity to conduct post-authorization studies of the medicinal product's efficacy and (or) safety. For these conditions to be fulfilled, the applicant may also submit data obtained in real-world clinical practice settings. As part of controlling the applicant's compliance with these requirements, the authorized authority (expert organization) of the reference state shall assess compliance of the submitted real-world clinical practice data and evidence obtained on their basis with the provisions of these Guidelines, as well as acts of the Union's governing bodies in the field of collection, analysis and use of real-world clinical practice data in medicinal product circulation.