ANNEX

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

GUIDELINES
for Determining the Scope of Laboratory Tests within the Medicinal Product Marketing Authorization

I. General provisions

1. These Guidelines define the criteria for making decisions on the scope of laboratory tests for medicinal product samples to evaluate the reproducibility of medicinal product quality control methods and the compliance of medicinal product samples with the claimed requirements of the regulatory document on quality during marketing authorization, making variations to or ensuring harmonization of the marketing authorization dossier in accordance with the Rules of Marketing Authorization and Assessment of Medicinal Products for Human Use approved by Decision No. 78 of the Council of the Eurasian Economic Commission dated November 3, 2016 (hereinafter – the Rules of Marketing Authorization and Assessment).

2. Laboratory tests are performed with respect to medicinal products when authorizing and making variations to the marketing authorization dossier of a medicinal product (including the marketing authorization dossier harmonization) in accordance with the Rules of Marketing Authorization and Assessment.

3. Laboratory tests of pharmaceutical substance samples are performed in cases stipulated by Annex No. 14 to the Rules of marketing authorization and assessment.

4. The provision of samples, specific reagents and other materials is not required when testing cannot be performed in an expert organization due to the inaccessibility of product samples (including when categorized as orphan, narcotic, psychotropic, radiopharmaceutical products, or intended for the high-cost nosology treatment due to their high cost), when compliance with the conditions of the specified samples transportation to the territory of a Member State of the Eurasian Economic Union (hereinafter – Member States, the Union) and (or) their storage cannot be ensured, and when special equipment and consumables are not available in the expert organization. In these cases, laboratory tests are conducted in the quality control laboratory of the medicinal product manufacturer in the presence of representatives of the expert organization or in the contract laboratory used by the manufacturer, in the presence of representatives of the expert organization.

5. Laboratory tests are conducted at the request of an expert organization to harmonize the marketing authorization dossier with the Union’s requirements and to continue the medicinal product’s circulation on the territory of the Member State where it is authorized.

6. Terms, such as a major variation of Type II, a minor variation of Type IA, a minor variation of Type IB, used in these Guidelines, should be interpreted as defined by the Rules of Marketing Authorization and Assessment.

II. Scope of laboratory tests during marketing authorization

7. Laboratory tests of product samples produced at one manufacturing site are performed for all indicators, when the evaluation is conducted as part of a single marketing authorization dossier of a medicinal product manufactured at different manufacturing sites (i.e. the manufacturing of a bulk medicinal product) using a pharmaceutical substance of the same manufacturer.

8. Laboratory tests of product samples produced at a specified manufacturing site with the pharmaceutical substance of a single manufacturer are performed for all indicators, when the evaluation is conducted as part of a single marketing authorization dossier of a medicinal product manufactured at a single manufacturing site (i.e. the manufacturing of a bulk medicinal product) using a pharmaceutical substance of different manufacturers.

9. Laboratory tests of samples produced at one manufacturing site with the pharmaceutical substance of a single manufacturer are performed for all indicators (except for biological medicinal products), when evaluation is conducted as part of a single marketing authorization dossier of a medicinal product manufactured at different manufacturing sites (i.e. the manufacturing of a bulk medicinal product) using a pharmaceutical substance of different manufacturers. For biological medicinal products, laboratory tests are performed for all indicators, all sites and all specified manufacturers of the pharmaceutical substance.

10. When a medicinal product is manufactured at different strengths or concentrations, laboratory tests of samples are performed for all strengths or concentrations, except for the following cases:

in case of proportional composition or the same base composition, including for the cores of coated tablets:

for powders that are the bulk of pharmaceutical substances - for the minimum strength for all indicators (repeated laboratory tests at the new minimum strength is not required if the minimum strength is excluded during the evaluation);

for other dosage forms - only for the minimum and maximum (strength, concentration) for all indicators (repeated laboratory tests at the new minimum strength is not required if the minimum strength is excluded during the evaluation);

11. For semisolid and liquid dosage forms (of the same composition) of different volumes or weights, laboratory tests are performed on samples of any volume or weight.

12. For sprays and aerosols of the same composition for different volume packages or with different number of doses, laboratory tests are performed for a sample of any volume or with any number of doses.

13. For semisolid and liquid dosage forms with glass and polymer packaging, laboratory tests of samples are performed for one type of packaging (preferably polymer packaging).

14. Medicinal product samples containing any of the possible flavorant and (or) flavoring agent and (or) coloring agent are subject to laboratory testing for all indicators when evaluation is conducted as part of a single marketing authorization dossier of a medicinal product differing only in flavorants and (or) flavoring agents and (or) coloring agents; for the other options, if the marketing authorization dossier shows that flavoring agents, colorants, flavorants have impact on the reproducibility of procedures for certain performances, then laboratory tests are required for these indicators.

II. Quality evaluation when making changes to marketing authorization dossier of a medicinal product

1. Classification of changes in accordance with Decision No. 78 of the Council of the Eurasian Economic Commission dated November 3, 2016

On the Rules of Authorization and Assessment of Medicinal Products for Human Use

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
B. Quality changes B.I. Active pharmaceutical ingredient		
B.I. a) Manufacture		
B.I.a.1 Change in the manufacturer of a starting material (reagent, intermediate) used in the manufacturing process of the active pharmaceutical ingredient or change in the manufacturer of the active pharmaceutical ingredient (including where relevant quality control sites), if no Ph. Eur. Certificate of Compliance is part of the marketing authorization dossier		
e) the change relates to a biological active pharmaceutical ingredient or a starting material (reagent, intermediate) used in the manufacture of a biological (immunological) medicinal product	initiated by request	for the indicators specified in the request
h) introduction of a new manufacturer of the active pharmaceutical ingredient without a master file and requiring a substantial update of the relevant section of the active pharmaceutical ingredient dossier	required only for biological medicinal products	for all indicators
B.I.a.2. Changes in the active pharmaceutical ingredient’s manufacturing process		
b) substantial change to the manufacturing process of the active	initiated by request	for the indicators

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
pharmaceutical ingredient which may have a significant impact on the quality, safety or efficacy of the medicinal product.		specified in the request
c) the change refers to a biological (immunological) substance or use of a different chemically derived substance in the manufacture of a biological (immunological) medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product and is not related to a protocol.	required	for all indicators
B.I. b) Quality control of the active pharmaceutical ingredient		
B.I.b.1. Change in the specification parameters and (or) acceptance criteria of a pharmaceutical ingredient, starting material (intermediate, reagent) used in the active pharmaceutical ingredient's manufacturing process		
f) change outside the approved range of specification acceptance criteria for the active pharmaceutical ingredient	required only for biological medicinal products initiated by request for all other medicinal	for the indicators interconnected with a variable parameter for the indicators specified in the request

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
	products	
1. Changes in active pharmaceutical ingredients:		
a) replacement of the chemically derived active pharmaceutical ingredient with another salt (ether, complex, derivative) with the same active moiety without significant differences in efficacy and (or) safety;	required	for all indicators
b) replacement of the active pharmaceutical ingredient with another isomer, another isomer mixture, a mixture of individual isomers (for example, a racemoid for a single enantiomer) without significant differences in efficacy and (or) safety;	required	for all indicators
c) replacement of a biological active pharmaceutical ingredient with another one of a slightly modified molecular structure without significant differences in efficacy and (or) safety, except for changes in the active pharmaceutical ingredient in a seasonal, prepandemic or pandemic vaccine for the prevention of human influenza;	required	for all indicators
g) modifications of the vector used to obtain the antigen or starting material, including the new Master Cell Bank from another source without significant differences in efficiency and (or) safety;	required	for all indicators
e) a new ligand or binding mechanism of a radiopharmaceutical	required	for all indicators

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
medicinal product without significant differences in efficacy and (or) safety;		
f) change in the extraction solvent or the ratio of herbal material and herbal pharmaceutical substance without significant differences in efficacy and (or) safety.	required	for all indicators
B.II Medicinal product B.II.a.2. Change in the shape or dimensions of the dosage form c) addition of new kit for radiopharmaceutical medicinal product with a different priming volume	required	for all indicators
B.II.a.3. Changes in the composition (excipients) of the medicinal product b) other excipients 2. Qualitative or quantitative changes in one or more excipients, which may have a significant impact on the safety, quality or efficacy of the medicinal product.	required	for all indicators
3. Change that relates to a biological (immunological) product	required	for all indicators
4. Any new excipient that may include materials of human or animal	required with the significant	for all indicators

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
origin for which assessment is required of viral safety data and (or) TSE risk	change in composition (Decision of the Council of the Eurasian Economic Commission On approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Eurasian Economic Union dated November 3, 2016) (recommended criteria for establishing a high comparability of medicinal products on the quantitative composition of excipients)	

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
5. Change that is supported by the results of a bioequivalence study	required with the significant change in composition (Rules for Conducting Bioequivalence Studies of Medicinal products within the Eurasian Economic Union (recommended criteria for establishing a high comparability of medicinal products on the quantitative composition of excipients)	for all indicators

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
B.II. a.4. Change in coating weight of oral dosage forms or change in weight of capsule shells b) delayed, modified or prolonged release dosage forms where the coating is a critical factor for the release mechanism	required	for Dissolution and (or) Disintegration indicators
B.II. b Manufacture of the medicinal product B.II. b.1. Replacement or addition of a manufacturing site for a part of the medicinal product's manufacturing process or for its entirety c) site where any manufacturing operations take place, except for batch release, batch control, and secondary packaging, for biological (immunological) medicinal products or dosage forms produced with complex manufacturing processes	initiated by request	for the indicators specified in the request
d) site which requires an initial or product specific inspection	initiated by request	for the indicators specified in the request
B.II. b.3 Change in the medicinal product's manufacturing process including intermediates used in the medicinal product's manufacture		

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
b) substantial changes to a manufacturing process that may have a significant impact on the quality, and efficacy of the medicinal product	required	for all indicators
c) medicinal product is a biological (immunological) product and the change requires an assessment of comparability	required	for all indicators
B.II. d) Quality control of the medicinal product		
B.II.d.2 Change in analytical procedure for the medicinal product c) change in (replacement of) a biological (immunological, immunochemical) test or a method where a biological reagent or replaced biological comparator that is not covered by an approved protocol is used.	required	for this specific indicator
B.V Changes to a marketing authorization dossier due to other regulatory procedures B.V. a) PMF (VAMF)		
B.V. a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorization dossier of a medicinal product (PMF 2nd step procedure) a) first-time inclusion of a new Plasma Master File affecting the properties of the medicinal product	required	for all indicators
B.V. a.2 Inclusion of a new, updated or amended		

Introduced changes according to change type	Need for laboratory testing of medicinal products	Indicators for which laboratory tests should be conducted
Vaccine Antigen Master File in a marketing authorization dossier of the medicinal product (VAMF 2nd step procedure) a) first-time inclusion of a new Vaccine Antigen Master File	required, except for influenza vaccines	for all indicators
1. Change or addition of a new strength (potency)	required	defined by the expert pursuant to p. I.4.
2. Change or addition of a new dosage form	required	for all indicators

III. Evaluation criteria for minor changes in excipient composition of the authorized medicinal product, which cannot have a significant impact on the safety, quality or efficacy of the medicinal product

15. Recommended criteria for evaluating minor changes in excipient composition of the authorized medicinal product, as provided in Annex 4 to the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Eurasian Economic Union.

16. Minor changes in excipient composition include:

excluding a flavorant and (or) flavoring agent and (or) coloring agent from excipient composition, replacing it by other agent permitted for use in the food industry, if the marketing authorization dossier shows that flavorants and (or) flavoring agents and (or) coloring agents do not have impact on the reproducibility of the procedures;

modifying a film coating by no more than 1%;

when the total amount of changes in excipient composition is not more than 5% at unchanged nominal values of the dosage form weight.

Liquid and semisolid dosage forms (solutions, syrups, ointments, creams and other)

17. Minor changes in excipient composition include:

excluding a flavorant and (or) coloring agent from excipient composition, or replacing it by other agent permitted for use in the food industry;

changing the content of any excipient by not more than 5.0%;

changing the amount of substances in the multi-component excipient composition by not more than 5.0%;

concentration of the excipient in two aqueous solutions of the medicinal product varying by not more than 10%;

preservative content decreasing by not more than 10.0% (if preservative efficacy data at a lower limit of content are available).

Table

An example of evaluating the significance of changes in excipient composition for a medicinal product in the tablet dosage form

Composition of the authorized medicinal product in % (m/m)	Proposed composition of the medicinal product in % (m/m)
Active ingredient – 75 %	Active ingredient – 75 %
Excipient – 1-15 %	Excipient – 1-12.5 %
Excipient – 2-10 %	Excipient – 2-12.5 %

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Calculations:

The change in the amount of excipient 1 is minus 2.5%

The change in the amount of excipient 2 is plus 2.5%

Both excipients are filling materials, change percentage acceptable for filling materials is not exceeded.

The total amount of change is 5.0%

Conclusion: these changes may be considered minor.