Pursuant to the Article 66 paragraph 3, Article 71 paragraph 3 and Article 73 paragraph 4 of Law on medicines (»Official Gazette of Montenegro« No. 56/11 and 6/13), the Ministry of Health passes the

RULEBOOK
ON MORE DETAILED CONDITIONS AND DOCUMENTATION REQUIRED FOR APPROVAL AND CONDUCT OF CLINICAL TRIALS OF MEDICINES FOR HUMAN USE

I GENERAL PROVISIONS

Article 1

Clinical trial of medicines for human use shall be approved and conducted under the conditions of and according to the manner and procedure determined by this Rulebook.

Article 2

Clinical trial shall be conducted in accordance with Guidelines for Good Clinical Practice, which ensures protection of rights, safety and wellbeing of subjects, as well as the credibility of data obtained through the trial.

Clinical trials are conducted in accordance with the latest updated version of the Guidelines of the European Medicines Agency, "Note for Guidance on Good Clinical Practice".

Beside guidelines referred to in paragraph 2 of this Article, clinical trials on minors are also conducted in accordance with the guidelines of the European Medicines Agency, "Clinical Investigation of Medicinal Products in the Paediatric Population"

Guidelines from paragraphs 2 and 3 of this article shall be published on the website of the Ministry of Health and the Agency for Medicines and Medical Devices (hereinafter: the Agency).

Article 3

Clinical trials are conducted in a manner that minimizes pain, discomfort, fear and risk to the subject, especially risk related to the possibility of genetic material change of the subject.

Article 4

Medicines are clinically tested on the basis of the existing results of pharmaceutical and pharmacological-toxicological testing (hereinafter: non-clinical trials).

Clinical trial also includes non-interventional clinical trial of a medicine, non-commercial clinical trial conducted by a scientific-research institutions without participation of medicines manufacturers and also clinical trials of bioavailability, i.e. bioequivalence.

II PROCEDURE OF A CONDUCT OF A CLINICAL TRIAL

1. Approval for a conduct of a clinical trial

Article 5

An application with documentation for the approval for a clinical trial of a medicine that has not been granted authorisation for placing onto the market (hereinafter: marketing authorisation) as well as for a clinical trial that is not conducted in accordance with a marketing authorisation or requires additional diagnostic procedures, as well as monitoring procedures determined by the Protocol of clinical trials, is submitted to the Agency.

An application with documentation is submitted in Montenegrin.

The documentation referred to in paragraph 1 of this Article shall be submitted both in electronic and written form.

Article 6

Documentation for approval for clinical trial includes:

1) cover letter from the applicant, indicating legal person, or legal persons in Montenegro where the conduct of a clinical trial shall take place;
2) completed form for approval for a clinical trial;
3) Protocol of a clinical trial (hereinafter: Protocol);
4) summary of the Protocol;
5) positive opinion of the Ethics Committee or a statement that identical documentation is submitted to the Ethics Committee as well;
6) Brochure for the investigator;
7) Investigational medicinal Product Dossier (IMPD), in case that a medicine has not been granted marketing authorisation;
8) Summary of Product Characteristics for a medicine that has been granted marketing authorisation;
9) written statement of a professional collegium, director or other authorised person in authorised facility institution in which a clinical trial shall be conducted, giving consent to the appointment of the principal investigator and investigating team, to the use of premises, staff and equipment during the course of a clinical trial, and creating conditions for a conduct of a clinical trial and undisturbed smooth operation of the auditor, monitor and inspector of Good Clinical Practice in a clinical trial;
10) signed statement by the principal investigator that he is familiar with the properties of an investigational medicine and with objective of the trial and that the trial shall be conducted in accordance with the Protocol and applicable regulations and Guidelines of Good Clinical Practice;
11) brief biography and references of the principal investigator;
12) documentation on an investigational medicine, a valid Good Manufacturing Practice certificate (GMP certificate) of an investigational medicine;
13) valid GMP certificate for the site of manufacture of biologically active substance, or a statement of a person qualified for batch release confirming that the biologically active substance is manufactured in accordance with GMP;

14) proof of insurance of the subject against possible hazardous consequences of a clinical trial;
15) informed consent form, other written information for the subject, as well as the original text, if the translation is in question;
16) report on known adverse reactions to the investigational medicine, if any, if it is not part of the Investigator's brochure;
17) list of countries in which the medicine has been granted marketing authorization, if available;
18) list of countries in which the same clinical trial has been approved, i.e. approvals of authorised bodies;
19) list of centres in which the same clinical trial is conducted, if a multicentre clinical trial is in question;
20) list of submitted documentation, indicating versions and dates;
21) sample of the test list/CRF;
22) TSE certificate confirming that the material of animal or human origin used in the manufacture of a medicine does not pose a risk for transmissible spongiform encephalopathy, if required;
23) verified copy of the contract on transfer of authorisation from the sponsor of the clinical trial to the applicant, if they differ;
24) proof that prescribed fees have been paid to the Agency;
25) additional information relating to health protection of the subject, at the request of the Agency;
26) additional requirements for medicines for advanced therapy.

Notwithstanding Article 5, paragraph 2 of this Rulebook, documentation referred to in paragraph 1, items 3, 6, 7, 12, 13, 16, 21, 22 and 26 of this Article may be submitted in English.

The form referred to in paragraph 1 item 2 of this Article shall be published on the portal of the Agency.

Article 7

Cover letter from Article 6 paragraph 1 of this Rulebook contains:

1) logo, name and address of a sponsor of a clinical trial;
2) name of a clinical trial;
3) subject-matter/summary of the application for approval for a clinical trial;
4) name of an investigational medicine;
5) pharmaceutical form, strength and packaging of an investigational medicine;
6) name of the manufacturer;
7) date and signature of the person responsible for the documentation for clinical trials;
8) list of the documentation.

Article 8

Protocol contains:

1) general information;
2) basic information;
3) objectives and purpose of the trial;

4) plan of the trial;
5) criteria for inclusion and exclusion of the subjects (selection of the subjects);
6) data on the subjects' treatment;
7) efficacy assessment;
8) safety assessment;
9) statistical data;
10) data on direct access to original data or documents;
11) quality control and quality assurance data;
12) ethical aspects of the trial;
13) information on keeping records and handling of data and documentation archiving;
14) information on financing and insurance of the subjects;
15) manner of publishing the results of clinical trials;
16) other annexes.

Article 9

Investigator' s brochure (hereinafter: Brochure) is the document containing clinical and non-clinical data on investigational medicine.

Brochure contains:

1) cover page;
2) statement on confidentiality;
3) contents;
4) summary;
5) introduction;
6) physical, chemical and pharmacological properties of the pharmaceutical form of the medicine;
7) data on non-clinical trials;
8) data on the effect of a medicine on a human;
9) conclusion.

In addition to data referred to in paragraph 2 of this Article, the Brochure contains information about quality, safety and efficacy of the medicine and current assessment of benefit-risk ratio of the investigational medicine.

Information referred to in paragraph 3 of this Article, refer to both investigational and comparative medicine.

Article 10

Detailed content of the Protocol and Brochure shall be published on the portal of the Agency in the form of an instruction.

Article 11

The Agency shall issue the approval after obtaining positive opinion of the Ethics Committee, within time limits defined by the Law.

Time limits for issuance of the approval for a clinical trial may be extended when xenogenic medicines are in question.

2. Clinical Trial Notification

Article 12

Prior to the commencement of investigation of a medicine that has been granted marketing authorisation, the applicant shall submit application for non-interventional clinical trial to the Agency which shall record it.

Notification with documentation for non-interventional investigation of safety or efficacy of a medicine shall be submitted to the Agency in Montenegrin, regardless of whether the applicant conducts investigation voluntarily or pursuant to the conditions under which the marketing authorisation has been issued.

Article 13

Documentation from Article 12 paragraph 2 of this Rulebook contains:

1) cover letter from Article 6 paragraph 1 item 1 of this Rulebook;
2) completed clinical trial notification form;
3) plan of the trial;
4) approved Summary of Product Characteristics and Patient Information Leaflet;
5) positive opinion of the Ethics Committee or a statement that identical documentation is submitted to the Ethics Committee as well;
6) decision on issuance of marketing authorisation;
7) proof that prescribed fees have been paid to the Agency;
8) decision of the Pharmacovigilance Risk Assessment Committee (hereinafter: PRAC) of the European Medicines Agency, if it was involved in the decision making;
9) additional information related to subjects' health protection, at the request of the Agency.

Documentation from paragraph 1 of this Article shall be submitted both in written and electronic form.

The Agency shall issue a confirmation of recording of non-interventional clinical trial within 30 days of the date of receipt of complete notification.

Clinical trial notification form from paragraph 1 item 2 of this Article shall be published on the portal of the Agency.

3. Amendments to a clinical trial of a medicine

Article 14

If during a conduct of a clinical trial substantial amendments, prescribed by the Law, occur, clinical trial approval holder shall submit to the Agency application with documentation for approval for substantial amendments to the Protocol or to the approval of a conduct of a clinical trial of a medicine.

Documentation submitted with the application contains:

1) cover letter;

2) completed application form;
3) documentation referring to substantial amendments;
4) positive opinion of the Ethics Committee;
5) proof that PRAC has approved the amendment (if post-marketing study of safety or efficacy of a medicine is in question) if it was included in the process;
6) proof that prescribed fees have been paid to the Agency.

The Agency approves substantial amendments to the Protocol or to the approval for a conduct of a clinical trial, within 30 days of receipt of the application.

The form referred to in paragraph 2 item 2 of this Article shall be published on the portal of the Agency.

Article 15

Cover letter from Article 14 paragraph 2 item 1 of this Rulebook contains:

1) logo, name and address of a proposer of a clinical trial;
2) brief explanation of substantial amendments;
3) name of the clinical trial;
4) name of an investigational medicine;
5) pharmaceutical form, strength and packaging of an investigational medicine;
6) name of a manufacturer of a medicine;
7) list of the documentation;
8) date and signature of the person responsible for a clinical trial of a medicine.

Article 16

Clinical trial approval holder shall report to the Agency administrative amendments to the Protocol or to the approval of a clinical trial of a medicine.

III RIGHTS AND OBLIGATIONS OF PARTICIPANTS IN A CLINICAL TRIAL

Article 17

A clinical trial is conducted in a health care institution that meets the following conditions:

- has investigating team that shall conduct clinical trial, headed by principal investigator with experience in this area,
- has adequate premises and equipment that enable a conduct of a clinical trial according to the plan of a clinical trial.

Article 18

Applicant of a clinical trial shall:

1) enter into a contract with a health care institution in which a clinical trial shall be conducted. This contract determines: total costs of the conduct of the clinical trial; costs borne by the applicant, including the costs of medical and other services provided by the health care institution in which clinical trial is conducted; amount of fee intended for

health care institution, investigating team and subjects, obligations of the applicant to bear the costs for all diagnostic procedures and tests envisaged by the plan of the trial;

2) prepare documentation required for obtaining an authorisation of a clinical trial of a medicine, prepares documentation for notification for non-interventional clinical trial (including post-marketing study of safety or efficacy of a medicine), and documentation submitted with the application for approval for substantial amendments to the Protocol or to the approval for a clinical trial;
3) appoint principal investigator with whom he enters into a contract defining the amount of fee for performing activities related to the clinical trial;
4) obtain consent from the director of health care institution for use of premises, staff and equipment for the purpose of the conduct of the clinical trial in accordance with the Protocol, GCP Guidelines and applicable regulations, as well as for undisturbed clinical trial monitoring and control;
5) in accordance with applicable regulations and prior to commencement of the clinical trial, insure subjects against possible health damage caused by the trial;
6) inform principal investigator and the Agency on any new significant data related to investigational medicine;
7) ensure updates of the Brochure at least once a year;
8) ensure information about the quality of investigational medicine, as well as on previously conducted non-clinical and clinical trial of that medicine;
9) ensure that investigational medicine is manufactured in accordance with GMP;
10) ensure that investigational medicine is labelled:
    a. in accordance with Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use (Annex 13)
    b. in accordance with applicable regulations on labelling of medicines, if a medicine that has been granted marketing authorisation is in question;
11) ensure that the documentation on the clinical trial is archived according to the regulations and is available to the Agency for control purposes;
12) provide sufficient amount of investigational medicine for subsequent analysis, if necessary, and archive documentation of the analysis and characteristics of samples manufactured batch;
13) provide coding system for investigational medicine in blind studies which allows identification of a medicine in emergencies, but it does not enable improper termination of a clinical trial;
14) report the Agency and Ethic Committee on serious adverse reactions to investigational medicine;
15) provide full health care for subjects during the treatment of certain diseases or conditions that are the result of the clinical trial;
16) provide monitor and auditor;
17) submit an application for obtaining approval for substantial amendments to the clinical trial;
18) inform the Agency on the course of the clinical trial and administrative amendments, at least once a year, or more often if requested by the Agency;
19) inform the Agency in detail about temporary suspension or termination of a clinical trial that was not determined by the plan of the trial, within 15 days;

20) inform the Agency, within 90 days, on the completion of the trial, and completion is considered to be the day of the last examination of the last participant involved in the trial;
21) submit report on completion of the trial to the Agency within one year from the completion.

Instructions for preparation of the report on completion of the clinical trial referred to in paragraph 1 item 21 of this Article shall be published on the portal of the Agency.

Article 19

Principal investigator must be a person employed in health care facility where clinical trial is conducted.

Principal investigator must be a person with completed faculty in the field of health and possess a proof of additional knowledge acquired in the field of clinical trials (certificates on education in the field of clinical trials), must have at least two years of experience and a valid working permit.

Sub-investigators must be persons with completed faculty in the field of health and associates in investigating team must have appropriate medical education.

Article 20

Prior to commencement of a clinical trial of a medicine, principal investigator shall:

1) submit biography and documentation in accordance with the Article 19 paragraph 2 of this Rulebook to the proposer of the trial;
2) sign a statement that he is familiar with the properties of investigational medicine and with objectives of the clinical trials that will be conducted according to proposed Protocol, in accordance with applicable regulations;
3) in accordance with applicable regulations, sign a contract with the proposer of the clinical trial on performance of activities related to the trial;
4) submit a list of investigating team members who have been assigned tasks in a clinical trial to the applicant of the trial;
5) introduce investigating team members to objectives of the clinical trial, Protocol, results of previously conducted pre-clinical and clinical trials of a medicine, test charts and timely inform them on substantial amendments to the clinical trial of the medicine.

Article 21

During the clinical trial course, the principal investigator shall:

1) set the date of commencement and completion of the clinical trial in agreement with the applicant, and notify the applicant on the termination and completion of clinical trial;
2) register dispensation and consumption of investigational medicines for each subject (date, quantity, batch number, expiry date and a unique identification code assigned to investigational medicine and to subjects);
3) ensure that investigational medicines are kept in a manner suggested by the applicant and in accordance with regulations;
4) prepare final report on the completion of the clinical trial;

5) propose amendments to the Protocol or approval for the conduct of the clinical trial, if necessary, and if proposed amendments are accepted, he shall present them to the subjects and inform them on the continuation of the trial in accordance with amendments;
6) inform the applicant of the clinical trial on adverse reactions to the medicine.

Article 22

During the clinical trial course, the principal investigator and investigating team shall:

1) recruit sufficient number of subjects, in accordance with the Protocol;
2) according to the capacity of their understanding, provide oral and written explanation to the subjects on the data of investigational medicine, objective and clinical trial plan, risks and benefits, mode of selection of subjects, approximate number of subjects and other possible forms of treatment, as well as on advantages and disadvantages of such treatment.
3) provide signed informed consent from subjects for participating in a clinical trial;
4) provide adequate health care during the clinical trial and after the completion of it, if the treatment is continued or if the disease or condition is a result of the trial;
5) provide accuracy, completeness and legibility of data related to the trial, as well as confidentiality of data available to supervision of the proposer and control of the Agency;
6) keep codes of the subjects secret, perform randomisation procedure, if any, and ensure that the code is revealed only in cases envisaged by the Protocol or if health of subjects is endangered;
7) urgently explain and document to the applicant each early decryption of investigational medicine in the conduct of a blind study;
8) keep basic documentation related to clinical trials;
9) terminate clinical trial or make necessary amendments to the Protocol or approval for the clinical trial in cases of imminent risk to subjects and inform the applicant, Ethics Committee and the Agency on such actions.

Investigation team members shall inform the principal investigator on adverse reactions to investigational medicine and adverse events and measures necessary to be taken to protect health of the subjects.

Article 23

Prior to commencement of the clinical trial, subjects must be informed in oral and written form about objectives and methods of the trial, anticipated positive and negative effects of the trial, inconveniences, risks, other treatment options, ensuring the confidentiality of personal data, with the possibility of withdrawal from the trial at any time, and methods and results of such early exclusion from the clinical trial.

Data from paragraph 1 of this Article must be presented in a manner that is fully understandable to subjects.

Article 24

Control of compliance of clinical trial conduct with the Protocol, Guidelines of Good Clinical Practice and applicable regulations shall be performed by the Agency which shall take measures necessary to protect public health.

The Agency shall control the trial in accordance with the latest updated version of the regulations published on the website of the European Commission: EudraLex Vol 10. Clinical Trial Guidelines Ch IV.

The Agency shall perform control from paragraph 1 of this Article:

1) on sites where a clinical trial is conducted;
2) in laboratories in which analyses for the trial are performed;
3) on site of manufacture of investigational medicine;
4) on the location of the sponsor or parties of the Contract;

The Agency shall perform compliance control of the trial:

1) that is conducted on the territory of Montenegro (prior to commencement, during the trial and after completion of the trial);
2) as part of the procedure for obtaining marketing authorisation
3) during the period of validity of marketing authorisation.

Article 25

The Agency may also conduct control at the request of the applicant of the trial.

The Agency may accept control of the clinical trial which was in accordance with the Guidelines of Good Clinical Practice conducted in one of the Member States of European Union or in other states in which requirements for clinical trials conduct are the same as in Montenegro.

IV FINAL PROVISION

Article 26

This Rulebook shall enter into force eight days from the day of its publication in "Official Gazette of Montenegro".

Minister

Miodrag Radunović, MD, PhD. m.p.

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