Pursuant to the article 33 paragraph 3 of the Law on Medicines ("Official Gazzette of the Republic of Montenegro", No 80/04 and "Official Gazzette of Montenegro", No 18/08), Ministry of Health, Labour and Social Welfare passes

Rulebook on detailed content of pharmaceutical testing of medicines

Rulebook is published in the "Official Gazzette of Montenegro No 38/2009" from 12 June 2009

I GENERAL PROVISIONS

Article 1

This Rulebook determines in more detail content of chemical-pharmaceutical-biological testing of medicines for human use (hereinafter: analytical testing of medicines), as well as content of documentation on placing a medicines on the market.

Article 2

All data obtained from analytical testing of medicines shall be prepared in accordance with the scientific and technical achievements and guidelines of International Conference on Harmonization (ICH), European Medicines Agency (EMA) and World Health Organization (WHO) and in accordance with Directive 2003/63/EC.
All data obtained from analytical testing of medicines, regardless of whether they are positive or negative, shall be be included in marketing authorisation dossier.

Article 3

Certain terms used in this Rulebook shall have the following meanings:
1) EDQM is European Directorate for quality of medicines in charge for European pharmacopoeia;
2) immunological medicines are medicines that cause active or passive immunity or are intended to diagnose immunity and they come under sensitive medicines;
3) quality of medicine is a property of medicine which may be determined by investigating quality of all substances, including at least quantitative analysis of all active

substances and all other investigations necessary to ensure the quality of medicines in accordance with the requirements of marketing authorization;
4) specification is a set of parameters with limits of acceptability (specification limits) for each parameter with specified test method, i.e. reference to them;
5) specification limits are limiting values exppressed in units of measurement, ranges or other criteria for individual parameters which a medicine must comply to so it could be accepted for intended use, which are approved by the Agency for Medicines and Medical Devices (hereinafter: Agency) in the process of obtaining marketing authorisation and which are valid throughout shelf life of a medicine;
6) standard (routine) test methods represent testing of parameters performed by the manufacturer for each batch of a medicine before release on to the market, in accordance with previously set plan;
7) non-standard (non-routine) test methods mean testing of parameters on random sample of the batch of a medcinie before release on to the market;
8) special test methods are methods performed with the aim of determining presence of unexpected impurities and which are not required to be specified marketing authorisation dossier;
9) organisation of quality control includes all activities pertaining to sampling, obtaining required documentation and reference standards, reporting on results of analytical testing of a medicine, as well as to assessment of submitted certificates of analysis/testing of quality of a medicine;
10) starting materials are substances which active substance is produced or extracted from. Starting materials of biological medicines are all substances of biological origin, for example, micro-organisms, organs and tissues of plant and animal origin, cells or biological liquids (including blood and plasma) of human and animal origin, biotechnological cell constructs (cell substrates, whether recombined or not, including stem cells);
11) biological medicine is a medicine whose active substance is biological substance (immunological medicines, medicines derived from blood and plasma, medicines obtained by high technologies: genetic engineering, monoclonal antibodies, hybridoma ...) as well as advanced therapy medicines (gene therapy, somatic cell therapy – allogenic and xenogeneic);
12) biological substance is substance produced or extracted from biological source whose characterisation is required to be done by physico-chemical testings.

II ANALYTICAL TESTING

Article 4

When analytical testing is described in reckognised pharmacopoeias, detailed description of testing is replaced by specifying reference monograph: European Pharmacopoeia (hereinafter: Ph. Eur.) or national pharmacopoeia or pharmacopoeia of other states, in which case the applicant for marketing authorisation (hereinafter: applicant) shall submit

copy of that monograph and validation of analytical method from monograph with translation, as well as general requests for pharmaceutical form of a medicne.

Article 5

For analytical testing of active substance and/or other starting materials described in Ph. Eur. or national pharmacopoeia or pharmacopoeia of other states, the applicant may submit certificate of compliance issued by EDQM that replaces data from relevant parts of documentation.
For analytical testing of active substance and/or other starting materials which are not described in Ph. Eur. or national pharmacopoeia or pharmacopoeia of other states, or when the applicant fails to submit certificate of compliance issued by EDQM, the applicant shall submit documentation on active substance (drug masterfile DMF) to the Agency.
In case that the applicant fails to submit documentation from paragraph 2 of this article, the manufacturer of active substance is obliged to submit documentation on active substance to the Agency.
The manufacturer of a medicine is obliged to submit both open and closed part of documentation on active substance to the Agency, and only open part to the applicant.

III DOCUMENTATION ON ANALYTICAL TESTING OF MEDICINES

Article 6

Documentation on analytical testing of medicines contains data on:
1) active substance (S) (general data, data on manufacturing, characterisation of active substance, control of active substance, reference standards or materials and stability);
2) finished medicine (P) (description and composition, development, manufacturing, control of excipients and finished medicine, reference standards or materials, container closure system and stability);
3) space, equipment and safety evaluation in terms of by-products and
4) validation, medical devices and certificates.

1) Data on active substance (S)

Article 7

General information about active substance mean: nomenclature, name (INN, name of recognized pharmacopoeia or chemical name), structural formula, absolute and relative stereochemistry, molecular formula and relative molecular mass, physico-chemical, and

other important properties including biological activity of medicines of biological origin, as well as data on starting materials of biological resources.
Active substances given in Ph. Eur. are named after the headline of monograph relating to that medicine with specified pharmacopoeia, and substances which are not given in Ph. Eur. are named after the headline of national pharmacopoeia or other reckognized pharmacopoeia in which those substances are given.
Active substances which are not given in pharmacopoeias from paragraph 2 of this article are named after international non-proprietal name (INN), as recommended by World Health Organisation, other non-protected name or chemical, i.e. scientific name, and in respect of other substances, manner of preparation, ingredients which active substance is made of, as well as other necessary data must be provided.
Substances of plant origin must also have Latin name.

Article 8

Data on quantitative composition of active substances in a medicine are expressed in units of mass or units of biological activity per dose, mass or volume, for each active substance separately, depending on pharmaceutical form.
Units of biological activity are used for active substances that cannot be fully chemically determined, in which case international units of biological activity (IE) are used, under provisions of WHO.
If WHO has not set international units of biological activity, it is necessary to express them in such manner to gain information about the activity of these substances and, as a rule, biological activity shall be expressed in units of mass or volume.
Data on quantitative composition of a medicine need to be complemented:
- in medicines for parenteral use with units of mass or units of biological activity of each active substance per unit of packaging, which takes into account the volume of container, and, if necessary, also after reconstitution;
- in drops with mass or units of biological activity for each active substance per drop number corresponding to 1ml or 1g of a medicine;
- in syrups, emulsions, granules and other pharmaceutical forms that are administered in dosed quantities, with mass or units of biological activity of each active substance in dosed quantity.
Active substances present in the form of compounds with inactive entities of molecule or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule and shall comply to specifications approved in the state in which marketing authorization for that active substance has already been issued.
Choice of active substance, excipients, immediate packaging and pharmaceutical form must be based on scientific data that is given in the explanation. Any additional quantity of starting material must be given and justified in relation to envisaged losses.

Article 9

When description of starting materials is not given in pharmacopoeias from article 4 of this Rulebook, the applicant shall submit description of those substances in the form of monograph that contains:
- name of the substance supplemented by synonym of scientific name or by protected name;
- description of the substance in detail, as requested by Ph.Eur., description of the procedures of synthesis and, if necessary, description of the molecular structure;
- if the substance may only be described by manner of manufacturing, clearly stated composition and efficacy of the medicine shall be given in the description;
- testing of identification of active substance where it is required to describe all procedures used in manufacturing process and all tests necessary to be performed in standar/routine manner;
- testing of purity required to be described on total amount of foreseen impurities with potentially harmful impurities included,l and if necessary, testing of impurities which, in combination with other substances from a medicine, may adversely affect stability of a medicine or cause inaccurate analytical results;
- terms of storage and labelling of starting materials, storage precautions and, if necessary, maximum permitted storage time until new testing;
In starting materials of plant or animal origin it is necessary to perform physical, chemical or biological assessment of main substances having different and numerous pharmacological effects, while substances containing one or more groups of active substances with similar pharmacological effect may be assessed together.
In starting materials of animal origin it is required to decsribe safety measures taken due to presence of pathogenic substances.

Article 10

Description of active substances, whether described in pharmacopoeias or not, contains information about physical and chemical properties that may affect the bioavailability:
- crystallization and dissolution rate;
- particle size (where required);
- degree of solvation;
- coefficient of oil / water relation.
Data provided in indents 1, 2 and 3 of paragraph 1 of this article shall not apply to substances used only in solutions or in other specific forms.

Article 11

The applicant shall specify:
- starting materials used in manufacturing of active substance and medicine, phases in which they are used, as well as documentation on their quality, control and performed testings;
- name, adress and responsibility of each manufacturer of active substance inluding contractors, and all manufacturing sites involved in manufacturing and quality control;

- evidence that active substance is in accordance with the Guidance of the European Commission on minimising the risk of transmission of spongiform encephalopathies (TSE);
- evidence that, when cell banks are used, the cell characteristics have remained unchanged at the passage level used for the production, that there is no by-products in starting substances of biological origin, or even if there are, that following stages of manufacturing process warantee their elimination or inactivation;
- evidence that plasma and blood as starting materials have been collected in accordance with applicable legislation;
Documentation on the manufacturing process of active substance contains a description of production facilities and equipment, information on testing, validation and acceptance criteria for each critical stage of production.

Article 12

Standard/routine analysis conducted on each batch of starting materials shall correspond to the specifications from marketing authorization dossier.
If the specification contained in the monograph of Ph. Eur., national pharmacopoeia or pharmacopoeias of other states is assessed by the Agency as insufficient for the quality ensurance, the applicant or the marketing authorisation holder may be asked to supplement the specification in accordance with the requirements of the Agency.
The applicant or marketing authorisation holder shall infrom competent authoristies of the pharmacopoeia in question on the alledged insufficiency.
If the applicant refers to monograph of a third country in the description of manufacturing process, the applicant shall submit a copy of the monograph accompanied by the validation of analytical procedures contained in the monograph and by a translation, where appropriate, and if requested by the Agency.

Article 13

When starting materials of herbal or animal origin, microorganisms, cells or liquids of animal origin, biotechnologically modified cells are used in manufacturing of a medicine, it is necessary to describe and submit documentation on the source and origin of the starting material.
Description of starting materials contains processes of manufacturing, processes of purification, i.e. inactivation with validation and all processes of control during manufacturing which are foreseen to ensure quality, safety and consistency among batches of finished medicine.
When cell banks are used, the cell characteristics shall be shown to have remained unchanged at moment of transfer into manufacturing and later.
Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

Source materials from article 4 of this Rulebook may be used only when further processing ensures elimination and/or inactivation of potentially pathogenic adventitious agents and this shall be validated.

Article 14

Confirmation of the structure of active substance based on any physicol-chemical and/or immunochemical and/or biological methods, as well as information on impurities shall be provided by the applicant.

Article 15

Documentation on quality control of active substance contains data on parameters that are used in standard or routine test methods, the methodology of choice, validation of analytical methods and results of control of each batch produced during the development presented by the certificate of quality analysis.

Documentation from paragraph 1 of this article shall be accompanied by detailed information on manufacturing of starting materials, and when substances included in Ph.Eur. are in question, those data may be replaced by the certificate of compliance issued by the EDQM.

If active substance does not have monograph in pharmacopoeias from article 5 paragraph 2 of this Rulebook and is prepared by a method liable to leave impurities, the applicant shall submit documentation on active substance (drug master file DMF) to the Agency.

Documentation on active substance (drug master file DMF) shall be submitted in a manner prescribed in article 5 paragraph 2 of this Rulebook.

Article 16

The manufacturer is obliged to ensure consistency of batches and to notify the applicant and the Agency about modifications in manufacturing process.

Quality of starting materials shall correspond to the monograph of Ph. Eur., national pharmacopoeia or pharmacopoeia of other states.

For starting materials described in Ph.Eur., national pharmacopoeia or in pharmacopoeia of other states, description of analytical methods may be replaced with detailed reference to relevant pharmacopoeia.

Article 17

Where active substance contained in monograph in pharmacopoeias from article 5 paragraph 2 and prepared by a method liable to leave impurities which are not given in pharmacopoeaa and therefore may not be assessed, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.
Identification and testing of active substance is performed on represent samples or random units of finished medicine in a manner described in submitted documentation.
Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.
The applicant shall propose and specify the maximum acceptable deviation in the active substance content of the finished product throughout its shelf life.

Article 18

In certain cases, when mixture of finished medicine contains large number of active substances, i.e. small amount of active substance quality examination of which in each batch is hardly feasible, such examinations are not required provided that tests at an intermediate stage of the manufacturing process have been carried out, on which appropriate documentation shall be submitted.
Test methods must be submitted for quantitative assessment of all active substance of finished medicine.
In vivo or in vitro biological analysis are mandatory when appropriate data may not be provided by physico-chemical methods.
Examination from paragraph 3 of this article, shall include reference materials and statistical analysis used to calculate limits of acceptability.
If tests from paragraphs 3 and 4 of this article cannot be carried out on finished medicine, such tests must be carried out at as later intermediate stage of the manufacturing process as possible.
According to the assessment of the Agency, when surplus of active substance is used in manufacturing of a medicine, quality control shall also include chemical and parmacological-toxicological investigation of changes of active substance in question and, if possible, degradation products shall be identified and quantified.

Article 19

The applicant shall submit:
- specified and described in detail reference standards or materials (if possible, chemical and biological reference starting materials specified in reckognized pharmacopoeias shall be used);
- description of container and closure system and their properties;
- detailed results of the stability studies, including information on the analytical method used and its validation;
- summarised types of studies of stability conducted, protocols used, obtained results;
- post authorisation stability protocol and stability requirements.

2) Data on finished medicine (P)

Article 20

Data on description and composition of finished medicine include:
- description of pharmaceutical form and composition including all substances of finished medicine, their amount per unit of mass/volume (units of biological activity shall be used only for compounds which cannot be otherwise defined);
- function of active substance;
- function of excipients, regardless of their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.;
- description of of the outer covering of the medicine intended to be ingested or otherwise administered to the patient, (e.g. outer covering of gelatin capsule) ;
- description of immediate packaging and, if needed, its manner of closure, together with details of devices with which the medicine will be used or administered and which will be delivered with the medicine.

Article 21

Testing of finished medicine shall include investigation of general properties of the medicine in accordance with Ph.Eur. requirements for pharmaceutical forms, and if necessary, it shall also include investigation of uniformity of mass, maximum acceptable deviations, investigation of mechanical, physical or microbiological, as well as organoleptic properties (clarity, taste, colouring matter, density, pH, refraction index...).
The applicant shall provide specification limits, description or reference for each specified property given in paragraph 1 of this article.
If testing conditions, equipment used, standards and analytical methods are not specified in pharmacopoeias from article 5, paragraph 2 of this Rulebook, they shall be described in detail.
In vitro studies of dissolution and release rate of active substance shall be conducted for solid pharmaceutical forms for peroral use, as well as in cases of different route of administration, at the request of the Agency.l

Article 22

When part of medicine delevopment is concerned, the applicant shall submit:
- development studies conducted to establish that the pharmaceutical form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier;

- all critical parameters and characteristics of the process that can influence batch reproducibility, medicine quality and efficacy and, if necessary, the applicant shall refer to additional data from modules 4 and 5 of the marketing authorisation application dossier;
- compatibility of the active substance with excipients as well as key physico-chemical characteristics of the active substance that can influence the efficacy of the finished product or the compatibility of different active substances with each other in the case of combination products;
- choice of excipients, in terms of their functions and concentration;
- description of the development of the finished product taking into consideration proposed route of administration and usage;
- any overages in the formulation shall be warranted;
- beside physico-chemical and biological properties, all parameters relevant to the efficacy of finished medicine;
- optimisation of the manufacturing process as well as differences between the manufacturing process used to produce pivotal clinical batches and the process used for manufacturing finished medicine;
- choice of the container and closure system used for storage, shipping and use of the finished medicine as well as possible interaction between medicine and container;
- compatibility of finished medicine with reconstitution diluents or medical device used in the administration of the medicine;
- microbiological characteristics of the pharmaceutical form in relation with non-sterile and sterile products which shall be in accordance with reckognized pharmacopoeias.

Article 23

Description of manufacturing process must provide appropriate review and summary of operations employed and in particular:
- list of the various stages of manufacture so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents;
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished medicine;
- manufacturing formula with quantitative data of all active substances (quantity of excipients can be specified as approximate, if it is considered to be necessary because of pharmaceutical form);
- substances that are removed during technological process and which are no longer present in finished medicine as well as all surpluses shall be explained;.
- data on manufacturing stages in which samples for process control during manufacturing are taken, if documentation indicates that these data are necessary for monitoring the quality of finished medicine;
- validation of the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the quality of the medicine;
- for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used;

- name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of quality;
- data on test methods of quality of an intermediate with a view to ensuring the consistency with parameters of specification at interstages of manufacturing process;;
- description, protocol and validation results relating to the critical stage of the manufacturing process or critical tests in the manufacturing process.

Article 24

In process of quality testing of excipients, all substances used in manufacturing process shall be specified, together with data on their quality and test methods of quality, as well as data confirming that they meet quality standards for their intended use.
For each excipient it is necessary to submit:
- detailed characteristics and justification of choice in formulation, as well as description and validation of analytical processes; as for excipients of animal and plant origin, evidence that they are manufactured in accordance with the principles for minimising the risk of TSE (TSE certificate or other scientific data supporting this);
- for excipients used for the first time in a medicine or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to data from modules 4 and 5 confirming non-clinical and clinical safety of novel excipient;
- for certain excipients, where necessary, at least identification tests must be performed;
- analytical procedure to identify the colour matter for use in medicines, which enables verification of compliance of these colour matters with regulations on their permitted use;
- data on mandatory examination of upper and lower permitted limit of preservatives and examination of upper limit of excipients that may cause adverse reactions;
- data on mandatory examination of upper and lower limit of all excipients that may affect the bioavailability of active substance, unless the bioavailability is verified by other appropriate tests.

Article 25

General requirements of pharmacopoeias from article 5 paragraph 2 of this Rulebook must be complied when conducting quality control of finished medicine, and in cases in which analytical procedures and specifications not specified in mentioned pharmacopoeias are used, it is necessary to prove that finished medicine meets the requirements from pharmacopoeias for that pharmaceutical form.
Documentation on the control of intermediate examination shall include data associated with control tests of intermediates that can be performed at interstages of manufacturing process.
If testing of finished medicine does not include testing of all active substances or excipients to which the same requirements are applied, with the aim of verification of compliance with specifications, it is necessary to provide all required tests at interstages of the manufacturing process, if such tests give insight into the quality of finished medicine.

When quality control depends on intermediate examination, with the aim of verification of compliance with specifications, it is necessary to provide all required tests at interstages of the manufacturing process, if such tests give insight into the quality of finished.
For standard / routine quality control of medicines, in addition to pharmacological-toxicological tests provided in relevant part of the documentation, it is necessary to submit details on tests for determining safety (sterility tests, tests in the absence of bacterial endotoxins and other pyrogenic substances, as well as test of local tolerance to the medicine).

Article 26

A batch of a medicine is an entity which comprises all units of a pharmaceutical form which are made from same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.
In the marketing authorization dossier it is necessary to state all tests performed on each batch of the medicine, and as for tests which are not performed in standard/routine manner, it is necessary to specify frequency of testing.
Specification for release of finished medicine on to the market must be stated.

Article 27

The applicant shall specify and describe in detail:
- reference standards or materials used in quality testing of the medicine;
- container and closure system including the name of all materials used for packaging materials, their specifications and test methods which are not described in recognized pharmacopoeias;;
- immediate packaging, including information on type of material, its composition, specifications and routine test;
-outer packaging;
- certificates of analysis of quality of each batch of medicine.

Article 28

The applicant shall submit data on stability which include:
- summary of type of conducted study, its protocol and results;
- detailed results of the stability studies, including information on analytical procedures and validation of these procedures, in case of vaccines, information on cumulative stability shall be provided where appropriate;
- post authorisation stability protocol and stability commitment;
- description of studies which determined shelf life of medicine, proposed terms of storage, and specification to which a medicine must comply throughout shelf life;

- qualitative and quantitative test methods of degradation products if substances of finished medicine are biodegradable, while maximum accepted limit of degradation products throughout shelf life must be established;
- submitted studies in cases where there is a risk of interaction between a medicine and immediate packaging, especially in pharmaceutical forms for parenteral use or in sprays for internal use;
- proposed shelf life of product reconstituted in accordance with recommendations in medicines which are required to be reconstituted before use, as well as data confirming proposed shelf life;
- data on stability confirming shelf life after first opening (e.g. of solution for injection) when multi-dose vials are concerned;
- conclusion of stability studies with results confirming proposed shelf life under recommended terms of storage, and
- specification of finished medicine throughout shelf life.

IV FINAL PROVISION

Article 29

This Rulebook shall come into force on the 8th after being published the "Official Gazzette of Montenegro."
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Podgorica, 5 June 2009

Minister,
Doc. dr Miodrag Radunović