THE MINISTRY OF HEALTH

1118

Pursuant to Article 173, paragraph 4 of the Medicinal Products Act (Official Gazette 76/13), the Minister of Health hereby issues the

ORDINANCE

ON THE QUALITY CONTROL OF MEDICINAL PRODUCTS

Article 1

This Ordinance lays down the procedure for controlling the quality of medicinal products and officinal formulae/galenic preparations.

Article 2

This Ordinance transposes into the legal order of the Republic of Croatia Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28. 11. 2001).

Article 3

For the purposes of this Ordinance, the following terms shall have the following meanings:

1. *Specification* means a list of test parameters with the defined acceptable quality specification limits for an individual parameter and the specified analytical procedures.

2. *Quality specification limits for test parameters* means numerical limits, ranges or other measures to which an individual parameter must confirm in order for a medicinal product to be acceptable for its intended use, and which are accepted in the marketing authorisation procedure for the medicinal product.

3. *Official quality control of a medicinal product* means the procedure carried out by the Agency for Medicinal Products and Medical Devices (hereinafter: the Agency) to check the quality of a medicinal product by analytical testing and by verifying certificates of analysis, the outer and immediate labelling of the medicinal product, the text of package leaflet and other documents.

4. *Plasma pool* means the starting material used for the manufacture of blood/plasma-derived medicinal products, which is composed of plasma donations from donors.

REGULAR QUALITY CONTROL OF A MEDICINAL PRODUCT

Article 4

The manufacturer of a medicinal product who holds a marketing authorisation for the medicinal product in the Republic of Croatia shall perform regular quality control of each batch of the medicinal product, in the manner prescribed by the Medicinal Products Act (hereinafter: the Act) and the Ordinance on the conditions for issuing manufacturing authorisations, on the requirements of good manufacturing practice and on the certificate of good manufacturing practice for medicinal products.

SPECIAL QUALITY CONTROL OF A MEDICINAL PRODUCT

Article 5

1) Each batch of a medicinal product derived from human blood or human plasma and of vaccines shall be subject to a special quality control referred to in Article 175 of the Act, with the exception of batches in respect of which the competent authority of a Member State of the European Union, the European Economic Area (EEA) or Switzerland conducted quality control and issued a certificate of quality control (»EU Official Control Authority Batch Release Certificate«, hereinafter: EU OCABR certificate).

2) The special quality control of a medicinal product referred to in paragraph 1 of this Article shall include an expert-administrative assessment of the documents relating to the medicinal product batch undergoing special quality control and laboratory testing of the medicinal product.

3) The Agency shall carry out a special quality control on each batch of a medicinal product derived from human blood or human plasma or of starting materials and vaccines in respect of which the applicant has applied for an authorisation to place it on the market in the Republic of Croatia in accordance with paragraph 1 of this Article.

4) The Agency shall carry out the special quality control within 60 days of the receipt of a valid application and shall issue an EU OCABR certificate or a national certificate of special quality control of the medicinal product (hereinafter: national OCABR certificate) if the medicinal product is of an appropriate quality.

5) The content of the EU OCABR certificate and the national OCABR certificate has been determined in accordance with the applicable guidelines of the European Union.

6) The costs of quality control shall be borne by the applicant.

Article 6

1) Together with an application for special quality control, the applicant must provide a sufficient quantity of samples for analysis, a certificate of analysis for the batch in question, the manufacturing protocol, information about all raw materials incorporated in the batch of the medicinal product, as well as the prescribed reference standards and other information and documents, or documentation as may be requested by the Agency.

2) In the manufacturing protocol referred to in paragraph 1 of this Article, the manufacturer must indicate the methods used in the manufacturing process to inactivate/eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The manufacturing process and test methods must be validated and pre-approved during the marketing authorisation procedure.

3) The information and documents or documentation referred to in paragraph 1 of this Article shall be submitted in their original form or as certified copies, together with a statement from the applicant's responsible person confirming the authenticity of the information.

4) Within seven days of the receipt of an application for special quality control of a medicinal product, the Agency shall determine whether the application is in order and whether a sufficient quantity of samples and/or the prescribed reference standards have been submitted, or whether all the information and documents or documentation have been provided in accordance with this Ordinance.

5) Where the Agency finds that the application is not in order, that a sufficient quantity of samples and/or the prescribed reference standards have not been submitted and that all the information and documents or documentation have not been provided, it shall issue a written notice requiring that the application be corrected and/or supplemented and shall specify the deadline for the submission thereof.

6) Where the Agency requests that the application be corrected and/or supplemented as referred to in paragraph 5 of this Article, the time limit referred to in Article 5 paragraph 4 of this Ordinance shall be suspended until the date on which the corrected or supplemented application has been submitted.

7) If the applicant fails to submit the amendment in accordance with paragraph 5 of this Article within the time limit specified by the Agency, the Agency shall notify the applicant that it is not possible to carry out a special quality control of a medicinal product derived from human blood or human plasma or of a vaccine.

8) In the case referred to in paragraph 7 of this Article, the Agency shall notify the applicant that the batch of a medicinal product may not be placed on the market.

Article 7

1) For the purposes of special quality control, the Agency shall have the right to request an additional quantity of samples, which the applicant must submit to the Agency.

2) The Agency shall have the right to request to collect samples itself and the applicant must enable it to do so.

Article 8

1) The Agency shall carry out a quality control of a medicinal product in accordance with analytical procedures approved during the marketing authorisation procedure, to the extent to be determined by the Agency, which shall include, as a minimum, routine quality control of a medicinal product in accordance with the applicable guidelines of the European Union.

2) If the result of a special quality control of a medicinal product deviates from the accepted quality specification, the Agency shall issue a notice of non-compliance with the special quality control requirements, based on which the applicant may not place the concerned batch of the medicinal product on the market.

3) The applicant may require the Agency to issue a comprehensive report on the quality control conducted.

Article 9

1) When performing a special quality control of a medicinal product, the Agency shall also have the right to examine other quality parameters, in addition to those prescribed by the applicable guidelines of the European Union, where there are justified professional reasons for doing so.

2) The Agency shall have the right to perform a quality control using other analytical procedures, in addition to those prescribed by the applicable guidelines of the European Union or those accepted during the marketing authorisation procedure, where there are justified professional reasons for doing so.

Article 10

1) Special quality control of a medicinal product shall also include the verification of whether the information provided on the outer and immediate packaging and in the package leaflet conforms to that accepted during the marketing authorisation procedure.

2) When the information provided on the outer and immediate packaging and/or in the package leaflet does not conform to that accepted during the marketing authorisation procedure, the Agency shall give a written notice thereof to the applicant, who may not place the batch concerned on the market.

3) The applicant may correct the labelling of the medicinal product or submit a package leaflet which conforms to that approved during the marketing authorisation procedure and submit a new application for a special quality control of the same batch of the medicinal product.

Article 11

1) Together with an application for a special quality control of a medicinal product derived from human blood or human plasma, the applicant must provide evidence that the plasma pool used for the manufacture of the medicinal product has been tested for viral markers by an official medicines control laboratory in a Member State of the European Union, the EEA or Switzerland.

2) For a plasma pool manufactured in the Republic of Croatia that has not been previously subjected to quality control testing by an official medicines control laboratory in a Member State of the European Union, the EEA or Switzerland, the applicant must submit to the Agency an application for a special quality control.

3) The Agency shall carry out the quality control referred to in paragraph 2 of this Article within 60 days of the receipt of a valid application and shall issue a certificate of special quality control of the plasma pool.

4) The costs of quality control shall be borne by the applicant.

Article 12

A batch of a medicinal product derived from human blood or human plasma or of a vaccine manufactured in the Republic of Croatia may be placed on the market only on the basis of a special quality control certificate issued by the Agency.

Article 13

1) If a special quality control of a batch of a medicinal product derived from human blood or human plasma or of a vaccine or starting material has been carried out by an official medicines control laboratory in a Member State of the European Union, the EEA or Switzerland, the Agency shall recognise the results of the special quality control for the territory of the Republic of Croatia.

2) If the special quality control has been carried out in accordance with paragraph 1 of this Article, the marketing authorisation holder / the holder of a parallel import authorisation / the wholesale distributor must submit the following information and documents:

– OCABR certificate,

– date of placing the medicinal product on the market in the Republic of Croatia and the marketing information form (MIF),

– copies of the outer and immediate labelling of the medicinal product and the package leaflet.

3) The Agency shall verify the administrative-scientific data on the basis of the documentation referred to in paragraph 2 of this Article within seven days of the receipt of a valid application.

4) If the Agency identifies deficiencies in the documentation referred to in paragraph 2 of this Article, it shall inform thereof the marketing authorisation holder / the holder of a parallel import authorisation / the wholesale distributor.

5) If, within the time limit specified in paragraph 3 of this Article, the Agency does not inform the marketing authorisation holder / the holder of a parallel import authorisation / the wholesale distributor of deficiencies in the documentation, the medicinal product may be placed on the market.

QUALITY CONTROL OF MEDICINAL PRODUCTS THAT ARE ON THE MARKET

Article 14

1) The quality control of medicinal products and officinal formulae that are on the market shall be carried out by the Agency at the request of the pharmaceutical inspection service.

2) The request referred to in paragraph 1 of this Article shall be accompanied by a sufficient quantity of samples of the medicinal product or officinal formula for examination and by a sampling report.

Article 15

1) The Agency shall check the quality of a medicinal product in accordance with analytical procedures accepted during the marketing authorisation procedure or in accordance with pharmacopoeias and other internationally accepted standards and regulations, to the extent to be determined by the Agency.

2) The Agency shall also have the right to examine other quality parameters, in addition to those accepted during the marketing authorisation procedure, where there are justified professional reasons for doing so.

3) The Agency shall have the right to perform a quality control using other analytical procedures, in addition to those accepted during the marketing authorisation procedure, where there are justified professional reasons for doing so.

Article 16

1) The Agency shall check the quality of an official formula in accordance with pharmacopoeias and other internationally accepted standards.

2) Exceptionally, at the request of a good manufacturing practice inspector, the Agency shall also check the quality of active substances and excipients. The Agency shall check the quality of active substances and excipients in accordance with the manufacturer's analytical procedures accepted during the marketing authorisation procedure, pharmacopoeias and other internationally accepted standards.

Article 17

For the purposes of quality control of a medicinal product on the market, the holder of the marketing authorisation for the medicinal product in question, the holder of a parallel import authorisation, the wholesale distributor or the importer shall submit reference standards at the request of the Agency.

Article 18

1) The Agency shall carry out the quality control of a medicinal product or officinal formula on the market within 60 days of the receipt of a valid application and shall issue a report of the quality control.

2) The Agency shall issue a favourable report on the quality control of a medicinal product or officinal formula if, with regard to the tested parameters, its quality conforms to the accepted or prescribed quality specification.

3) The Agency shall issue an unfavourable report on the quality control of a medicinal product or officinal formula if the result obtained deviates from the accepted or prescribed quality specification.

4) In the case referred to in paragraph 3 of this Article, the Agency shall immediately notify thereof the pharmaceutical inspection service.

5) The report of the quality control of the medicinal product or officinal formula on the market shall be submitted to the marketing authorisation holder, the holder of a parallel import authorisation, the wholesale distributor or the importer or to the healthcare institution or pharmacy which prepared the officinal formula, and to the natural or legal person at whose premises the samples were collected, and to the pharmaceutical inspection service at its request.

Article 19

The Agency shall also carry out quality control of medicinal products on the market for which an authorisation for parallel import has been issued.

Article 20

Quality control of medicinal products on the market shall not be carried out for medicinal products authorised under the centralised marketing authorisation procedure, except in cases when a quality defect of medicinal product or falsified or suspicion of a falsified medicinal product has been reported.

EXTRAORDINARY QUALITY CONTROL OF MEDICINAL PRODUCTS

Article 21

An extraordinary quality control of a medicinal product shall be carried out in the event of any unusual signs or suspected quality defects or suspected falsified medicinal product or officinal formula.

Article 22

1) An extraordinary quality control shall be carried out at the request of the Ministry of Health (hereinafter: the Ministry) or the Agency.

2) An extraordinary quality control shall be carried out in accordance with Articles 15 and 16 of this Ordinance.

3) The request shall be accompanied by a sufficient quantity of samples for analysis and a sampling report.

4) The request for an extraordinary quality control shall explain the reason for conducting quality control of a medicinal product or officinal formula.

5) For the purposes of an extraordinary quality control of a medicinal product, the holder of the marketing authorisation for the medicinal product in question, the holder of a parallel

import authorisation, the wholesale distributor or the importer shall submit reference standards at the request of the Agency.

Article 23

1) The Agency shall carry out the quality control within 60 days of the receipt of a valid application and shall issue a report of the quality control.

2) The Agency shall issue a report on the findings of the extraordinary quality control of a medicinal product or officinal formula.

3) The report on the findings of the extraordinary quality control shall be submitted to the Ministry, the marketing authorisation holder, the holder of a parallel import authorisation, the wholesale distributor or the importer of the medicinal product and to the healthcare institution or pharmacy which prepared the officinal formula, and to the natural or legal person at whose premises the samples were collected on the basis of a report of a quality defect in a medicinal product or officinal formula or of a counterfeit medicinal product.

QUALITY CONTROL OF A MEDICINAL PRODUCT DURING THE PROCEDURE FOR THE GRANTING OR RENEWAL OF A MARKETING AUTHORISATION OR AN AUTHORISATION FOR PARALLEL IMPORT OF A MEDICINAL PRODUCT AND DURING THE PROCEDURE FOR APPROVAL OF A VARIATION TO THE DOSSIER OF A MEDICINAL PRODUCT

Article 24

Quality control of a medicinal product during the procedure for the granting or renewal of a marketing authorisation or an authorisation for parallel import of a medicinal product and during the procedure for approval of a variation to the dossier of a medicinal product shall be carried out in accordance with analytical procedures submitted for those procedures, to the extent to be determined by the Agency, where there are justified professional reasons for doing so.

Article 25

For the purposes of quality control of a medicinal product, the applicant for the issuance, renewal or variation of a marketing authorisation and the applicant for an authorisation for parallel import of a medicinal product shall submit to the Agency a sufficient quantity of samples for analysis, reference standards and, where necessary, active substances and excipients, including intermediate products, together with appropriate certificates of analysis.

METHOD OF QUALITY CONTROL OF MEDICINAL PRODUCTS

Article 26

Quality control of a medicinal product or officinal formula shall include:

a) sampling for quality control;

b) receiving of samples and reference standards for quality control;

c) receiving of documentation relating to the samples and reference standards submitted;

d) analytical testing and expert evaluation of the information and documents submitted;

e) issuance of test reports and/or certificates and/or notices of non-compliance with the special quality control requirements.

SAMPLING

Article 27

1) Quality control of medicinal products on the market shall be carried out according to an annual sampling plan adopted by the Agency on the basis of a risk assessment which takes into account the following criteria:

– an expert opinion about the medicinal product that presents a high risk to the patient,

– consumption of the medicinal product according to the ATC classification and the active substances contained in the product,

– approved variations to the dossier of the medicinal product,

– date of granting the marketing authorisation for the medicinal product.

2) Samples shall be taken from the market based on geographic and demographic criteria.

3) Samples shall be randomly selected to obtain a representative sample of the medicinal product.

4) Sampling sites for quality control of medicinal products shall be:

– warehouses and vehicles of the manufacturer and the importer of the medicinal product, after the medicinal product is released on to the market,

– warehouses and vehicles of natural and legal persons involved in the wholesale distribution of medicinal products,

– pharmacies and pharmacy depots,

– specialised shops for retail sale of medicinal products,

– healthcare institutions and other legal persons holding a healthcare license and

– private practices.

5) The number of samples to be taken shall be determined on the basis of the marketing authorisation dossier.

Article 28

1) When sampling a medicinal product or officinal formula, the pharmaceutical inspector or other authorised person performing sampling shall draw up a sampling report and hand a copy of the report to the natural or legal person at whose premises the sampling took place.

2) The sampling report must contain the following information:

– the name of the medicinal product or officinal formula,

– the batch number of the medicinal product,

– the name of the manufacturer,

– the expiry date,

– the quantity of the sampled medicinal product or officinal formula,

– a description of the conditions under which the medicinal product was stored at the time of sampling,

– the date of sampling,

– the signature of the person performing the sampling,

– the signature of the person at whose premises the sampling took place.

Article 29

The quality control report shall contain:

1) the type of the quality control performed;

2) the reference number of the report;

3) the name of the medicinal product or officinal formula;

4) the pharmaceutical form, strength and packaging of the medicinal product, where appropriate;

5) the declared composition of the medicinal product;

6) the batch number of the sample of the medicinal product;

7) the name of the manufacturer of the medicinal product, of the marketing authorisation holder or of the holder of a parallel import authorisation;

8) the date of receipt of the sample for analysis, the date of sampling if applicable;

9) the expiry date of the medicinal product;

10) the name and address of the natural or legal person who sent the samples for analysis or of the person at whose premises the samples were taken;

11) data about the assessment of the immediate and outer packaging and the package leaflet;

12) the date of issue of the quality control report;

13) the opinion about the quality of the medicinal product or officinal formula;

14) the signature of the person responsible for quality control;

15) quality specifications, the identification of the method(s) used and the results of the analytical tests.

Article 30

The certificate of special quality control shall contain:

1) the type of the quality control performed;

2) the reference number of the certificate;

3) the name of the medicinal product;

4) the INN name;

5) the type of container;

6) for vaccines, the number of doses per container;

7) the nominal dose per container for medicinal products derived from human blood or human plasma;

8) the batch number of the sample of the medicinal product appearing on the package;

9) the total number of approved containers in the batch in the Republic of Croatia;

10) the name of the manufacturer;

11) the name of the marketing authorisation holder / the holder of a parallel import authorisation;

12) the marketing authorisation number;

13) the expiry date of the medicinal product;

14) the date of start of the period of validity;

15) the date of issue of the certificate;

16) the signature of the person responsible for quality control.

Article 31

The certificate of special quality control of a plasma pool shall contain:

1) the type of the quality control performed;

2) the number of the plasma master file authorisation/certificate;

3) the code numberof the plasma pool;

4) the manufacturing dateof the plasma pool;

5) the identification of the country of origin of donations;

6) the volume of the pool;

7) the name and address of the manufacturer of the plasma pool;

8) the name and address of the marketing authorisation holder (if applicable);

9) the date of issue of the certificate;

10) the signature of the person responsible for the quality control of the plasma pool;

11) the reference number of the certificate.

Article 32

A notice of non-compliance with the special quality control requirements shall include:

1) the reference number of the notice;

2) the name of the medicinal product;

3) the INN name;

4) the batch number of the sample of the medicinal product appearing on the package;

5) the packaging of the medicinal product;

6) the size of the batch manufactured;

7) the number of doses per container;

8) the expiry date of the medicinal product;

9) the marketing authorisation number;

10) the name and address of the manufacturer responsible for batch release of the medicinal product;

11) the name and address of the marketing authorisation holder / the holder of a parallel import authorisation;

12) explanation;

13) comments (where applicable);

14) the signature of the person responsible for special quality control;

15) date of issue.

Article 33

On the date of entry into force of this Ordinance, the Ordinance on the manner of conducting quality control of medicinal products (Official Gazette 56/05) shall cease to have effect.

Article 34

This ordinance shall enter into force on the eighth day after the day of its publication in the Official Gazette.

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Zagreb, 6 May 2014

The Minister
Rajko Ostojić,
m. p.