MINISTRY OF HEALTH

1798

Pursuant to Article 74, paragraphs 2 and 3, Article 83, paragraph 5 and Article 89 of the Medicinal Products Act (Official Gazette 76/2013), the Minister of Health hereby issues the

ORDINANCE

ON THE REQUIREMENTS AND METHOD OF ESTABLISHING THE REQUIREMENTS OF GOOD MANUFACTURING PRACTICE AND GOOD PRACTICE IN THE WHOLESALE OF ACTIVE SUBSTANCES AND ON THE PROCEDURE OF THE ENTRY IN THE REGISTER OF MANUFACTURERS, IMPORTERS AND WHOLESALERS OF ACTIVE SUBSTANCES, AND ON ISSUING THE CERTIFICATE FOR THE IMPLEMENTATION OF GOOD MANUFACTURING PRACTICE

I. GENERAL PROVISIONS

Article 1

This Ordinance lays down conditions to be met by manufacturers, importers and wholesalers of active substances established in the Republic of Croatia for good manufacturing practice, good practice in the wholesale distribution of active substances, and the procedure of the entry in the register and the issuing of the certificates for the implementation of good manufacturing practice and good practice in the wholesale distribution.

Article 2

This Ordinance transposes the following Directives into the legislation of the Republic of Croatia:

1. 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),

2. Commission Directive 2003/63/EC of 25 June 2003 amending 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 159, 27.6.2003),

3. Commission Directive 2003/94/EC of 16 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (OJ L 262/22, 14.10.2003),

4. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 on traditional herbal medicinal products (OJ L 136, 30.4.2004),

5. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 136, 30.4.2004),

6. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending Directive 2001/83 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 276, 21.10.2011),

7. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83 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 174, 1. 7. 2011).

Article 3

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

1. *Pharmaceutical quality assurance system* means the total sum of the organised activities and procedures that ensure that the quality of active substances is in conformity with the quality required for their intended use.

2. *The certificate of the implementation of good manufacturing practice* is a certificate with a limited period of validation that represents the final assessment of compliance of the manufacturing or part of manufacturing of active substances with the requirements of carrying out good manufacturing practice.

3. *Place of production of the active substance* is the defined place on a defined address where the manufacturing procedure or individual parts of manufacturing unfolds.

4. *Dossier on the place of production* is a document developed by the manufacturer, which includes information on the quality management policy and on all activities unfolding in that place on production.

Article 4

1) Natural or legal entities established in the Republic of Croatia may manufacture and import, that is, engage in wholesale distribution of active substances if they have registered their activities and are entered in the register of manufacturers, importers, or wholesalers of active substances.

2) The holders of entry in the register of activities referred to in paragraph 1 of this Article shall comply with the requirements of good manufacturing practice for active substances and of good practice in the wholesale distribution of active substances.

II. CONDITIONS FOR THE MANUFACTURE OF ACTIVE SUBSTANCES

Article 5

The manufacturers of active substances shall meet the following conditions:

– have an adequate number of qualified persons. given the scope and complexity of manufacture of active substances,

– premises, installations and equipment shall be located, designed, constructed, adapted and maintained to suit the intended manufacture, supervision, safe keeping and transportation of active substances in compliance with good manufacturing practice for active substances,

– ensure that all manufacturing processes for active substances are carried out in compliance with good manufacturing practice, including active substances that are intended solely for export.

III. REQUIREMENTS AND GUIDELINES OF GOOD MANUFACTURING PRACTICE

Article 6

Detailed requirements and guidelines of good manufacturing practice for active substances and additional specificities for individual procedures and forms of medicinal products have been published in the EU document entitled "The Rules Governing Medicinal Products in the European Union", Volume 4 – Good Manufacturing Practices, Medicinal Products for Human and Veterinary use, with all its amendments, and they are available on Eudralex website.

IV. IMPORT OF ACTIVE SUBSTANCES

Article 7

1) The import or introduction of active substances may be carried out by the manufacturer of the medicinal product and the investigational medicinal product, the manufacturer and importer of active substances.

2) When the active substance is imported from a third country, the delivery shall include a statement by the competent authority of the exporting third country, confirming that:

a) the active substance was manufactured in the place of production where the requirements of good manufacturing practice comply with those prescribed by the European Union,

b) there is regular, strict and transparent supervision of good manufacturing practice in the place of production,

c) the exporting country is required to notify the European Union without delay of any established non-compliance during supervision.

3) If the active substance is imported from the third country which is on the list of countries approved by the European Union, the delivery does not have to include a written statement referred to in paragraph 2 of this Article.

4) In exceptional cases and in order to ensure the availability of the medicinal products, the manufacturer of medicinal products may, following the consent from the Agency for Medicinal Products and Medical Devices (hereinafter: Agency), introduce an active substance from the third country, which is not on the list of countries approved by the European Union, without the written statement referred to in paragraph 2 of this Article, if the supervision by the EU member state was carried out in the place of production and if the requirements of good manufacturing practice prescribed by the European Union for the active substance are met, and if the manufacturer possesses a valid certificate of good manufacturing practice for the active substance concerned.

5) The procedure of obtaining consent referred to in paragraph 4 of this Article for the import of the active substance shall start with an application submitted to the Agency by the applicant, and it shall include the completed form published on the web site of the Agency, with the following information:

– name of active substance (INN), packaging, quantity;

– name and address of the applicant;

– name and address of the manufacturer;

– name and address of the end-user;

– name and address of the supplier;

– copy of the certificate of good manufacturing practice for the place of production and the active substance concerned, issued by the European Union member state inspection,

– proof of payment of the costs of the procedure;

– proof of payment of the administrative fee.

6) The Agency may also request additional documentation in order to verify that the active substance was manufactured in accordance with the requirements of good manufacturing practice compliant with those prescribed by the European Union.

7) The Agency shall give its approval for the introduction or import of active substances within 15 days of the day of receipt of a complete application. Only the original approval shall be considered valid.

Article 8

Provisions of Article 7 of this Ordinance do not apply to the import of active substances intended for the manufacture of the investigational medicinal product and for research and development purposes.

V. REQUIREMENTS AND GUIDELINES OF GOOD MANUFACTURING PRACTICE IN THE WHOLESALE DISTRIBUTION OF ACTIVE SUBSTANCES

Article 9

In addition to the provisions of this Ordinance, the principles and guidelines of good manufacturing practice in the wholesale distribution of active substances published by the European Commission shall also apply to the wholesale distribution of active substances in the Republic of Croatia.

Article 10

The wholesale distribution of active substances includes the supply, receipt, safekeeping, transport, sale, delivery, taking in and taking out, and/or import and export of the active substance.

Article 11

All participants in the wholesale distribution of active substances shall establish a quality system for the activities they carry out, which includes quality risk management principles with clearly defined and fully documented responsibilities, procedures and risk management measures, involving the active participation of the management and personnel of all auxiliary departments, and appropriate facilities and equipment to ensure the quality of the active substance.

Article 12

A representative of the management shall be appointed in each safe keeping facility and have defined authorities and resources necessary to personally fulfil his duties and to implement and maintain the quality management system.

Article 13

1) Depending on the scope of activities at each location, the wholesale distributors shall provide an adequate number of competent and appropriately qualified personnel to ensure a safe distribution of active substances, as well as other technical personnel trained in proper storage and handling of active substances, who are also familiar with the principles of good practice in wholesale distribution.

2) The personnel shall be trained to perform the activities assigned to them.

3) The records on all training programmes shall be kept, and the review and assessment of efficiency shall be carried out periodically.

Article 14

1) All documents shall be made available to competent authorities.

2) Documents in electronic form shall be kept in accordance with chapter 5.4, Part II and Appendix 11 of principles and guidelines entitled “The Rules Governing Medicinal Products in the European Union”, Volume 4 – Good Manufacturing Practices, Medicinal Products for Human and Veterinary use.

Article 15

If an active substance is supplied by the wholesalers of active substances, they must be entered in the register of wholesalers of active substances.

Article 16

All operating procedures that may affect the quality of active substances or wholesale distribution activities shall be described in the quality system documents, which are dated, and approved and signed by the person responsible for the quality system.

Article 17

1) Records shall be kept on the receipt and delivery of active substances or an active substance distributed, either in the form of purchase/sales invoices, dispatches in electronic or other form.

2) The records shall provide at least the following information: date of the order or the sale, name of the active substance, batch, received or delivered quantity, and name and address of the manufacturer. The records should ensure traceability to the source of the active substance and all its suppliers.

3) Data should be recorded at the time of carrying out each activity and in the manner ensuring traceability of all significant activities or events, with the clearly stated time of the occurrence of the event. The records should be kept at least for 5 years.

Article 18

For the performance of the wholesale distribution of active substances the wholesalers are obliged to ensure premises, installations and equipment that are located, designed, constructed, adapted and maintained to suit the uninterrupted operations, and the safe and compliant location, safe keeping and distribution of active substances.

Article 19

1) The reception and dispatch area for active substances shall be separate from the storage area and protected from the weather conditions.

2) Deliveries shall be examined at receipt in order to establish whether the consignment corresponds to the order, that the containers have not been damaged and that all containers are provided with protective coverings. Active substances for which special storage conditions or specific safety measures have been prescribed shall be given priority at the receipt, all necessary checks shall be performed, and they shall be stored in a prescribed manner.

Article 20

The holder of the entry in the register of manufacturers, importers, or wholesalers shall, immediately and in writing, notify the Agency if he finds out that the active substance received or offered to them is counterfeit or suspected as counterfeit.

Article 21

Active substances shall be kept physically separate from other products that could affect their quality and, in accordance with the storage conditions prescribed by the manufacturer, to avoid damage due to the exposure to light, moisture, inadequate temperature and other external factors.

Article 22

Working and storage areas shall be clean, dry and protected from the pest infestation.

Article 23

1) The wholesalers shall ensure stock rotation based on expiry dates, or renewed inspection of batches in accordance with the FEFO principle - "First expiry, First Out").

2) Active substances whose shelf life has expired shall be immediately recalled from the stock, separated either physically or in some other, equivalent electronic method, and shall not be delivered.

3) Active substances with damaged protective coverings, packaging, or that are suspected of possible contamination shall be recalled and kept in a clearly separated area until they can be destroyed, in order to avoid the dispensation by mistake or contamination of other active substances.

Article 24

Wholesalers shall deliver active substances within the European Union only to natural and legal persons who possess the manufacturing authorisation or are entered in the register of manufacturers, importers, or wholesalers of active substances.

Article 25

Active substances shall be transported in such a way that:

– their identification is not lost;

– contamination is avoided;

– adequate precautions are taken against damage, spillage, breakage or theft;

– they are protected from unacceptable heat, cold, light, moisture or other adverse influence;

– they are secure against attack by microorganisms or pests;

– temperature conditions prescribed by the manufacturer are in place or are specified on the outer packaging and monitored during transport by means of the calibrated equipment.

Article 26

1) The wholesalers shall forward all information received from the manufacturer with relation to the quality and regulatory status to the customer and vice versa.

2) A copy of the certificate of analysis issued by the manufacturer shall be delivered to the customer.

Article 27

1) Returned active substances shall be kept in quarantine, separately from saleable stock, until a decision is made on how to proceed handling them.

2) If the active substance is kept or transported in a manner that could affect the quality, the active ingredient shall be destroyed.

3) Undamaged (intact) active substances may be returned to saleable stock if:

– the goods are in the original, unopened packaging and in good condition;

– it has been demonstrated that the goods have been stored and handled in accordance with the prescribed conditions;

– the remaining shelf life period is acceptable;

– they have been examined and assessed by an authorised person, taking into consideration all characteristics of the active substance, all specifications in terms of storage and the time elapsed since the delivery of the active substance, as well as the manner in which it was dispatched.

4) Records on returned active substances shall be kept and the documentation shall include:

– name and address of the customer;

– batch of the active substance and quantities returned;

– the reason why the active substance was returned,

– a decision on the returned active substance.

Article 28

Any objections relating to quality, whether received orally or in writing, shall be recorded and investigated in accordance with written procedures, that is, standard operating procedure.

Article 29

The written procedure, that is, standard operating procedure, shall define cases when the recall of an active substance must be considered, the authorised person involved in the evaluation of the information, the manner of initiating the recall, the person who should be informed of the recall and how to handle the quantities recalled.

Article 30

Self-inspections shall be conducted in accordance with the approved programme in order to monitor the implementation and abidance of good manufacturing practice in the wholesale distribution of the active substance and to propose any necessary corrective measures. Records shall be kept of such self-inspections and any corrective and preventive measures subsequently taken.

VI. PROCEDURE OF ENTRY IN THE REGISTER OF PRODUCERS, IMPORTERS AND WHOLESALERS OF ACTIVE SUBSTANCE

Article 31

1) For the purpose of entry in the register of manufacturers, importers and wholesalers of the active substance, a natural or legal person established in the Republic of Croatia shall submit an application to the Agency no later than 60 days prior to the scheduled commencement of the activity concerned.

2) In addition to the requirement referred to in paragraph 1 of this Article, the applicant shall enclose the following to the information and documents referred to in Article 85, paragraph 2 of the Medicinal Products Act (hereinafter: the Act):

– a completed registration form – MANUFACTURER, IMPORTER AND WHOLESALER OF ACTIVE SUBSTANCES,

– a written statement that he will manufacture, import and perform wholesale activities with regard to active substances in accordance with the decision on the entry in the register;

– proof of payment of the costs of the procedure;

– proof of payment of the administrative fee.

Article 32

1) In the procedure of the entry in the register, the Agency shall assess the regularity of the application, and decide, on the basis of risk assessment, on the implementation of supervision, and shall inform the applicant thereof in writing.

2) Following the supervision, or if the supervision was not carried out as a result of risk assessment, the Agency shall decide, within 60 days from the receipt of a complete application, or after supervision, to either approve or deny the entry into the register.

3) In the procedure of the entry in the register the inspector of the Agency shall give an opinion on the compliance with the requirements of good manufacturing practice for active substances.

Article 33

In the procedure of the entry in the register, the approval of the amendment and deletion from the register, the Agency shall act in accordance with the provisions of the Act, this Ordinance and the Compilation of Community Procedures on Inspections and Exchange of Information, published by the European Commission.

VII. APPROVAL OF AMENDMENTS

Article 34

1) The holder of the entry in the Register is obliged to report to the Agency once a year any amendments to the documentation, that is, the data and documents based on which the decision on the entry in the register has been granted, and shall submit a request to approve the entry of amendment(s) in the register.

2) In respect of any amendment(s) that might affect the quality or safety of the active substance, the holder of the entry in the Register shall immediately submit a request for the approval of amendment(s) of the entry in the Register.

3) In addition to the request referred to in paragraphs 1 and 2 of this Article, the holder of the entry in the Register shall, based on the type of amendment, submit the data and documents, that is, relevant documentation.

4) The Agency will either approve or deny the amendments to the entry in the Register within 30 days of the receipt of the valid request.

5) If the approved change requires amendment to the decision on the entry in the Register, the Agency shall issue a decision on such amendment, which cannot be appealed, but administrative proceedings can be instituted against it.

6) If the approved change does not require amendment to the decision on the entry in the Register, the Agency shall approve the change by means of a written notification.

VIII. DELETION FROM THE REGISTER

Article 35

The Agency shall issue a decision on the deletion of manufacturers, importers, or wholesalers of active substances from the Register in the following cases:

– at the request of the holder of the entry in the Register,

– if the holder of the entry in the Register is not registered in the court register, or crafts register,

– if it has been established after an inspectional supervision that the holder of the entry in the Register does not meet the requirements for the implementation of activities of manufacturing active substances pursuant to the Act and this Ordinance.

IX. PROCEDURE OF ISSUANCE OF A CERTIFICATE OF GOOD MANUFACTURING PRACTICE

Article 36

1) The inspection of the Agency shall issue a certificate of good manufacturing practice within 90 days from the conducted inspectional supervision of good manufacturing practice and at the request of the manufacturer.

2) The application for issuance of the certificate referred to in paragraph 1 of this Article may also be submitted by the representative of the manufacturer from a third country.

3) The certificate referred to in paragraph 1 of this Article shall be issued on the basis of supervision conducted by the Agency inspector.

Article 37

The application for the issuance of the certificate of good manufacturing practice shall contain:

– full name and seat of the applicant;

– copy of a decision on the entry in the register;

– place of production of the active substance for which the certificate is requested;

– purpose/reason for requesting the certificate;

– class and registration numbers of earlier issued certificates (where applicable);

– proof of payment of the costs of the procedure;

– proof of payment of the administrative fee.

Article 38

The certificate is issued for the place of production of active substances manufactured in that place, with mention of the date of supervision, in accordance with the form contained in the Compilation of Community Procedures on Inspections and Exchange of Information, published by the European Commission.

Article 39

1) The certificate testifies to the compliance with the conditions and requirements of good manufacturing practice for the period of three years from the conducted supervision.

2) The period of validity may be extended or reduced on the basis of the risk management applied by the inspection of the Agency.

X. PROCEDURE OF ISSUANCE OF A CERTIFICATE OF GOOD MANUFACTURING PRACTICE FOR WHOLESALE DISTRIBUTION OF ACTIVE SUBSTANCES

Article 40

1) The pharmaceutical inspection shall issue the certificate on good manufacturing practice in the wholesale distribution of active substances within 90 days from the supervision of good manufacturing practice in the wholesale distribution of active substances and at the request of the importer and wholesaler of active substances.

2) The certificate referred to in paragraph 1 of this Article shall be issued on the basis of the supervision conducted by the pharmaceutical inspector.

XI. SUPERVISION

Article 41

1) The Agency inspector shall supervise the compliance with the conditions prescribed by this Ordinance with regard to the manufacturing or the import of active substances of active substances in the Republic of Croatia.

2) The Agency inspector shall conduct regular and extraordinary supervision of manufacturers of active substances.

3) Regular supervision of manufacturers of active substances shall be conducted, as a rule, every two to three years.

4) Extraordinary supervision of manufacturers of active substances shall be conducted in the event of an incident, significant complaint, product recall, establishment of a deficiency in the medicinal product by the Agency, suspicions as to the quality or signs of unusual appearances, and other situations for the purpose of verifying the quality of medicinal products.

Article 42

1) The pharmaceutical inspector shall supervise the compliance with the conditions prescribed by this Ordinance with regard to the wholesale distribution of active substances in the Republic of Croatia.

2) The pharmaceutical inspection shall conduct regular and extraordinary supervision of the wholesale distribution of active substances.

3) Regular supervision of the wholesale distribution of active substances shall be conducted, as a rule, every two to three years.

4) Extraordinary supervision of the wholesale distribution of active substances shall be conducted in the event of an incident, significant complaint, product recall, establishment of a deficiency in the medicinal product by the Agency, suspicions as to the quality or signs of unusual appearances, and other situations for the purpose of verifying the quality of active substances.

Article 43

1) The pharmaceutical inspector and the Agency inspector shall exchange information on scheduled and conducted supervision with other competent authorities in the European Union Member States.

2) When conducting supervision, the pharmaceutical inspectors and the Agency inspector shall act in accordance with the provisions of the Act, this Ordinance and the Compilation of Community Procedures on Inspections and Exchange of Information, published by the European Commission.

Article 44

1) On the basis of cooperation between the member states, the requirements of the competent authority in the member state, the Agency for Medicinal Products and Medical Devices or the European Commission, the inquiry by the competent authority or the legal or natural person from the European Union or a third country, the Agency inspector shall conduct the supervision in accordance with the Regulation (EC) No 726/2004, Directive 2001/83/EC and Directive 2001/20/EC, and the Compilation of Community Procedures on Inspections and Exchange of Information published by the European Commission for the purpose of verifying the compliance with the conditions of good manufacturing practice in the manufacturing of medicinal products, active substances or ancillary substances in the business entity established in any European Union member state or a third country.

2) Upon the conducted supervision, the Agency inspector shall issue a certificate on good manufacturing practice.

Article 45

1) The information contained in issued certificates on the entry in the register of manufacturers, importers or wholesalers of active substances shall be entered into the EudraGMP. The entry and supervision of amendments to information are carried out by the Agency.

2) The issued certificates on good manufacturing practice shall be entered into the EudraGMDP database. The entry and supervision of amendments to information in the database shall be carried out by the inspection of the Agency.

3) The issued certificates on good manufacturing practice in the wholesale distribution of active substances shall be entered into the EudraGMDP database. The entry and supervision of amendments to information in the database shall be carried out by the pharmaceutical inspection.

Article 46

1) Costs of the supervision, entry in the register and the issuance of certificates shall be borne by the applicant, that is, the holder of the entry in the register, in accordance with the pricelist of the Agency, which is approved by the Minister responsible for health.

2) In the case of supervision in third countries, the costs referred to in paragraph 1 of this Article shall also include travelling and accommodation costs of the Agency inspector.

XII. TRANSITIONAL AND FINAL PROVISIONS

Article 47

The manufacturers, importers and wholesalers of active substances of medicinal products shall harmonise their work and operations with the provisions of this Ordinance within one year from its entry into force.

Article 48

This Ordinance shall be published in the Official Gazette and shall enter into force on 2 July 2013.

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Zagreb, 26 June 2013

Minister

Prof. Rajko Ostojić, MD, PhD,

m.p.