MINISTRY OF HEALTH

1799

Pursuant to Article 73, paragraph 2, Article 74, paragraph 2 and Article 89, paragraph 2 of the Medicinal Products Act (Official Gazette 76/2013), the Minister of Health hereby issues 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

I GENERAL PROVISIONS

Article 1

This Ordinance lays down the requirements of good manufacturing practice to be observed by manufacturers and importers of medicinal products and investigational medical products established in the Republic of Croatia, and the requirements for issuing manufacturing authorisations and certificates of good manufacturing practice.

Article 2

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

2. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001),

3. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (OJ L 91/13, 9.4.2005),

4. 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),

5. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 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 33/30, 8.2.2003),

6. 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),

7. 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),

8. 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),

9. 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),

10. Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008 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 81, 20.3.2008),

11. Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 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 168, 30.3.2009),

12. Commission Directive 2009/120/EC of 14 October 2009 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 242. 15.9.2009),

13. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 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 276, 21.10.2011),

14. 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),

15. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance (OJ L 299, 27.10.2012).

Article 3

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

1. *Pharmaceutical quality assurance* means the total sum of organised activities and procedures with the objective of ensuring that medicinal products and investigational medicinal products are of the quality required for their intended use.

2. *Blinding* means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor.

3. *Unblinding of the identity of investigational medicinal product* means the disclosure of the identity of a blinded product.

4. *Individual parts of manufacturing of medicinal products* include all operations from the supply of materials and products, the manufacture of medicinal products in the narrow sense, immediate packaging, outer packaging, quality control, batch release, import, storage and delivery to wholesale distributors. The manufacturing of medicinal products in the narrow sense is divided according to manufacturing procedures and pharmaceutical forms and includes all manufacturing procedures from receiving starting materials, pharmaceutical and technological forming to packaging of medicinal products. Quality control is divided according to types of conducted tests and includes physical and chemical, biological and microbiological tests that may include microbiological testing of non-sterile and sterile products.

5. *Certificate of good manufacturing practice* is a certificate with limited validity term which represents final evaluation of compliance of a manufacturing process or its parts with the requirements of good manufacturing practice.

6. *Manufacturing site* means a defined area on the address where an integral manufacturing process or its individual parts are carried out.

7. *Documentation on the manufacturing site* means a document developed by the manufacturer of the medicinal product which includes information on the quality management policy and all activities carried out on that manufacturing site.

8. *Cross-contamination* means contamination of starting materials or products with other materials or products.

9. *Batch release* means inspection of all relevant documentation with the objective of establishing the compliance of a batch with the marketing authorisation for a medicinal product and requirements of good manufacturing practice, and providing a final assessment of the batch compliance.

II. CONDITIONS FOR THE MANUFACTURE OF MEDICINAL PRODUCTS

Article 4

(1) Medicinal products and/or investigational medicinal products may be manufactured by natural or legal persons established in the Republic of Croatia only on the basis of and in accordance with the manufacturing authorisation.

(2) Importers shall also hold the manufacturing authorisation for the activities of importing medicinal products and/or investigational medicinal products from third countries.

(3) Holders of manufacturing authorisations must fulfil the requirements prescribed by Articles 73 and 74 of the Medicinal Products Act (hereinafter: the Act) and provisions of this Ordinance.

(4) The manufacturer of medicinal products referred to in paragraph 2 of this Article must ensure that the quality check of each batch imported from a third country is carried out in the European Union, with the exception of the case referred to in Article 81, paragraph 5 of the Medicinal Products Act (hereinafter: the Act).

Article 5

The manufacturer of medicinal products is required to use active substances manufactured in compliance with the requirements of good manufacturing practice which conform to those prescribed by the European Union.

Conformity with good manufacturing practice

Article 6

The manufacturer and the importer of medicinal products shall ensure that all manufacturing operations for medicinal products and/or investigational medicinal products are carried out in compliance with good manufacturing practice and the manufacturing authorisation; this shall also apply to medicinal products intended only for export.

Conformity with marketing authorisation

Article 7

(1) The manufacturer shall ensure that all manufacturing operations for specific medicinal products are carried out in accordance with the approved documentation in the frames of the procedure for issuing the marketing authorisation. In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information submitted to the ministry responsible for health (hereinafter: the Ministry) in the frames of the procedure for clinical trials authorisation.

(2) The manufacturer shall regularly review his manufacturing methods and quality control procedures in the light of their adjustment to scientific and technical progress.

(3) If a modification of a medicinal product dossier is necessary, based on which the marketing authorisation or clinical trials authorisation has been granted, the authorisation holder shall submit an application for the modification approval procedure.

Compliance with the manufacturing authorisation

Article 8

(1) The manufacturer or the importer of medicinal products shall manufacture only medicinal products or investigational medicinal products for which they hold valid manufacturing authorisations.

(2) During the procedure of the issuance or the modification of the manufacturing authorisation, the manufacturers of medicinal products and/or investigational medicinal products shall ensure conformity of all manufacturing operations with the information submitted to the Agency for Medicinal Products and Medical Devices (hereinafter: the

Agency), or to the competent authority in the European Union member state, or in the third country.

Pharmaceutical quality assurance system

Article 9

(1) The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and of the personnel of auxiliary departments.

(2) The holder of manufacturing authorisation shall manufacture medicinal products in accordance with their intended purpose and not compromise the health of the patients in respect of the quality, safety of use or efficiency of the medicinal product.

(3) In the frames of the quality assurance system the holder of manufacturing authorisation shall ensure the use of excipients of adequate quality for the manufacture of medicinal products, during which principles and guidelines of good manufacturing practice apply, and shall carry out the risk assessment in accordance with the guidelines published by the European Commission.

Personnel

Article 10

(1) At each manufacturing site, the manufacturer shall have employed a sufficient number of competent and appropriately qualified personnel to achieve the pharmaceutical quality assurance objectives.

(2) In accordance with the parts of production he conducts, the holder of the manufacturing authorisation shall employ:

– key personnel,

– a master of pharmacy to supervise storage and delivery, as a person responsible for wholesale distribution of medicinal products,

– employees with adequate undergraduate and graduate university qualifications or integrated undergraduate and graduate university qualifications with appropriate specialisation and at least one year of experience, to supervise manufacturing of finished medicinal products and carry out in-coming, in-process and final quality control inspections,

– employees with secondary school backgrounds and adequate specialisations, who are trained for jobs of technicians and auxiliary technical jobs, directly involved in the manufacture and quality control.

(3) Key personnel of the manufacturers consist of a person responsible for manufacture, a person responsible for quality control and a person responsible for batch release of medicinal products.

(4) The person responsible for manufacturing and the person responsible for quality control shall act independently of each other.

Article 11

(1) The person responsible for batch release of medicinal products shall be a person with undergraduate and graduate university qualifications or integrated undergraduate and graduate university qualifications with the specialisations in one of the following: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, and biology.

(2) The study programme shall include the proficiency in the following subjects: experimental physics, general and inorganic chemistry, organic chemistry, analytical chemistry, pharmaceutical chemistry, including analysis of medicinal products, general and applied biochemistry (medical), physiology, microbiology, pharmacology, pharmaceutical technology, toxicology, pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).

(3) If the study programme does not include the proficiency in some of the subjects referred to in paragraph 2 of this Article, the responsible person shall provide evidence of adequate proficiency in the subjects involved.

(4) The person responsible for the batch release of medicinal products shall have at least two years of experience with one or more legal or natural persons, who are holders of the manufacturing authorisation, to obtain practical experience in the area of analysis of medicinal products, quantitative analysis of active substances and all the other tests of the quality of medicinal products. Practical experience may be reduced by one year if the university study programme lasted for at least five years, or by a year and a half if the university study programme lasted for at least six years.

(5) The person responsible for batch release of medicinal products may also be the person responsible for quality control or for the manufacturing of medicinal products.

(6) The Agency shall have a procedure in place for the review of evidence of the fulfilment of conditions by the person responsible for batch release of medicinal products.

Article 12

(1) The duties and tasks of the managerial and supervisory staff responsible for implementing and operating good manufacturing practice, including the qualified persons referred to in Article 10, paragraph 3 of this Ordinance, shall be defined in their job descriptions.

(2) The hierarchal relationships of the staff referred to in paragraph 1 of this Ordinance should be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

(3) The manufacturer shall give sufficient authority to the staff referred to in paragraph 1 of this Article to discharge their responsibilities correctly.

(4) The manufacturer shall ensure initial and ongoing theoretical and practical training for the staff, covering the concept of the total quality assurance and implementation of the principles of good manufacturing practice.

(5) The manufacturer shall establish, implement and monitor the observance of appropriate health and hygiene programmes, including also the use of protective clothing and overalls.

Article 13

(1) The person responsible for batch release of a medicinal product shall ensure that each batch of a medicinal product has been manufactured and controlled in accordance with regulations in force and data provided in the documentation attached to the marketing authorisation application for medicinal products.

(2) In the case of medicinal products coming from third countries, irrespective of whether the products have been manufactured in the European Union, the person responsible for batch release shall ensure that each imported batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

(3) The person responsible for batch release of a medicinal product intended for the European Union market shall ensure that there is safety label provided on the packaging of their medicinal products, where applicable.

(4) The signature of the responsible person from paragraph 1 of this Article in the special logbook or equivalently important document approves the release of an individual batch of medicinal products onto the market.

Premises and equipment

Article 14

(1) Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended manufacturing operations.

(2) Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and maintenance in order to avoid contamination, cross contamination and all other adverse effects on product quality.

(3) Premises and equipment to be used for manufacturing operations, and which are critical to product quality, shall be subjected to appropriate qualification and validation.

Documentation

Article 15

(1) The manufacturer and the importer shall establish and maintain a documentation system based upon product quality specifications, manufacturing formulae, processing and packaging

instructions, procedures and records covering the various manufacturing operations performed. Documents shall be clear, free from error and kept up to date.

(2) Documents concerning general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch prior to the start of manufacture.

(3) The documents from paragraph 2 of this Article should enable the traceability of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product. The batch documentation should be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the placement of the batch on the market, whichever is the longer period.

(4) The manufacturer of an investigational medicinal product shall be required to retain the batch documentation for at least five years after the completion of the last clinical trial or the official termination of the clinical trial in which the batch was used.

(5) The manufacturer or the importer shall retain other documentation as long as required by the critical nature of the process to which the documentation is related, which is subject to justification.

(6) The marketing authorisation holder or the sponsor of the clinical trial, if different, shall be responsible for ensuring that records are retained in accordance with the approved procedure for marketing authorisation, if required for a subsequent marketing authorisation.

(7) When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be submitted to the competent authorities at their request. When electronically stored data is used, it shall be protected against unauthorised access and an indelible record of each entry or database scanning shall be provided with information about the person and time of database use.

(8) The data recorded as described in paragraph 8 of this Article shall be protected against loss or damage by methods such as back-up and transfer to another storage system.

Manufacture

Article 16

(1) The different manufacturing operations shall be carried out in accordance with pre-established written instructions and procedures and in accordance with good manufacturing practice. Adequate and sufficient resources shall be made available for the in-process controls. All process deviations and product defects shall be correspondingly documented and thoroughly investigated.

(2) All appropriate technical or organisational measures shall be taken to avoid cross-contamination and mix-ups. In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.

(3) Any new manufacturing process or important modification of the existing manufacturing process of a medicinal product shall be validated. Critical phases of manufacturing processes shall be regularly re-validated.

(4) For investigational medicinal products, the manufacturing process should be validated in its entirety, taking into account the stage of product development. Critical process steps, such as sterilisation, must be validated. All steps in the design and development of the manufacturing process shall be fully documented.

(5) The procedure of manufacturing immunological medicinal products should be validated in order to confirm the uniform quality of the manufactured batches.

Quality control

Article 17

(1) The manufacturer and the importer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

(2) The person referred to in paragraph 1 of this Article shall have at his disposal one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examinations (the testing of the starting materials and packaging materials and the testing of intermediate and finished products). Subject to a written contract, other laboratories qualified for the purpose may also be used if they observe good manufacturing practice and have been approved in the manufacturing authorisation procedure.

(3) For investigational medicinal products, the sponsor of the clinical trial or his representative shall ensure that in carrying out all procedures the contract laboratory complies with the documentation attached to the clinical trials application.

(4) During the final control of the medicinal product before its batch release or before release of an investigational medicinal product, in addition to analytical results, all other information, such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications, including the final finished pack, shall be taken in account.

(5) The manufacturer shall retain samples of each batch of medicinal product for at least one year after the expiry date.

(6) For an investigational medicinal product, sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished product batch shall be retained for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

(7) Samples of starting materials (other than solvents, gases or water) used in the manufacturing process shall be retained for at least two years after the market release of the product.

(8) The period referred to in paragraph 7 of this Article may be shortened if the period of stability of the material, as indicated in the relevant quality specification, is shorter.

(9) All those samples shall be maintained at the disposal of the competent authority.

(10) Other conditions may be defined, by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities, or when their storage could raise special problems.

Work contracted out

Article 18

(1) The manufacturer or the importer shall sign a written contract for any manufacturing operation or operation linked thereto which is carried out for the manufacturer by another natural or legal person.

(2) The contract referred to in paragraph 1 of this Article shall clearly define the responsibilities of each contractual party and shall define, in particular, the observance of good manufacturing practice to be followed by the contract-acceptor and the manner in which the person responsible for certifying each batch is to discharge his responsibilities.

(3) When the authorisation holder is different from the manufacturer, there shall be an adequate contract signed between them in compliance with the requirements and principles of good manufacturing practice.

(4) The contract-acceptor referred to in paragraph 2 of this Article shall not subcontract to a third natural or legal person any of the work entrusted to him under the contract without written authorisation from the contract-giver.

(5) The contract-acceptor shall apply the principles and guidelines of good manufacturing practice and shall enable pharmaceutical inspections of his work to be conducted by the Agency.

Complaints, product recall and emergency unblinding

Article 19

(1) The manufacturer and the importer of a medicinal product shall establish and implement a system for recording and reviewing all complaints received together with an effective system for prompt recall of medicinal products in the distribution network.

(2) Any complaint concerning a defect shall be recorded and investigated by the manufacturer and the importer of the medicinal product.

(3) The manufacturer and the importer of the medicinal product shall inform the Agency of any defect that could result in a recall or abnormal restriction on use of the medicinal product and, in so far as possible, indicate the countries of destination.

(4) In cases referred to in paragraph 3 of this Article, the manufacturer shall take all measures specified by the Agency inspection.

Article 20

(1) In the case of investigational medicinal products, the manufacturer shall, in co-operation with the sponsor, establish and implement a system for recording and reviewing complaints together with an effective system for prompt recall of the medicinal products.

(2) The manufacturer or the importer of a medicinal product shall record and investigate any complaint concerning a defect referred to in paragraph 1 of this Article and shall inform the Ministry and the Agency of any defect that could result in a recall or abnormal restriction on use of the medicinal product.

(3) In the case of investigational medicinal products, all trial sites shall be identified and, in so far as is possible, the countries of destination shall be indicated.

(4) In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product shall, in co-operation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised medicinal product.

(5) The sponsor shall establish a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall.

(6) The sponsor shall ensure that the procedure referred to in paragraph 5 of this Article discloses the identity of the blinded product only in so far as is necessary to protect trial subjects.

Self-inspection

Article 21

The manufacturer or the importer shall conduct self-inspections as part of the pharmaceutical quality assurance system in order to monitor and supervise the implementation and observance of good manufacturing practice and to propose any necessary measures for improvement of the pharmaceutical quality assurance system. Records shall be maintained of such self-inspections and any corrective action subsequently taken.

Labelling of investigational medicinal products

Article 22

Labelling of an investigational medicinal product shall be such as to ensure protection of the subjects and traceability, identification of the product and clinical trial, and to facilitate proper use of the investigational medicinal product.

III REQUIREMENTS AND GUIDLINES OF GOOD MANUFACTURING PRACTICE

Article 23

In addition to provisions laid down in the Act and this Ordinance, the production of medicinal products is governed by the requirements and guidelines of good manufacturing practice for medicinal products as well as by specifics concerning individual procedures and forms of medicinal products "The Rules Governing Medicinal Products in the European Union, Volume 4 – Good Manufacturing Practices, Medicinal Products for Human and Veterinary use", including all amendments, and they are available on the Eudralex website.

IV ISSUING OF MANUFACTURING AUTHORISATIONS

Article 24

(1) For the purpose of issuing of manufacturing authorisations, the natural or legal person established in the Republic of Croatia shall submit an application to the Agency.

(2) In addition to the written application referred to in paragraph 1 of this Article, the applicant shall be required to enclose a completed application form "MANUFACTURE AND IMPORT" published on the web site of the Agency, together with the documents and data prescribed by Article 75, paragraph 2 of the Act, as well as the following documentation:

– a written statement by the applicant, declaring that he shall enable the person responsible for batch release of medicinal product to carry out his activities independently, and ensure all requisite resources,

– a written statement by the applicant, declaring that he shall carry out the manufacturing activities in compliance with good manufacturing practice,

– a written statement by the applicant, declaring that he shall use for the manufacture of medicinal products only active substances which are produced in line with good manufacturing practice,

– a written statement by the applicant, declaring that he shall manufacture only medicinal products, or investigational medicinal products, for which he holds a valid manufacturing authorisation,

– proof of payment of costs of procedure,

– proof of payment of administrative fees.

Article 25

(1) The importer shall be required to indicate the manufacturing site for all medicinal products from the list, in respect of which he has submitted an application for the issuance of the manufacturing authorisation.

(2) The importer shall be required to hold a certificate on good manufacturing practice issued by the competent authority of the European Union member state concerned for all manufacturing sites and pharmaceutical forms that are the subject of the manufacturing authorisation for the import of medicinal products from third countries.

(3) The importer shall be required to regularly maintain and renew authorisations referred to in paragraph 2 of this Article and submit them for examination during inspectional supervision.

Article 26

(1) In the procedure of issuing manufacturing authorisations the Agency shall inspect the regularity of the application and the Agency inspector shall give his opinion on compliance with good manufacturing practice.

(2) The Agency inspector shall determine the compliance with good manufacturing practice. For the purpose of determining the compliance with the requirements of good manufacturing practice, the Agency may appoint a commission, which may include experts from individual fields.

(3) When determining the compliance with the requirements of good manufacturing practice a record shall be compiled on the confirmed factual state and signed by the Agency inspector, the members of the commission and the representative of the applicant.

Article 27

(1) Within 30 days of the date of the inspection of good manufacturing practice, the Agency inspector shall compile a report on the fulfilment of requirements of good manufacturing practice and submit it to the applicant.

(2) In the event shortcomings are identified during inspection referred to in paragraph 1 of this Article, the applicant is obliged to submit a written explanation on the established shortcomings to the Agency inspector within 30 days of the inspection.

(3) The Agency inspector shall give his written opinion on the fulfilment of the requirements of good manufacturing practice for the activity of manufacturing medicinal products on the basis of the inspection report, and in the event shortcomings are identified, on the basis of the written statement of the applicant.

V TEMPORARY MANUFACTURING AUTHORISATION

Article 28

(1) If during the procedure for the issuance of manufacturing authorisation it is ascertained that the applicant does not fully meet all the prescribed requirements of good manufacturing practice, the Agency may issue a temporary manufacturing authorisation and set the deadlines for the elimination of identified shortcomings.

(2) The authorisation referred to in paragraph 1 of this Article shall cease to be valid upon the expiry of the deadline set for the elimination of identified shortcomings, if such shortcomings have not been eliminated within the specified deadline.

VI CHANGE APPROVAL

Article 29

(1) The manufacturer of medicinal products shall submit to the Agency a request for the approval of any change in documentation, or in the data and documents based on which the manufacturing authorisation was granted.

(2) In the procedure of the change approval referred to in paragraph 1 of this Article, the Agency inspector shall give his opinion on the compliance with the requirements of good manufacturing practice if the change affects the fulfilment of the requirements of good manufacturing practice.

(3) The applicant shall enclose the documentation on the change to the written application for change approval referred to in paragraph 1 of this Article, confirmation of the payment of administrative fee and of the costs of procedure.

(4) The provisions of Articles 26 and 27 of this Ordinance shall adequately apply to the procedure for change approval, where the inspection of good manufacturing practice is conducted.

(5) If an approved change does not require any data amendment in the manufacturing authorisation, the Agency shall approve the change by means of a written notification.

VII CERTIFICATE OF GOOD MANUFACTURING PRACTICE

Article 30

(1) The Agency inspection shall issue a certificate of good manufacturing practice (hereinafter: the certificate) within 90 days after the inspection of good manufacturing practice and at the request of the manufacturer or the importer.

(2) The application for the issuance of the certificate may also be submitted by the manufacturer from the third country through his representative in the Republic of Croatia.

(3) The certificate shall be issued if requirements of good manufacturing practice have been observed as established during the manufacturing authorisation procedure or inspection conducted by the Agency.

Article 31

(1) The applicant shall enclose the following data and documents to the application for the issuance of the certificate:

– full name and seat of the applicant,

– copy of the manufacturing authorisation,

– manufacturing site, manufacturing parts, manufacturing processes and pharmaceutical forms of the medicinal product for which the certificate is requested,

– indication of purpose for requesting the certificate,

– classes and file numbers of earlier certificates (where applicable),

– proof of the payment of the costs of procedure,

– proof of the payment of administrative fee.

(2) In respect of the requirements referred to in Article 30, paragraph 2 of this Ordinance, the applicant shall be required to enclose the following to the data and documents from paragraph 1 of this Article:

– documentation referred to in Article 24 of this Ordinance,

– copies of issued certificates of good manufacturing practice for the manufacturing site,

– a written authorisation which authorises a person for the communication with the Agency inspection.

Article 32

The certificate shall be issued for the manufacturing site, manufacturing parts, manufacturing processes carried out and pharmaceutical forms manufactured at the production site concerned, with mention of the date of inspection, and in accordance with the form as contained in the Compilation of Community Procedures on Inspections and Exchange of Information, issued by the European Commission.

Article 33

(1) The certificate testifies to the fulfilment of the requirements of good manufacturing practice for the manufacturing site at the time of inspection and to the conformity with good manufacturing practice for the period of three years following the day of inspection.

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

Article 34

If during inspectional supervision it is established that the holder of manufacturing authorisation has failed to carry out his activities in conformity with good manufacturing practice, the Agency inspection may revoke the certificate.

VIII SUPERVISION

Article 35

(1) The Agency inspector shall supervise the fulfilment of the requirements laid down in this Ordinance by manufacturers and importers with production sites in the Republic of Croatia.

(2) The Agency inspection shall conduct regular and extraordinary supervisions of the holders of manufacturing authorisations.

(3) Regular supervisions of manufacturers and importers of medicinal products shall be conducted, as a rule, every two to three years.

(4) Extraordinary supervisions of manufacturers and importers of medicinal products 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.

(5) The Agency inspection exchanges information on scheduled and conducted supervision with other competent authorities of the European Union member states.

Article 36

In performing supervision the Agency inspection shall take into consideration the Compilation of Community Procedures on Inspections and Exchange of Information, issued by the European Commission.

Article 37

(1) Based on the cooperation among European Union member states, the requirements of the competent authority of the European Union member state, the European Medicines Agency or the European Commission, the requirements of the competent authority or a legal or natural person from the European Union or a third country, the Agency inspection shall conduct the supervision for the purpose of establishing the fulfilment of good manufacturing practice in the manufacture of medicinal products, investigational medicinal products, active substances or excipients.

(2) The supervision shall be carried out with manufacturers and importers of medicinal products and/or investigational medicinal products, manufacturers of active substances, manufacturers or importers of excipients and with holders of marketing authorisations established in the European Union member state or a third country.

(3) Upon the conducted inspection from paragraph 1 of this Article, where applicable, the Agency inspection shall issue the certificate on good manufacturing practice.

Article 38

Should the person responsible for batch release of medicinal products fail to meet the obligations prescribed by the Act and this Ordinance, the Agency inspector may suspend the activities of the person responsible for the batch release of medicinal products.

Article 39

(1) The data on the issued manufacturing authorisations shall be entered into the EudraGMP database. The entry and supervision of data change in the manufacturing authorisations shall be carried out by the Agency.

(2) The issued certificates on good manufacturing practice shall be entered into the EudraGMP database. The entry and supervision of data change in the database shall be carried out by the Agency inspection.

Article 40

(1) The costs of the supervision shall be borne by the applicant, that is, the holder of manufacturing authorisation or the holder of marketing authorisation.

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

IX TRANSITIONAL AND FINAL PROVISIONS

Article 41

Manufacturers of medicinal products shall align their work and operations with the provisions of this Ordinance within one year from the date of entry into force of this Ordinance.

Article 42

Persons having authorisations for carrying out batch release of medicinal products, who are discharging the responsibilities of the person responsible for batch release at the time of the entry into force of this Ordinance, and who were authorised for the manufacturer in the procedure of issuing or amending the manufacturing authorisation pursuant to the provisions of the Medical Products Act (Official Gazette 71/07, 45/09 and 124/11) and the Ordinance on good manufacturing practice for medicinal products (Official Gazette 74/09) shall submit, within one year, the evidence on the fulfilment of requirements prescribed by this Ordinance.

Article 43

The procedures of issuing or amending manufacturing authorisations, or issuing certificates of good manufacturing practice, which commenced in accordance with the provisions of the Ordinance on good manufacturing practice for medicinal products (Official Gazette 74/09), shall be completed in accordance with the provisions of this Ordinance.

Article 44

On the date of entry into force of this Ordinance, the Ordinance on good manufacturing practice for medicinal products (Official Gazette 74/09) shall cease to have effect.

Article 45

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

Class: 011-02/13-02/94

Reg. no: 534-10-1-2-2/4-13-1

Zagreb, 26 June 2013

Minister

Prof. Rajko Ostojić, MD, PhD,

m.p.