SUBSIDIARY LEGISLATION 458.42

GOOD MANUFACTURING PRACTICE IN RESPECT OF MEDICINAL PRODUCTS AND ACTIVE SUBSTANCES FOR HUMAN USE REGULATIONS

xx th January, 2018

LEGAL NOTICE xxx of 2018

Citation.

1. The title of these regulations is the Good Manufacturing Practice in Respect of Medicinal Products and Active Substances for Human Use Regulations.

Scope.

2. These regulations, which transpose Directive 2017/1572 and Directive 2011/62/EU, lay down the principles and guidelines of good manufacturing practice in respect of the manufacture of medicinal products and active substances for human use.

Interpretation.

3. For the purposes of these regulations and unless the context otherwise requires:

"the Authority" means the Medicines Authority;

"good manufacturing practice" means the part of quality assurance which ensures that products are consistently produced, imported and controlled in accordance with the quality standards appropriate to their intended use and in linee with the current detailed good manufacturingg practice guidelines published by the EuropeanUnion Commission;

"manufacturer" means any person engaged in the activities for which the licence referred to in the Manufacture and Importation of Medicinal Products for Human Use Regulations is required or has to register his activities in accordance with regulation 3A of the said regulations;

"medicinal product" means any product as defined in Article 1(2) of Directive 2001/83/EC;

"pharmaceutical quality system" means the total sum of the organised arrangements made with the object of ensuring that medicinal products or active substances are of the quality required for their intended use;

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Deleted: "blinding" means the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;

Deleted: "investigational medicinal product" means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already having a marketing authorization b u t which are used o r assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

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"qualified person" means any person who is a qualified person as provided by regulation 9 of Manufacture and Importation of Medicinal Products for Human Use Regulations;

Inspections.

4. (1) The Authority shall, by means of repeated inspections in the case of medicinal products for human use, ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by these regulations.

(2) The Authority shall, by means of repeated inspections, ensure that manufactures and importers of active substances, including active substances that are intended for export, comply with European Union good manufacturing practice for active substances.

(3) The Authority shall also take into account the compilation, published by the Commission, of Community procedures on inspections and exchange of information.

(4) For the interpretation of the principles and guidelines of good manufacturing practice, the Authority and the manufacturers shall take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in the "Guide to good manufacturing practice for medicinal products and for investigational medicinal products". In the case of advanced therapy medicinal products, the guidelines on good manufacturing practice specific to advanced therapy medicinal products referred to in Article 5 of Regulation (EC) No 1394/2007 on advanced therapy medicinal products shall be taken into account.

(5) The Medicines Authority shall establish and implement in its inspectorate a properly designed quality system that shall be complied with by inspectorates' personnel and management. The quality system shall be updated as appropriate.

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Conformity with good manufacturing practice.

5. (1) It shall be the duty of the manufacturer to ensure that manufacturing operations, including those of medicinal products intended only for export, and of intermediate products, active substances and excipients, are carried out in accordance with European Union good manufacturing practice and with themanufacturing authorisation.

(2) It shall be the duty of the manufacturers and importers of active substances, including active substances that are intended for export, to comply with the current European Union good manufacturing practice for active substances.

(3) For medicinal products imported from third countries, the importer shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down in the Union and that such products have been manufactured by manufacturers duly authorised to do so.

Compliance with marketing authorisation.

6. (1) It shall be the duty of the manufacturer to ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as accepted by the Licensing Authority.

(2) It shall be the duty of the manufacturer to review regularly his manufacturing methods in the light of scientific and technical progress.

(3) If a variation to the marketing authorisation dossier is necessary, the application for modification shall be submitted to the Authority.

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7. It shall be the duty of the manufacturer to establish, implement and maintain an effective pharmaceutical quality assurance system involving the active participation of the management and personnel of the different departments.

Pharmaceutical quality system.

8. It shall be the duty of the manufacturer to ensure that:

Personnel.

(*a*) there is at each manufacturing site, a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the pharmaceutical quality assurance objective;

(*b*) the duties of the managerial and supervisory staff, including the qualified persons, responsible for implementing and operating good manufacturing practice, are defined in the job descriptions;

(*c*) the hierarchical relationships of the manufacturer's staff are defined in an organisation chart;

(*d*) the organisation charts and job descriptions are approved in accordance with the manufacturer's internal procedures;

(*e*) the staff have sufficient authority to discharge their responsibility correctly;

(*f*) the personnel receives initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance and good manufacturing practice;

(*g*) the hygiene programmes adapted to the activities to be carried out shall be established and observed and such programmes shall, in particular include procedures relating to health, hygiene practice and clothing of personnel.

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

Premises and equipment.

(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, in general, any adverse effect on the quality of the product.

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Deleted: (2) In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information provided by the sponsor as provided in t h e Clinical Trial s Regulations, and as accepted by the Licensing Authority.

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(3) Premises and equipment to be used for manufacturing operations or import operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation.

Documentation.

10.(1)(*a*) It shall be the duty of the manufacturer to establish and maintain a documentation on system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed. The documentation system shall ensure data quality and integrity.

(*b*) Documents shall be clear, free from error and kept up todate. Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. Such set of documents shall enable the history of the manufacture of each batch to be traced.

(2) For a medicinal product, the batch documentation shall 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 certification referred to in the Manufacture and Importation of Medicinal Products for Human Use Regulations, whichever is the longer period.

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(3) (*a*) 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.

(*b*) Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request.

(*c*) The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against unlawful access, loss or damage of data, and audit trails shall be maintained.

Production.

11.(1)(*a*) The different production operations shall be carried out in accordance with pre-established instructions an d procedures and in accordance with good manufacturing practice.

(*b*) Adequate and sufficient resources shall be made available for the in-process controls.

(*c*) All process deviations and product defects shall be documented and thoroughly investigated.

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Deleted: (*b*) In the case of an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation.

(2) Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups.

(3) In the case of medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated and the critical phases of manufacturing processes shall be regularly re-validated.

12. (1)(*a*) It shall be the duty of the manufacturer to establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

(*b*) Such person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of the starting materials and packaging materials and the testing of intermediate and finished products.

(2) (*a*) In the case of medicinal products, including those imported from third countries, contract laboratories may be used if authorised in accordance with regulation 13.

(3) During the final control of the finished product, before its release for sale or distribution, the quality control system shall take into account, in addition to analytical results, any essential 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.

(4) (*a*) In the case of a finished medicinal product, samples of each batch shall be retained for at least one year after the expiry date.

(b) In the case of samples of starting materials, other than solvents, gases or water, used in the manufacturing process, such samples shall be retained for at least two years after the release of the product:

Provided that such period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter.

(c) All such samples shall be maintained at the disposal of the competent authorities.

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

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Provided that when such products are imported from third countries, analytical control shall not be mandato

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Deleted: (*b*) In the case of 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.

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Outsourced operations

13. (1) Any manufacturing operation or import operation or operation linked thereto which is outsourced shall be the subject of a written contract.

(2) The contract shall clearly define the responsibilities of each 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 qualified person responsible for certifying each batch is todischarge his responsibilities.

(3) The contract-acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract-giver.

(4) The contract-acceptor shall comply with the principles and guidelines of good manufacturing practice applicable to the operations concerned laid down in the European Union and shall submit to inspections carried out by the competent authorities as provided by the Medicines Act.

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Complaints, and product recall

14. (1) The manufacturer shall:

(*a*) implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network;

(*b*) record and investigate any complaint concerning a defect;

(*c*) inform the competent authority and, if applicable, the marketing authorization holder of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination. Any recall shall be made in accordance with the requirements referred to in the Medicines Act.

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15. The manufacturer shall:

Self-inspection.

(*a*) conduct repeated self-inspections as part of the quality system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures and/or preventive actions; and

(*b*) maintain records of such self-inspections and any corrective action subsequently taken.

Importation of active substances

16. (1) Active substances shall only be imported if the following conditions are fulfilled:

(*a*) the active substances have been manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the European Union pursuant to the third paragraph of article 47; and

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(*b*) the active substances are accompanied by a written confirmation from the competent authority of the exporting third country of the following:

(i) the standards of good manufacturing practice applicable to the plant manufacturing the exported active substance are at least equivalent to those laid down by the European Union;

(ii) the manufacturing plant concerned is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the European Union; and

(iii) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the European Union without any delay.

(2) This written confirmation shall be without prejudice to any other obligations set out in the Act and regulations and, or rules made thereunder. The requirement set out in sub-regulation (1)(*b*) shall not apply if the exporting country is included in the list published by the European Union Commission as referred to in Article 111b of Directive 2001/83/EC, as amended.

(3) Exceptionally and where necessary to ensure the availability of medicinal products, when a plant manufacturing an active substance for export has been inspected by a European Union Member State and was found to comply with the principles and guidelines of good manufacturing practice as defined in these regulations, the requirement set out in sub-regulation (1)(*b*) may be waived for a period not exceeding the validity of the certificate of good manufacturing practice. When such waiver is used, this shall be communicated to the European Union Commission.

Offences and penalties. Cap. 458.

17. Any breach to these regulations shall be liable to penalties under article 99(1)(*b*) of the Medicines Act.

18. Publication of these regulations shall repeal Legal Notice 477 of 2012 titled 'Good Manufacturing Practice in Respect of Medicinal Products, Active Substances and Investigational Medicinal Products For Human Use Regulations',

Deleted: 16. In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product

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