Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use (Text with EEA relevance)

COMMISSION DELEGATED REGULATION (EU) No 1252/2014

of 28 May 2014

supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to 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[(1)], and in particular the third paragraph of Article 47 thereof,

Whereas:

(1) All active substances manufactured in the Union, including active substances intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice for active substances which at present are set out in the technical guidelines on manufacturing of active substances published by the Commission. It is necessary to lay down principles and guidelines of good manufacturing practice for active substances in a legally binding act.

(2) In order to promote the use of harmonised standards at global level, principles and guidelines of good manufacturing practice for active substances should be laid down in line with the guidelines for active substances established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

(3) Principles and guidelines of good manufacturing practice should be set out in relation to all issues, operations and processes that are key to determining the quality of active substances, such as quality management, personnel, premises and equipment, documentation, material management, production, in-process quality controls, packaging, labelling, laboratory controls, returns, complaints and recalls, contracting out and repackaging. In order to ensure compliance with those principles and guidelines, the manufacturers of active substances should be required to establish and implement an effective system for managing the quality of those substances.

(4) Personnel in unsanitary conditions, wearing unsuitable clothing or practicing potentially contaminating activities in the manufacturing area may compromise the

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quality of the active substance. This should be prevented by practicing sanitation and health habits that are appropriate to the manufacturing operations performed. Those practices should be provided for in the quality management system established by the manufacturer of the active substance.

(5) In order to ensure an adequate quality of the active substance, it is necessary to minimise potential contamination and cross-contamination by requiring the use of facilities, production processes and containers designed for this purpose, as well as appropriate contamination controls.

(6) It is of particular importance to prevent cross-contamination when producing active substances harmful to human health. Contamination of other products with highly sensitising active substances could pose a serious threat to public health since exposure to these substances very often results in the development of hypersensitivity and allergic reactions. For that reason, manufacturing of those active substances should only be allowed to take place in separate production areas. The use of separate production areas may also be necessary for the production of active substances with the potential to be harmful to human health because of their potency or their infective or toxic nature. For those substances, the manufacturer should perform an assessment of the risks to human health and the need for separate production areas.

(7) In order to facilitate the tracing, identification and solving of potential quality problems as well as to verify compliance with good manufacturing practice, the manufacturer should keep detailed written records of all processes he performs that relate to the manufacturing of active substances, including of deviations from those processes.

(8) In order to ensure that medicinal products have the appropriate standards of quality, safety and efficacy and to protect public health, manufacturers of an active substance should communicate without delay any changes which may affect the quality of the active substance to manufacturers of medicinal products using the active substance.

(9) It is necessary to have in place appropriate procedures to record and investigate quality-related complaints and perform product recalls in order to rapidly address quality concerns and remove from the market active substances that do not meet quality standards or pose a serious threat to public health.

(10) When the manufacturer of the active substance entrusts any part of the manufacturing to another party, it is important to clarify in writing the responsibilities of that other party with regard to compliance with good manufacturing practices and quality measures.

(11) The application of good manufacturing practices to the process of repackaging and relabelling is necessary to avoid that active substances are wrongly labelled or become contaminated in the process,

HAS ADOPTED THIS REGULATION:

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Article 1

Scope

This Regulation lays down the principles and guidelines of good manufacturing practice for active substances for medicinal products for human use, including active substances intended for export.

Article 2

Definitions

For the purposes of this Regulation, the following definitions shall apply:

(1) ‘manufacturing’ means any total or partial operation of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control or release of active substances, and the related controls;

(2) ‘active substance starting material’ means any substance from which an active substance is manufactured or extracted;

(3) ‘active substance intermediate’ means a substance which is obtained during the production of an active substance and which is intended for further processing;

(4) ‘raw material’ means any substance, reagent or solvent which is intended for use in the production of an active substance and from which the active substance is not directly manufactured or extracted.

Article 3

Quality management

1 Manufacturers of active substances (‘the manufacturer’) shall establish, document and implement an effective system for managing the quality of those substances during the manufacturing operations performed by them (the ‘manufacturing process’). The system shall provide for the active participation of the management and manufacturing personnel.

The system shall ensure that the active substances meet the specifications for their quality and purity established in accordance with Article 12(1).

The system shall incorporate quality risk management.

2 The manufacturer shall appoint a quality unit that is independent of the production unit to be responsible for quality assurance and quality control.

3 The manufacturer shall conduct regular internal audits and follow-up on the findings.

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Article 4

Personnel

1 The manufacturer shall ensure an adequate number of personnel having the necessary qualifications acquired through education, training or experience to carry out and supervise the manufacturing of active substances.

2 Personnel shall practice good sanitation and hygiene in the manufacturing area. Personnel shall not access the manufacturing area if they:

a suffer from an infectious disease or have open lesions or other dermatological conditions on the exposed surface of the body that could negatively affect the quality and purity of the active substance;

b wear clothing which is visibly dirty, or does not protect the active substance from potential contamination coming from personnel, or does not protect personnel from exposure to active substances potentially harmful to human health;

c at the moment of entering the manufacturing area, are performing activities that could contaminate or otherwise compromise the quality of the active substance.

Article 5

Buildings and facilities

1 Buildings and facilities used in the manufacturing of active substances shall be located, designed and constructed to suit the intended operations and to facilitate cleaning and maintenance having regard to the type and stage of manufacturing which the buildings and facilities are used for.

Facilities and the flow of material and personnel through the facilities shall be designed to ensure that different substances and materials are kept separate and do not contaminate each other.

2 Buildings shall be properly maintained and repaired and kept in a clean condition.

3 Highly sensitising active substances shall be produced in separate production areas.

When carrying out production operations, the manufacturer shall assess the need for separate production areas for other active substances with the potential to be harmful to human health because of their potency or their infective or toxic nature. The assessment shall evaluate the risk to human health posed by those active substances by taking account of the active substance potency, toxicity, infectivity and the risk minimisation procedures in place. The assessment shall be documented in writing.

Where the assessment shows a risk of harm to human health, the active substance shall be produced in separate production areas.

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Article 6

Equipment

1 Equipment used in the manufacturing of active substances shall be appropriately designed, sized and located for its intended use, cleaning, maintenance and, where appropriate, sanitisation.

Equipment shall be constructed and operated so that surfaces that come into contact with raw materials, active substance starting materials, active substance intermediates or active substances do not alter the quality of the raw materials, the active substance starting materials, the active substance intermediates or the active substances to the extent that they no longer comply with the specifications established in accordance with Article 12(1).

2 The manufacturer shall establish written procedures for the cleaning of equipment and the subsequent verification of its suitability for use in the manufacturing process.

3 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of the active substance shall be calibrated in accordance with written procedures and an established schedule.

Article 7

Documentation and records

1 The manufacturer shall establish and maintain a documentation system and written procedures covering the manufacturing process.

All documents in relation to the manufacturing process shall be prepared, reviewed, approved and distributed in accordance with written procedures.

The manufacturer shall maintain records of at least the following elements in relation to the manufacturing process:

(1) equipment cleaning and use;

(2) origins of raw materials, active substance starting materials and active substance intermediates;

(3) controls in relation to raw materials, active substance starting materials and active substance intermediates;

(4) use of raw materials, active substance starting materials and active substance intermediates;

(5) labelling of the active substances and of the packaging materials;

(6) master production instructions;

(7) batch production and control;

(8) laboratory controls.