EUROPEAN
COMMISSION

Brussels, XXX
[…](2013) XXX draft

COMMISSION DELEGATED REGULATION (EU) No …/..

of XXX

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)

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE DELEGATED ACT

EU pharmaceutical legislation provides for a high level of public health protection through stringent rules guaranteeing the quality, safety and efficacy of the medicines circulating in the EU market. In particular, Directive 2011/62/EU[1], amending Directive 2001/83/EC[2] on the Community code relating to medicinal products for human use, introduces new provisions on the manufacturing of active substances, the active ingredients of medicines. These provisions aim to ensure that only active substances that are safe and of high quality are used in the manufacturing of medicines in the Union.

As of 2 January 2013, the manufacturing of active substances is subject to good manufacturing practice for active substances regardless of whether those active substances are manufactured in the Union or imported.

With regard to the importation of active substances manufactured in third countries, active substances imported into the Union have to be manufactured in accordance with standards of good manufacturing practice for active substance at least equivalent to those of the Union. As of 2 July 2013, this has to be certified by the competent authority of the third country through a written confirmation accompanying the imported active substance[3], unless the third country has been listed as having a regulatory framework for active substances equivalent to that of the EU.[4]

In addition, manufacturers of medicinal products are now obliged to use only active substances manufactured in accordance with principles and guidelines of good manufacturing practice for active substances.

In this context, it is necessary to set EU-wide standards with regards to the manufacturing of active substances and harmonise their implementation and enforcement throughout the EU. To this end, the Commission is mandated[5] to adopt, by means of delegated acts, measures supplementing the provisions of Directive 2001/83/EC with regards to good manufacturing practice for active substances.

The principles of good manufacturing practice for active substances included in this Delegated Regulation are largely based on the existing technical guidelines on the manufacturing of active substances published by the Commission in *EudraLex – the rules governing medicinal products in the European Union, volume 4*.[6] In practice, this Delegated Regulation will not modify the current EU standards of good manufacturing practice for active substances but structure them into a legal framework to facilitate their enforcement. This is important in the context of the recent rules on active substance importation[7]. The alignment between the content of this delegated act and the existing guidelines implies that written confirmations that have been issued prior to this Regulation will still be acceptable once this Regulation enters into force. The same applies to third countries having been

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1 Directive 2011/62/EU of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p.74.

2 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, p. 67.

3 Article 46b(2)(b) of Directive 2001/83/EC.

4 Article 111b of Directive 2001/83/EC.

5 Article 47, third paragraph, of Directive 2001/83/EC.

6 http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

7 Articles 46b and 111b of Directive 2001/83/EC.

assessed as having manufacturing standards equivalent to those in the EU according to article 111b of Directive 2001/83/EC: these countries will still be considered as “equivalent” after the entry into force of this Regulation.

2. CONSULTATIONS PRIOR TO THE ADOPTION OF THE ACT

With a view to preparing this Delegated Regulation, the Commission conducted a public consultation on a concept paper[8] for a "delegated act on the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use". The consultation took place between January and April 2012. In addition, an Expert Group "on the preparation of delegated acts relating to manufacturing, import and introduction of medicinal products for human use and their active substances"[9] was set up and met on 21 September 2012 to discuss the concept paper and the results of the public consultation. The Expert Group was consulted a second time in writing in September 2013. Comments stemming from both rounds of consultations were taken into account when preparing this Delegated Regulation.

3. LEGAL ELEMENTS OF THE DELEGATED ACT

The legal basis for this Delegated Regulation is Article 47, third paragraph, of Directive 2001/83/EC on the Community code relating to medicinal products for human use.

This Delegated Regulation supplements Directive 2001/83/EC by establishing and detailing principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.

8 http://ec.europa.eu/health/files/gmp/2012_01_20_gmp_cp_en.pdf

9 http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=2752

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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[10], 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 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.

[10] OJ L 311, 28.11.2001, p. 67.

(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 sensitizing 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:

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.

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 sensitizing 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.

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, sanitization.

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.

The issuance, revision, replacement and withdrawal of documents related to the manufacturing process shall be controlled, and records of their revision, replacement and withdrawal shall be kept.

2. All quality related activities carried out during the manufacturing process shall be recorded at the time they are performed. Any deviation from the written procedures referred to in Article 7(1) shall be documented and explained. Deviations affecting the quality of the active substance or preventing the active substance from meeting the specifications referred to in Article 12(1) shall be investigated, and the investigation and its conclusions shall be documented.

3. After carrying out production and control operations, the manufacturer shall retain all production and control records for at least one year after the expiry date of the batch. For an active substance with retest dates, the manufacturer shall retain records for at least three years after the complete batch has been placed on the market.

Article 8
Material management

1. The manufacturer shall have written procedures in place for ensuring the quality of incoming material covering the following elements:

(1) receipt;

(2) identification;

(3) quarantine;

(4) storage;

(5) handling;

(6) sampling;

(7) testing;

(8) approving;

(9) rejection.

2. The manufacturer shall have a system in place for evaluating suppliers of critical materials.

Article 9
Production and in-process control

1. Production operations shall be subject to controls in order to monitor and adjust the production process or verify that the active substance conforms to the specifications of quality and purity pursuant to Article 12(1). Production operations which are critical to ensure that the active substance meets the quality specifications referred to in Article 12(1) shall be carried out under the visual supervision of qualified personnel or subjected to an equivalent control.

2. Weighing and measuring of raw materials and active substance starting materials shall be accurate and shall be conducted in a manner which does not affect their suitability for use.

3. Production operations, including any operation after purification of the active substance intermediates or the active substance, shall be conducted in a manner that prevents raw materials, active substance starting materials, active substance intermediates and active substances from being contaminated by other materials.

Article 10
Packaging and labelling

1. Containers shall provide adequate protection against deterioration or contamination of the active substance from the moment the active substance is packaged to the moment it is used in the manufacturing of medicinal products.

2. Storage, print and use of labels on the packaging of active substances shall be controlled. Labels shall contain the information necessary to assure the quality of the active substance.

Article 11
Placing on the market

An active substance shall only be placed on the market after it has been released for sale by the quality unit.

Article 12
Laboratory controls

1. The manufacturer shall establish specifications for the quality and purity of the active substances he manufactures and for the raw materials, active substance starting materials and active substance intermediates used in that process.

2. Laboratory tests shall be conducted to verify compliance with the specifications referred to in the first paragraph.

The manufacturer shall issue certificates of analysis for each batch of active substance upon the request of:

(a) the competent authorities of a Member State;

(b) manufacturers of active substances supplied directly or indirectly with the active substance for the purpose of further processing, packing, repacking, labelling or relabelling the active substance;

(c) distributors and brokers of active substances;

(d) manufacturers of medicinal products supplied directly or indirectly with the active substance.

3. The manufacturer shall monitor the stability of the active substance through stability studies. Dates for the expiry or retest of active substances shall be set on the basis of an evaluation of data derived from the stability studies. Appropriately identified samples of the active substance shall be retained in accordance with a sampling plan established on the basis of the shelf-life of the active substance.

Article 13
Validation

The manufacturer shall set up and implement a validation policy for those processes and procedures that are critical to ensure that the active substance meets the quality and purity specifications established in accordance with Article 12(1).

Article 14
Change control

1. The manufacturer shall evaluate the potential impact on the quality of the active substance of any changes to the manufacturing process that may affect the production and control of the active substance before implementing those changes.

2. Changes to the manufacturing process that negatively affect the quality of the active substance shall be not be implemented.

3. The manufacturer of an active substance shall notify without delay the manufacturers of medicinal products which he supplies with the active substance of any changes to the manufacturing process that may impact the quality of the active substance.

Article 15
Rejection and returns

1. Batches of active substances and active substance intermediates failing to conform to the specifications established in accordance with Article 12(1) shall be rejected, labelled as such and quarantined.

2. The manufacturer who reprocesses or reworks rejected batches of an active substance that do not conform to specifications, or recovers raw materials and solvents for re-use in the manufacturing process, shall follow the procedures established in accordance with Article 7(1) and shall perform appropriate controls to ensure that:

(a) the reprocessed or reworked active substance meets the quality specifications established in accordance with Article 12(1);

(b) the recovered raw materials and solvents are suitable for their intended use in the manufacturing process.

3. Returned active substances shall be identified as such and quarantined.

Article 16
Complaints and recalls

1. The manufacturer shall record and investigate all quality related complaints.

2. The manufacturer shall establish procedures for the recall of active substances from the market.

3. In the event of the recalled active substance posing a serious threat to public health, the manufacturer shall inform the competent authorities without delay.

Article 17
Contract manufacturing

1. A manufacturing operation or an operation linked thereto which is to be carried out on behalf of the manufacturer of the active substance by another party ('the contract manufacturer') shall be the subject of a written contract.

The contract shall clearly define the responsibilities of the contract manufacturer with regards to good manufacturing practice.

2. The manufacturer of the active substance shall control that operations carried out by a contract manufacturer comply with good manufacturing practice.

3. A manufacturing operation or an operation linked thereto which has been entrusted to a contract manufacturer shall not be subcontracted to a third party without the written consent of the manufacturer of the active substance.

Article 18
Repackaging

Where the active substance is repackaged by a manufacturer in a container which differs from the original container with regard to its volume, or the material it is made of, or its opaqueness to light, he shall conduct stability studies on the active substance and assign an expiration or retest date for it on the basis of those studies.

Article 19
Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from [6 months after publication].

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

For the Commission
The President