

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

TITLE IV

**MANUFACTURE AND IMPORTATION**

*Article 40*

1 Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

2 The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3 Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Title and Article 118 shall have corresponding application to such imports as they have to manufacture.

[<sup>F14</sup> Member States shall enter the information relating to the authorisation referred to in paragraph 1 of this Article in the Union database referred to in Article 111(6).]

**Textual Amendments**

- F1** Substituted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).

*Article 41*

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

- (a) specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;
- (b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 20;
- (c) have at his disposal the services of at least one qualified person within the meaning of Article 48.

The applicant shall provide particulars in support of the above in his application.

*Article 42*

1 The competent authority of the Member State shall issue the manufacturing authorization only after having made sure of the accuracy of the particulars supplied pursuant to Article 41, by means of an inquiry carried out by its agents.

2 In order to ensure that the requirements referred to in Article 41 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.

3 The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.

*Article 43*

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.

*Article 44*

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in points (a) and (b) of the first paragraph of Article 41, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

*Article 45*

The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 41 and concerning the qualified person referred to in Article 48; where the competent authority concerned exercises this right, application of the time-limits referred to in Article 43 and 44 shall be suspended until the additional data required have been supplied.

*Article 46*

The holder of a manufacturing authorization shall at least be obliged:

- (a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;
- (b) to dispose of the authorized medicinal products only in accordance with the legislation of the Member States concerned;
- (c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 is replaced unexpectedly;
- (d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;
- (e) to enable the qualified person referred to in Article 48 to carry out his duties, for example by placing at his disposal all the necessary facilities;
- (f) <sup>F1</sup>to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use only active substances, which have been manufactured

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in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances. To this end, the holder of the manufacturing authorisation shall verify compliance by the manufacturer and distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. The holder of the manufacturing authorisation shall verify such compliance either by himself or, without prejudice to his responsibility as provided for in this Directive, through an entity acting on his behalf under a contract.

The holder of the manufacturing authorisation shall ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is. This shall be ascertained on the basis of a formalised risk assessment in accordance with the applicable guidelines referred to in the fifth paragraph of Article 47. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The holder of the manufacturing authorisation shall ensure that the appropriate good manufacturing practice so ascertained, is applied. The holder of the manufacturing authorisation shall document the measures taken under this paragraph;

- (g) to inform the competent authority and the marketing authorisation holder immediately if he obtains information that medicinal products which come under the scope of his manufacturing authorisation are, or are suspected of being, falsified irrespective of whether those medicinal products were distributed within the legal supply chain or by illegal means, including illegal sale by means of information society services;
- (h) to verify that the manufacturers, importers or distributors from whom he obtains active substances are registered with the competent authority of the Member State in which they are established;
- (i) to verify the authenticity and quality of the active substances and the excipients.]

#### Textual Amendments

- F1** Substituted by Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products (Text with EEA relevance).

#### *[<sup>F2</sup>Article 46a*

1 For the purposes of this Directive, manufacture of active substances used as starting materials shall include both total and partial manufacture or import of an active substance used as a starting material as defined in Part I, point 3.2.1.1 (b) Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of starting materials.

*[<sup>F3</sup>2* The Commission is empowered to adopt delegated acts in accordance with Article 121a to amend paragraph 1 to take account of scientific and technical progress.]]

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#### Textual Amendments

- F2** Inserted by [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.](#)
- F3** Substituted by [Regulation \(EU\) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union \(Text with EEA relevance\).](#)

#### *F<sup>4</sup> Article 46b*

1 Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with good manufacturing practice and good distribution practices for active substances.

- 2 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 Union pursuant to the third paragraph of Article 47; and
  - 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 Union pursuant to the third paragraph of Article 47;
    - (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 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 Union without any delay.

This written confirmation shall be without prejudice to the obligations set out in Article 8 and in point (f) of Article 46.

3 The requirement set out in point (b) of paragraph 2 of this Article shall not apply if the exporting country is included in the list referred to in Article 111b.

4 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 Member State and was found to comply with the principles and guidelines of good manufacturing practice laid down pursuant to the third paragraph of Article 47, the requirement set out in point (b) of paragraph 2 of this Article may be waived by any Member State for a period not exceeding the validity of the certificate of Good Manufacturing Practice. Member States that make use of the possibility of such waiver, shall communicate this to the Commission.]

#### Textual Amendments

- F4** Inserted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,](#)

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as regards the prevention of the entry into the legal supply chain of falsified medicinal products (Text with EEA relevance).

#### Article 47

[<sup>F3</sup>The Commission is empowered to adopt delegated acts in accordance with Article 121a in order to supplement this Directive by specifying the principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f).]

Detailed guidelines in line with those principles will be published by the Commission and revised necessary to take account of technical and scientific progress.

[<sup>F1</sup>The Commission shall adopt, by means of delegated acts in accordance with Article 121a and subject to the conditions laid down in Articles 121b and 121c, the principles and guidelines of good manufacturing practice for active substances referred to in the first paragraph of point (f) of Article 46 and in Article 46b.

The principles of good distribution practices for active substances referred to in the first paragraph of point (f) of Article 46 shall be adopted by the Commission in the form of guidelines.

The Commission shall adopt guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in the second paragraph of point (f) of Article 46.]

#### Textual Amendments

- F1** Substituted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).
- F3** Substituted by [Regulation \(EU\) 2019/1243 of the European Parliament and of the Council of 20 June 2019 adapting a number of legal acts providing for the use of the regulatory procedure with scrutiny to Articles 290 and 291 of the Treaty on the Functioning of the European Union \(Text with EEA relevance\)](#).

#### [<sup>F4</sup>Article 47a

1 The safety features referred to in point (o) of Article 54 shall not be removed or covered, either fully or partially, unless the following conditions are fulfilled:

- a the manufacturing authorisation holder verifies, prior to partly or fully removing or covering those safety features, that the medicinal product concerned is authentic and that it has not been tampered with;
- b the manufacturing authorisation holder complies with point (o) of Article 54 by replacing those safety features with safety features which are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product. Such replacement shall be conducted without opening the immediate packaging as defined in point 23 of Article 1.

Safety features shall be considered equivalent if they:

- (i) comply with the requirements set out in the delegated acts adopted pursuant to Article 54a(2); and

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- (ii) are equally effective in enabling the verification of authenticity and identification of medicinal products and in providing evidence of tampering with medicinal products;
  - c the replacement of the safety features is conducted in accordance with applicable good manufacturing practice for medicinal products; and
  - d the replacement of the safety features is subject to supervision by the competent authority.
- 2 Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1 of this Article, shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC.]

#### Textual Amendments

- F4** Inserted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).

#### Article 48

1 Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

2 If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

#### Article 49

1 Member States shall ensure that the qualified person referred to in Article 48 fulfils the [<sup>F5</sup>minimum] conditions of qualification set out in paragraphs 2 and 3.

2 A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

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The course shall include theoretical and practical study bearing upon at least the following basic subjects:

- [<sup>F6</sup>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).

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.

3 The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

#### Textual Amendments

- F5** Deleted by 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.
- F6** Substituted by 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.

#### Article 50

1 A person engaging in the activities of the person referred to in Article 48 from the time of the application of Directive 75/319/EEC, in a Member State without complying with the provisions of Article 49 shall be eligible to continue to engage in those activities [<sup>F6</sup>within the Community].

2 The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognized as equivalent by the Member State concerned — in a scientific discipline allowing him to engage in the activities of the person referred to in Article 48 in accordance with the laws of that State may — if he began his course prior to 21 May 1975 — be considered as qualified to carry out in that State the duties

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of the person referred to in Article 48 provided that he has previously engaged in the following activities for at least two years before 21 May 1985 following notification of this directive in one or more undertakings authorized to manufacture: production supervision and/or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 48 to ensure the quality of the medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph before 21 May 1965, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.

#### Textual Amendments

- F6** Substituted by [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.](#)

#### Article 51

1 Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:

- a in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;
- [<sup>F6</sup>b in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production 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.]

[<sup>F4</sup>The qualified person referred to in Article 48 shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features referred to in point (o) of Article 54 have been affixed on the packaging.]

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2 In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3 In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal

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of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

#### Textual Amendments

- F4** Inserted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).
- F6** Substituted by [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](#).

#### Article 52

Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

#### *<sup>F4</sup>Article 52a*

1 Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.

2 The registration form shall include, at least, the following information:

- (i) name or corporate name and permanent address;
- (ii) the active substances which are to be imported, manufactured or distributed;
- (iii) particulars regarding the premises and the technical equipment for their activity.

3 The persons referred to in paragraph 1 shall submit the registration form to the competent authority at least 60 days prior to the intended commencement of their activity.

4 The competent authority may, based on a risk assessment, decide to carry out an inspection. If the competent authority notifies the applicant within 60 days of the receipt of the registration form that an inspection will be carried out, the activity shall not begin before the competent authority has notified the applicant that he may commence the activity. If within 60 days of the receipt of the registration form the competent authority has not notified the applicant that an inspection will be carried out, the applicant may commence the activity.

5 The persons referred to in paragraph 1 shall communicate annually to the competent authority an inventory of the changes which have taken place as regards the information provided in the registration form. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.

6 Persons referred to in paragraph 1 who had commenced their activity before 2 January 2013 shall submit the registration form to the competent authority by 2 March 2013.

7 Member States shall enter the information provided in accordance with paragraph 2 of this Article in the Union database referred to in Article 111(6).

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8 This Article shall be without prejudice to Article 111.

**Textual Amendments**

- F4** Inserted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).

*Article 52b*

1 Notwithstanding Article 2(1), and without prejudice to Title VII, Member States shall take the necessary measures in order to prevent medicinal products that are introduced into the Union, but are not intended to be placed on the market of the Union, from entering into circulation if there are sufficient grounds to suspect that those products are falsified.

2 In order to establish what the necessary measures referred to in paragraph 1 of this Article are, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions laid down in Articles 121b and 121c, measures supplementing paragraph 1 of this Article as regards the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced into the Union but not intended to be placed on the market.]

**Textual Amendments**

- F4** Inserted by [Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products \(Text with EEA relevance\)](#).

*Article 53*

The provisions of this Title shall also apply to homeopathic medicinal products.