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 XI

SUPERVISION AND SANCTIONS

Article 111

[[F1]1 The competent authority of the Member State concerned shall, in cooperation with the Agency, ensure that the legal requirements governing medicinal products are complied with, by means of inspections, if necessary unannounced, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples. This cooperation shall consist in sharing information with the Agency on both inspections that are planned and that have been conducted. Member States and the Agency shall cooperate in the coordination of inspections in third countries. The inspections shall include but not be limited to the ones mentioned in paragraphs 1a to 1f.

1a Manufacturers, located in the Union or in third countries, and wholesale distributors of medicinal products shall be subject to repeated inspections.

1b The competent authority of the Member State concerned shall have a system of supervision including by inspections at an appropriate frequency based on risk, at the premises of the manufacturers, importers, or distributors of active substances, located on its territory, and effective follow-up thereof.

Whenever it considers that there are grounds for suspecting non-compliance with the legal requirements laid down in this Directive, including the principles and guidelines of good manufacturing practice and good distribution practices referred to in point (f) of Article 46 and in Article 47, the competent authority may carry out inspections at the premises of:

a manufacturers or distributors of active substances located in third countries;

b manufacturers or importers of excipients.

1c Inspections referred to in paragraphs 1a and 1b may also be carried out in the Union and in third countries at the request of a Member State, the Commission or the Agency.

1d Inspections may also take place at the premises of marketing authorisation holders and of brokers of medicinal products.

1e In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia (the European Directorate for the Quality of Medicines and Healthcare) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.

1f The competent authority of the Member State concerned may carry out inspections of starting material manufacturers at the specific request of the manufacturer.

1g Inspections shall be carried out by officials representing the competent authority who shall be empowered to:

a inspect the manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;

b take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;

c examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;

d inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.

1h Inspections shall be carried out in accordance with the guidelines referred to in Article 111a.**]**

2 Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch-to-batch consistency.

[F1 3 After every inspection as referred to in paragraph 1, the competent authority shall report on whether the inspected entity complies with the principles and guidelines of good manufacturing practice and good distribution practices referred to in Articles 47 and 84, as applicable, or on whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those reports to the inspected entity.

Before adopting the report, the competent authority shall give the inspected entity concerned the opportunity to submit comments.

4 Without prejudice to any arrangements which may have been concluded between the Union and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in this Article.

5 Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice or good distribution practices shall, when applicable, be issued to the inspected entity if the outcome of the inspection shows that it complies with the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Union legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6 Member States shall enter the certificates of good manufacturing practice and good distribution practices which they issue in a Union database managed by the Agency on behalf of the Union. Pursuant to Article 52a(7), Member States shall also enter information in that database regarding the registration of importers, manufacturers and distributors of active substances. The database shall be publicly accessible.**]**

[F2 7 If the outcome of the inspection as referred to in points (a), (b) and (c) of **[**F1 paragraph 1g**]** or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients**[**F3 used as starting materials**]** is that the inspected entity does not comply with the legal requirements and/or the principles and guidelines of good manufacturing

practice or good distribution practices as provided for by Union law, the information shall be entered in the Union database as provided for in paragraph 6.**]**

[[F4]8 If the outcome of the inspection referred to in **[**[F1]point (d) of paragraph 1g**]** is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Title IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give him the opportunity to submit comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties.**]**

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).

F2 Substituted by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance).

F3 Deleted 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).

F4 Inserted by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance).

I[F5]*Article 111a*

The Commission shall adopt detailed guidelines laying down the principles applicable to inspections referred to in Article 111.

Member States shall, in cooperation with the Agency, establish the form and content of the authorisation referred to in Articles 40(1) and 77(1), of the reports referred to in Article 111(3), of the certificates of good manufacturing practice and of the certificates of good distribution practices referred to in Article 111(5).

Textual Amendments

F5 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 111b

1 At the request of a third country, the Commission shall assess whether that country's regulatory framework applicable to active substances exported to the Union and the respective

control and enforcement activities ensure a level of protection of public health equivalent to that of the Union. If the assessment confirms such equivalence, the Commission shall adopt a decision to include the third country in a list. The assessment shall take the form of a review of relevant documentation and, unless arrangements as referred to in Article 51(2) of this Directive are in place that cover this area of activity, that assessment shall include an on-site review of the third country's regulatory system and, if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances. In the assessment particular account shall be taken of:

a the country's rules for good manufacturing practice;

b the regularity of inspections to verify compliance with good manufacturing practice;

c the effectiveness of enforcement of good manufacturing practice;

d the regularity and rapidity of information provided by the third country relating to non-compliant producers of active substances.

2 The Commission shall adopt the necessary implementing acts to apply the requirements set out in points (a) to (d) of paragraph 1 of this Article. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 121(2).

3 The Commission shall verify regularly whether the conditions laid down in paragraph 1 are fulfilled. The first verification shall take place no later than 3 years after the country has been included in the list referred to in paragraph 1.

4 The Commission shall perform the assessment and verification referred to in paragraphs 1 and 3 in cooperation with the Agency and the competent authorities of the Member States.**]**

Textual Amendments

F5 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 112

Member States shall take all appropriate measures to ensure that the holder of the marketing authorization for a medicinal product and, where appropriate, the holder of the manufacturing authorization, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Article 113

For the purpose of implementing Article 112, Member States may require manufacturers of immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 51.

Article 114

1 Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:

— live vaccines,

— immunological medicinal products used in the primary immunization of infants or of other groups at risk,
— immunological medicinal products used in public health immunization programmes,
— new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,

to submit samples from each batch of the bulk and/or the medicinal product for examination **[**F6by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose**]** before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority of that Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

2 Where, in the interests of public health, the laws of a Member State so provide, the competent authorities may require the marketing authorization holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk and/or the medicinal product for testing **[**F6by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose**]** before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

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 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

[*F2Article 116*

The competent authorities shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

[X1A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 8, 10, 10a, 10b, 10c or 11] are incorrect or have not been amended in accordance with Article 23, or where any conditions referred to in Articles 21a, 22 or 22a have not been fulfilled or where the controls referred to in Article 112 have not been carried out.

[F5The second paragraph of this Article also applies in cases where the manufacture of the medicinal product is not carried out in compliance with the particulars provided pursuant to point (d) of Article 8(3), or where controls are not carried out in compliance with the control methods described pursuant to point (h) of Article 8(3).]]

Editorial Information

X1 Substituted by Corrigendum to Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal of the European Union L 348 of 31 December 2010).

Textual Amendments

F2 Substituted by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance).

F5 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 117

[F61 Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

[F2a the medicinal product is harmful; or]

b it lacks therapeutic efficacy; or

[F2c the risk-benefit balance is not favourable; or]

d its qualitative and quantitative composition is not as declared; or

e the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.]

2 The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

[F43 The competent authority may, for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.]

Textual Amendments

F2 Substituted by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance).

F4 Inserted by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (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.

[F5 Article 117a

1 Member States shall have a system in place which aims at preventing medicinal products that are suspected to present a danger to health from reaching the patient.

2 The system referred to in paragraph 1 shall cover the receipt and handling of notifications of suspected falsified medicinal products as well as of suspected quality defects of medicinal products. The system shall also cover recalls of medicinal products by marketing authorisation holders or withdrawals of medicinal products from the market ordered by national competent authorities from all relevant actors in the supply chain both during and outside normal working hours. The system shall also make it possible to recall, where necessary with the assistance of health professionals, medicinal products from patients who received such products.

3 If the medicinal product in question is suspected of presenting a serious risk to public health, the competent authority of the Member State in which that product was first identified shall, without any delay, transmit a rapid alert notification to all Member States and all actors in the supply chain in that Member State. In the event of such medicinal products being deemed to have reached patients, urgent public announcements shall be issued within 24 hours in order to recall those medicinal products from the patients. Those announcements shall contain sufficient information on the suspected quality defect or falsification and the risks involved.

4 Member States shall by 22 July 2013 notify the Commission of the details of their respective national systems referred to in this Article.**]**

Textual Amendments

F5 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 118

1 The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2 In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

[F5 Article 118a

1 The Member States shall lay down the rules on penalties applicable to infringements of the national provisions adopted pursuant to this Directive and shall take all necessary measures to ensure that those penalties are implemented. The penalties must be effective, proportionate and dissuasive.

Those penalties shall not be inferior to those applicable to infringements of national law of similar nature and importance.

2 The rules referred to in paragraph 1 shall address, inter alia, the following:

a the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as the sale of falsified medicinal products at a distance to the public by means of information society services;

b non-compliance with the provisions laid down in this Directive on manufacturing, distribution, import and export of active substances;

c non-compliance with the provisions laid down in this Directive on the use of excipients.

Where relevant, the penalties shall take into account the risk to public health presented by the falsification of medicinal products.

3 The Member States shall notify the national provisions adopted pursuant to this Article to the Commission by 2 January 2013 and shall notify any subsequent amendment of those provisions without delay.

By 2 January 2018, the Commission shall submit a report to the European Parliament and to the Council giving an overview of the transposition measures of Member States as regards this Article, together with an evaluation of the effectiveness of those measures.

Textual Amendments

F5 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 118b

Member States shall organise meetings involving patients 'and consumers' organisations and, as necessary, Member States' enforcement officers, in order to communicate public information about the actions undertaken in the area of prevention and enforcement to combat the falsification of medicinal products.

Textual Amendments

F5 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 118c

Member States, in applying this Directive, shall take the necessary measures to ensure cooperation between competent authorities for medicinal products and customs authorities.**]**

Textual Amendments

F5 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*Article 119*

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

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.