Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance)

TITLE II

AUTHORISATION AND SUPERVISION OF MEDICINAL PRODUCTS FOR HUMAN USE

[F1Chapter 3

Pharmacovigilance

Article 21

1 The obligations of marketing authorisation holders laid down in Article 104 of Directive 2001/83/EC shall apply to marketing authorisation holders for medicinal products for human use authorised in accordance with this Regulation.

Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 2 July 2012 shall, by way of derogation from Article 104(3)(c) of Directive 2001/83/EC not be required to operate a risk management system for each medicinal product.

2 The Agency may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in point (c) of Article 104(3) of Directive 2001/83/EC, if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the Agency shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

The imposition of such obligations shall be duly justified, notified in writing, and shall include the timeframe for submission of the detailed description of the risk-management system.

3 The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

4 On the basis of the written observations submitted by the marketing authorisation holder, and of the opinion of the Agency, the Commission shall withdraw or confirm the obligation. Where the Commission confirms the obligation, the marketing authorisation shall be varied accordingly, to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in point (ca) of Article 9(4).

Article 22

The obligations of marketing authorisation holders laid down in Article 106a(1) of Directive 2001/83/EC, and the obligations of the Member States, the Agency and the Commission laid down in paragraphs 2, 3 and 4 of that Article shall apply to the safety

announcements referred to in point (e) of Article 57(1) of this Regulation concerning medicinal products for human use authorised in accordance with this Regulation.

[F2 Article 23

1 The Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring.

That list shall include the names and active substances of:

a medicinal products authorised in the Union that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the Union;

b any biological medicinal product not covered by point (a) that was authorised after 1 January 2011;

c medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in point (cb) of Article 9(4), point (a) of the first subparagraph of Article 10a(1) or Article 14(7) or (8);

d medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (b) and (c) of the first paragraph of Article 21a, Article 22, or point (a) of the first subparagraph of Article 22a(1) thereof.

1a At the request of the Commission, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to this Regulation, subject to the conditions referred to in points (c), (ca) or (cc) of Article 9(4), point (b) of the first subparagraph of Article 10a(1) or Article 21(2), may also be included in the list referred to in paragraph 1 of this Article.

At the request of a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in points (a), (d), (e) or (f) of the first paragraph of Article 21a, point (b) of the first subparagraph of Article 22a(1) or Article 104a(2) thereof, may also be included in the list referred to in paragraph 1 of this Article.

2 The list referred to in paragraph 1 shall include an electronic link to the product information and to the summary of the risk management plan.

3 In the cases referred to in points (a) and (b) of paragraph 1 of this Article, the Agency shall remove a medicinal product from the list five years after the Union reference date referred to in Article 107c(5) of Directive 2001/83/EC.

In the cases referred to in points (c) and (d) of paragraph 1 and in paragraph 1a of this Article, the Agency shall remove a medicinal product from the list once the conditions have been fulfilled.**]**

[F2 4 For medicinal products included in the list referred to in paragraph 1, the summary of product characteristics and the package leaflet shall include the statement ‘This medicinal product is subject to additional monitoring’. That statement shall be preceded by a black symbol which shall be selected by the Commission by 2 July 2013, following a recommendation of the Pharmacovigilance Risk Assessment Committee, and shall be followed by an appropriate standardised explanatory sentence.**]**

[F2 4a By 5 June 2018, the Commission shall present to the European Parliament and the Council a report on the use of the list referred to in paragraph 1 based on the experience and data provided by the Member States and the Agency.

The Commission shall, if appropriate, on the basis of that report, and after consultation with the Member States and other appropriate stakeholders, present a proposal in order to adjust the provisions relating to the list referred to in paragraph 1.**]**

Textual Amendments

F2 Substituted by Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance (Text with EEA relevance).

Article 24

1 The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing network (hereinafter the 'Eudravigilance database') to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.

The Eudravigilance database shall contain information on suspected adverse reactions in human beings arising from use of the medicinal product within the terms of the marketing authorisation as well as from uses outside the terms of the marketing authorisation, and on those occurring in the course of post-authorisation studies with the medicinal product or associated with occupational exposure.

2 The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the Eudravigilance database, together with a timeframe for their implementation.

The Agency shall prepare an annual report on the Eudravigilance database and send it to the European Parliament, the Council and the Commission. The first annual report shall be prepared by 2 January 2013.

The Management Board of the Agency shall on the basis of an independent audit report that takes into account the recommendation of the Pharmacovigilance Risk Assessment Committee confirm and announce when the Eudravigilance database has achieved full functionality and the system meets the functional specifications drawn up pursuant to the first subparagraph.

Any substantial change to the Eudravigilance database and the functional specifications shall take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations.

The Agency shall ensure that healthcare professionals and the public have appropriate levels of access to the Eudravigilance database, while guaranteeing personal data protection. The Agency shall work together with all stakeholders, including research institutions, healthcare professionals, and patient and consumer organisations, in order to define the 'appropriate level of access' for healthcare professionals and the public to the Eudravigilance database.

The data held on the Eudravigilance database shall be made publicly accessible in an aggregated format together with an explanation of how to interpret the data.

3 The Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the Eudravigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the Eudravigilance database.

4 Individual suspected adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically upon receipt to the competent authority of the Member State where the reaction occurred.

Article 25

The Agency shall, in collaboration with the Member States, develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 107a of Directive 2001/83/EC.

Article 25a

The Agency shall, in collaboration with the national competent authorities and the Commission, set up and maintain a repository for periodic safety update reports (hereinafter the 'repository') and the corresponding assessment reports so that they are fully and permanently accessible to the Commission, the national competent authorities, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter the 'coordination group').

The Agency shall, in collaboration with the national competent authorities and the Commission, and after consultation with the Pharmacovigilance Risk Assessment Committee, draw up the functional specifications for the repository.

The Management Board of the Agency shall, on the basis of an independent audit report that takes into account the recommendations of the Pharmacovigilance Risk Assessment Committee, confirm and announce when the repository has achieved full functionality and meets the functional specifications drawn up pursuant to the second paragraph.

Any substantial change to the repository and the functional specifications shall always take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

Article 26

1 The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the Union. By means of that portal, the Agency shall make public at least the following:

a the names of members of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the members of the coordination group, together with their professional qualifications and with the declarations referred to in Article 63(2) of this Regulation;

b agendas and minutes from each meeting of the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and of the coordination group as regards pharmacovigilance activities;

c a summary of the risk management plans for medicinal products authorised in accordance with this Regulation;

d the list of medicinal products referred to in Article 23 of this Regulation;

e a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union;

f information about how to report to national competent authorities suspected adverse reactions to medicinal products and the standard structured forms referred to in Article 25 for their web-based reporting by patients and healthcare professionals, including links to national websites;

g Union reference dates and frequency of submission of periodic safety update reports established in accordance with Article 107c of Directive 2001/83/EC;

h protocols and public abstracts of results of the post-authorisation safety studies referred to in Articles 107n and 107p of Directive 2001/83/EC;

i the initiation of the procedure provided for in Articles 107i to 107k of Directive 2001/83/EC, the active substances or medicinal products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;

j conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and by the coordination group, the national competent authorities and the Commission in the framework of the procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 and Chapter 4 of Title IX of Directive 2001/83/EC.

2 Before the launch of this portal, and during subsequent reviews, the Agency shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives.

Article 27

1 The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring.

2 The Agency shall enter into the Eudravigilance database relevant information from the selected medical literature.

3 The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the Eudravigilance database.

Article 28

1 The obligations of marketing authorisation holders and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

2 The obligations of marketing authorisation holders laid down in Article 107b of Directive 2001/83/EC and the procedures under Article 107b and Article 107c of that Directive shall apply to the submission of periodic safety update reports, the establishment of Union reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

The provisions applicable to the submission of periodic safety update reports laid down in the second subparagraph of Article 107c(2) of that Directive shall apply to holders of marketing authorisations which were granted before 2 July 2012 and for which the frequency and dates of submission of the periodic safety update reports are not laid

down as a condition to the marketing authorisation until such time as another frequency or other dates of submission of the reports are laid down in the marketing authorisation or are determined in accordance with Article 107c of that Directive.

3 The assessment of the periodic safety update reports shall be conducted by a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal products concerned.

The rapporteur shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the members of the Pharmacovigilance Risk Assessment Committee. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the marketing authorisation holder and the members of the Pharmacovigilance Risk Assessment Committee may submit comments to the Agency and to the rapporteur.

Following the receipt of the comments referred to in the third subparagraph, the rapporteur shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a, and forward both to the marketing authorisation holder.

4 In the case of an assessment report that recommends any action concerning the marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

Where the opinion states that regulatory action concerning the marketing authorisation is necessary, the Commission shall adopt a decision to vary, suspend or revoke the marketing authorisation. Article 10 of this Regulation shall apply to the adoption of that decision. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.

5 In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) of Directive 2001/83/EC which includes at least one marketing authorisation granted in accordance with this Regulation, the procedure laid down in Articles 107e and 107g of that Directive shall apply.

6 The final recommendations, opinions and decisions referred to in paragraphs 3 to 5 of this Article shall be made public by means of the European medicines web-portal referred to in Article 26.

Article 28a

1 Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:

a monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8);

b assess updates to the risk management system;

c monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance.

2 The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3 The Agency and national competent authorities and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the risk-benefit balance being detected.

Article 28b

1 For non-interventional post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which fulfil one of the requirements referred to in Articles 10 and 10a of this Regulation, the procedure provided for in paragraphs 3 to 7 of Article 107m, Articles 107n to 107p and Article 107q(1) of Directive 2001/83/EC shall apply.

2 Where, in accordance with the procedure referred to in paragraph 1 of this Article, the Pharmacovigilance Risk Assessment Committee issues recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation, and the Commission shall adopt a decision in accordance with Article 10.

Where the opinion of the Committee on Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee on Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences, together with the recommendation.

Article 28c

1 The Agency shall collaborate with the World Health Organisation in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Union which may have a bearing on public health protection in third countries.

The Agency shall make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organisation.

2 The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall exchange information that they receive on the abuse of medicinal products including information related to illicit drugs.

Article 28d

At the request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 28e

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the Union.

Article 28f

The Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis.

Article 29

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Agency on 2 January 2014 at the latest and subsequently every 3 years thereafter.**]**

Textual Amendments

F1 Substituted by Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (Text with EEA relevance).

Status:
Point in time view as at 31/01/2020.

Changes to legislation:
There are currently no known outstanding effects for the Regulation (EC) No 726/2004 of the European Parliament and of the Council, Chapter 3.