

# DIRECTIVES

## 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)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee <sup>(1)</sup>,

Having regard to the opinion of the Committee of the Regions <sup>(2)</sup>,

Having regard to the opinion of the European Data Protection Supervisor <sup>(3)</sup>,

Acting in accordance with the ordinary legislative procedure <sup>(4)</sup>,

Whereas:

(1) 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 <sup>(5)</sup> lays down harmonised rules for the authorisation, supervision and pharmacovigilance of medicinal products for human use within the Union.

(2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess

adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

(3) In the light of the experience acquired and following an assessment by the Commission of the Union system of pharmacovigilance, it has become clear that it is necessary to take measures in order to improve the operation of Union law on the pharmacovigilance of medicinal products.

(4) While the fundamental objective of the regulation of medicinal products is to safeguard public health, this aim should nevertheless be achieved by means that do not impede the free movement of safe medicinal products within the Union. It has emerged from the assessment of the Union system of pharmacovigilance that divergent actions by Member States in relation to safety issues pertaining to medicinal products are creating obstacles to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Union level should be strengthened and rationalised.

(5) For the sake of clarity, the definition of the term 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting. Therefore, the term 'suspected adverse reaction' should be used when referring to reporting obligations. Without prejudice to the existing Union and national provisions and practices on medical confidentiality, Member States should ensure that reporting and processing of personal data related to suspected adverse reactions, including those associated with medication errors is carried out on a confidential basis. This should not affect Member States' obligations regarding the mutual exchange of

<sup>(1)</sup> OJ C 306, 16.12.2009, p. 28.

<sup>(2)</sup> OJ C 79, 27.3.2010, p. 50.

<sup>(3)</sup> OJ C 229, 23.9.2009, p. 19.

<sup>(4)</sup> Position of the European Parliament of 22 September 2010 [not yet published in the Official Journal] and Council Decision of 29 November 2010.

<sup>(5)</sup> OJ L 311, 28.11.2001, p. 67.

- information on pharmacovigilance issues or their obligation to make available to the public important information on pharmacovigilance concerns. Furthermore, the principle of confidentiality should not affect the obligations of the persons concerned to provide information under criminal law.
- (6) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem. Member States should consider measures to monitor and evaluate the risk of environmental effects of such medicinal products, including those which may have an impact on public health. The Commission should, based, *inter alia*, on data received from the European Medicines Agency, the European Environment Agency and Member States, produce a report on the scale of the problem, along with an assessment on whether amendments to Union legislation on medicinal products or other relevant Union legislation are required.
- (7) The marketing authorisation holder should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products, recorded in a pharmacovigilance system master file which should be permanently available for inspection. The competent authorities should undertake to supervise those pharmacovigilance systems. Applications for marketing authorisations should therefore be accompanied by a brief description of the corresponding pharmacovigilance system, which should include a reference to the location where the pharmacovigilance system master file for the medicinal product concerned is kept and available for inspection by the competent authorities.
- (8) Marketing authorisation holders should plan pharmacovigilance measures for each individual medicinal product in the context of a risk management system. The measures should be proportionate to the identified risks, the potential risks, and the need for additional information on the medicinal product. It should also be ensured that any key measures included in a risk management system are made conditions of the marketing authorisation.
- (9) It is necessary from a public health perspective to complement the data available at the time of authorisation with additional data about the safety and, in certain cases, the efficacy of authorised medicinal products. Competent authorities should therefore be empowered to impose on the marketing authorisation holder the obligation to conduct post-authorisation studies on safety and on efficacy. It should be possible to impose that obligation at the time of the granting of the marketing authorisation or later, and it should be a condition of the marketing authorisation. Such studies may be aimed at collecting data to enable the assessment of the safety or efficacy of medicinal products in everyday medical practice.
- (10) It is essential that a strengthened system of pharmacovigilance not lead to the premature granting of marketing authorisations. However, some medicinal products are authorised subject to additional monitoring. This includes all medicinal products with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance. Competent authorities may also require additional monitoring for specific medicinal products that are subject to the obligation to conduct a post-authorisation safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product. Medicinal products subject to additional monitoring should be identified as such by a black symbol and an appropriate standardised explanatory sentence in the summary of product characteristics and in the package leaflet. A publicly available list of medicinal products subject to additional monitoring should be kept up to date by the European Medicines Agency established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency<sup>(1)</sup> (hereinafter referred to as the 'Agency').
- (11) The Commission should, in collaboration with the Agency and national competent authorities and following consultations with organisations representing patients, consumers, doctors and pharmacists, social health insurers, and other interested parties, present to the European Parliament and the Council an assessment report regarding the readability of the summaries of product characteristics and the package leaflets and their value to the healthcare professionals and the general public. Following an analysis of that data, the Commission should, if appropriate, make proposals to improve the layout and content of the summaries of product characteristics and of the package leaflets to ensure that they represent a valuable source of information for healthcare professionals and the general public respectively.
- (12) Experience has shown that the responsibilities of marketing authorisation holders with regard to pharmacovigilance of authorised medicinal products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is kept up to date. As medicinal products could be used outside the terms of the marketing authorisation, the marketing authorisation holder's responsibilities should include providing all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorisation. It is also appropriate to ensure that all relevant information

<sup>(1)</sup> OJ L 136, 30.4.2004, p. 1.

collected on the safety of the medicinal product is taken into account when the marketing authorisation is being renewed.

- (13) In order to ensure close cooperation between the Member States in the area of pharmacovigilance, the mandate of the coordination group set up by Article 27 of Directive 2001/83/EC should be enlarged to include the examination of questions related to the pharmacovigilance of all medicinal products authorised by the Member States. In order to fulfil its new tasks, the coordination group should be further strengthened through the adoption of clear rules as regards the expertise required, the procedures for reaching agreements or positions, transparency, independence and professional secrecy of its members, and the need for cooperation between Union and national bodies.
- (14) With a view to ensuring the same level of scientific expertise in the area of pharmacovigilance decision-making at both Union and national levels, the coordination group should rely on the recommendations of the Pharmacovigilance Risk Assessment Committee when fulfilling its pharmacovigilance tasks.
- (15) In order to avoid duplication of work, the coordination group should agree on a single position for pharmacovigilance assessments concerning medicinal products authorised in more than one Member State. Agreement within the coordination group should suffice for pharmacovigilance measures to be implemented throughout the Union. Where no agreement is reached within the coordination group, the Commission should be authorised to adopt a decision concerning the necessary regulatory action in respect of the marketing authorisation, addressed to the Member States.
- (16) A single assessment should also be conducted in the case of pharmacovigilance issues which concern medicinal products authorised by the Member States and medicinal products authorised in accordance with Regulation (EC) No 726/2004. In such cases, the Commission should adopt harmonised measures for all medicinal products concerned on the basis of an assessment at Union level.
- (17) Member States should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors, and suspected adverse reactions associated with occupational exposure. Member States should ensure the quality of the pharmacovigilance system through the follow-up of cases of suspected adverse reactions. For those tasks, Member States should establish a permanent pharmacovigilance system, supported by the appropriate expertise, so that the obligations under this Directive can be fully met.
- (18) In order to further increase the coordination of resources between the Member States, Member State should be authorised to delegate certain pharmacovigilance tasks to another Member State.
- (19) In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holders and the Member States should report those reactions only to the Union pharmacovigilance database and data-processing network referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 (the 'Eudravigilance database'). The Eudravigilance database should be equipped to immediately forward reports on suspected adverse reactions received from marketing authorisation holders to the Member States on whose territory the reaction occurred.
- (20) In order to increase the level of transparency of the pharmacovigilance processes, the Member States should create and maintain medicines web-portals. To the same end, the marketing authorisation holders should provide the competent authorities with prior or simultaneous warnings about safety announcements and the competent authorities should also provide each other with advance notice of safety announcements.
- (21) Union rules in relation to pharmacovigilance should continue to rely on the crucial role of healthcare professionals in monitoring the safety of medicinal products, and should take account of the fact that patients are also well placed to report suspected adverse reactions to medicinal products. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make methods for such reporting available to them.
- (22) As a result of the submission of all suspected adverse reaction data directly to the Eudravigilance database, it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product rather than a detailed listing of individual case reports already submitted to the Eudravigilance database.

- (23) Obligations imposed in respect of periodic safety update reports should be proportionate to the risks posed by medicinal products. Periodic safety update reporting should therefore be linked to the risk management system for newly authorised medicinal products and routine reporting should not be required for generic medicinal products, for medicinal products containing an active substance for which well-established medicinal use has been demonstrated, for homeopathic medicinal products or for traditional-use registered herbal medicinal products. However, in the interests of public health, the competent authorities should require periodic safety update reports for such medicinal products when concerns arise relating to pharmacovigilance data or as a result of the lack of available safety data when the use of the active substance concerned is concentrated in medicinal products for which periodic safety update reporting is not routinely required.
- (24) It is necessary to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. A single assessment of periodic safety update reports for medicinal products authorised in more than one Member State should be provided for. Moreover, procedures should be established to set single frequency and submission dates of periodic safety update reports for all medicinal products containing the same active substance or the same combination of active substances.
- (25) Following a single assessment of periodic safety update reports, any resulting measures as regards the maintenance, variation, suspension or revocation of the marketing authorisations concerned should be adopted through a Union procedure leading to a harmonised result.
- (26) The Member States should automatically submit certain safety issues related to medicinal products to the Agency thereby triggering a Union-wide assessment of the issue. Therefore it is appropriate to establish rules for an assessment procedure by the Pharmacovigilance Risk Assessment Committee, and for the subsequent follow-up as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.
- (27) In connection with the clarification and strengthening of the provisions relating to pharmacovigilance activities in Directive 2001/83/EC, it is also appropriate to further clarify the procedures for all Union-wide post-authorisation assessments of safety issues concerning medicinal products. To that end, the number of procedures for Union-wide assessment should be limited to two, one of which allows for a swift assessment and should be applied when urgent action is considered necessary. Regardless of whether the urgent procedure or the normal procedure is applied, and whether the medicinal product was authorised through the centralised or non-centralised procedure, the Pharmacovigilance Risk Assessment Committee should always give its recommendation when the reason for taking action is based on pharmacovigilance data. It is appropriate that the coordination group and the Committee for Medicinal Products for Human Use should rely on this recommendation when performing their assessment of the issue.
- (28) It is necessary to introduce harmonised guiding principles for, and regulatory supervision of, post-authorisation safety studies that are requested by competent authorities and that are non-interventional, that are initiated, managed or financed by the marketing authorisation holder, and that involve the collection of data from patients or healthcare professionals and that therefore fall outside of the scope of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use<sup>(1)</sup>. The supervision of such studies should be the responsibility of the Pharmacovigilance Risk Assessment Committee. Studies requested after the marketing authorisation of a medicinal product by only one competent authority to be conducted in only one Member State should be supervised by the national competent authority of the Member State in which the study is to be conducted. Provision should also be made for the subsequent follow-up, if appropriate, as regards the marketing authorisations concerned with a view to the adoption of harmonised measures across the Union.
- (29) In order to enforce the provisions relating to pharmacovigilance, the Member States should ensure that effective, proportionate and dissuasive penalties are applied to marketing authorisation holders for non-compliance with pharmacovigilance obligations. If the conditions included in the marketing authorisation are not fulfilled within the given deadline, the national competent authorities should have the power to review the marketing authorisation.

<sup>(1)</sup> OJ L 121, 1.5.2001, p. 34.

- (30) In order to protect public health, the pharmacovigilance activities of national competent authorities should be adequately funded. It should be ensured that adequate funding is possible for pharmacovigilance activities by empowering the national competent authorities to charge fees to marketing authorisation holders. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.
- (31) It should be possible for Member States to allow the relevant actors, under certain conditions, to deviate from certain provisions of Directive 2001/83/EC related to the requirements for labelling and packaging in order to address severe availability problems related to the potential lack of authorised medicinal products or of medicinal products placed on the market or shortages thereof.
- (32) Since the objective of this Directive, namely to improve the safety of medicinal products placed on the market in the Union in a harmonised way across the Member States, cannot be sufficiently achieved by the Member States and can, by reason of the scale of the measures, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union (TEU). In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve this objective.
- (33) This Directive shall apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data <sup>(1)</sup> and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data <sup>(2)</sup>. In order to detect, assess, understand and prevent adverse reactions, and to identify and take actions to reduce the risks of, and increase the benefits from, medicinal products for the purpose of safeguarding public health, it should be possible to process personal data within the Eudravigilance system while respecting Union legislation relating to data protection. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data can be justified if identifiable health data are processed only when necessary and only when the parties involved assess this necessity at every stage of the pharmacovigilance process.
- (34) The provisions on the monitoring of medicinal products in Directive 2001/83/EC constitute specific provisions within the meaning of Article 15(2) of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products <sup>(3)</sup>.
- (35) The pharmacovigilance activities provided for in this Directive require that uniform conditions be established as concerns the contents and maintenance of the pharmacovigilance system master file, as well as the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and marketing authorisation holders, the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities, and the minimum requirements for the monitoring of the data contained in the Eudravigilance database to determine whether there are new risks or whether risks have changed. The format and content of the electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders, the format and content of electronic periodic safety update reports and risk management plans as well as the format of protocols, abstracts and final study reports for the post-authorisation safety studies should also be established. In accordance with Article 291 of the Treaty on the Functioning of the European Union (TFEU), rules and general principles concerning mechanisms for the control by Member States of the Commission's exercise of implementing powers are to be laid down in advance by a regulation adopted in accordance with the ordinary legislative procedure. Pending the adoption of that new regulation, Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission <sup>(4)</sup> continues to apply, with the exception of the regulatory procedure with scrutiny, which is not applicable.
- (36) The Commission should be empowered to adopt delegated acts in accordance with Article 290 TFEU in order to supplement the provisions in Articles 21a and 22a of Directive 2001/83/EC. The Commission should be empowered to adopt supplementary measures laying down the situations in which post-authorisation efficacy studies may be required. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level.
- (37) In accordance with point 34 of the Interinstitutional Agreement on better law-making <sup>(5)</sup>, Member States are encouraged to draw up, for themselves and in the interests of the Union, their own tables illustrating, as far as possible, the correlation between this Directive and the transposition measures, and to make them public.
- (38) Directive 2001/83/EC should be amended accordingly,

<sup>(1)</sup> OJ L 281, 23.11.1995, p. 31.

<sup>(2)</sup> OJ L 8, 12.1.2001, p. 1.

<sup>(3)</sup> OJ L 218, 13.8.2008, p. 30.

<sup>(4)</sup> OJ L 184, 17.7.1999, p. 23.

<sup>(5)</sup> OJ C 321, 31.12.2003, p. 1.

HAVE ADOPTED THIS DIRECTIVE:

*Article 1*

**Amendments to Directive 2001/83/EC**

Directive 2001/83/EC is hereby amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

‘11. Adverse reaction: A response to a medicinal product which is noxious and unintended.’;

(b) point 14 is deleted;

(c) point 15 is replaced by the following:

‘15. Post-authorisation safety study: Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.’;

(d) the following points are inserted:

‘28b. Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

28c. Risk management plan: a detailed description of the risk management system.

28d. Pharmacovigilance system: a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

28e. Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.’.

2. Article 8(3) is amended as follows:

(a) point (ia) is replaced by the following:

‘(ia) A summary of the applicant’s pharmacovigilance system which shall include the following elements:

— proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,

— the Member States in which the qualified person resides and carries out his/her tasks,

— the contact details of the qualified person,

— a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,

— a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.’,

(b) the following point is inserted after point (ia):

‘(iaa) The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.’;

(c) point (l) is replaced by the following:

‘(l) Copies of the following:

— any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;

— the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21 and the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61;

— details of any decision to refuse authorisation, whether in the Union or in a third country, and the reasons for such a decision.’,

(d) point (n) is deleted;

(e) the following subparagraphs are added after the second subparagraph:

‘The risk management system referred to in point (iaa) of the first subparagraph shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

The information referred to in the first subparagraph shall be updated where and when appropriate.’.

3. In Article 11 the following subparagraphs are added:

‘For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: “This medicinal product is subject to additional monitoring”. This

statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system referred to in Article 107a(1). Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1).'

4. Article 16g(1) is replaced by the following:

'1. Article 3(1) and (2), Article 4(4), Article 6(1), Article 12, Article 17(1), Articles 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, Article 111(1) and (3), Articles 112, 116, 117, 118, 122, 123, 125, the second paragraph of Article 126, and Article 127 of this Directive as well as Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (\*) shall apply, by analogy, to traditional-use registration granted under this Chapter.

(\*) OJ L 262, 14.10.2003, p. 22.'

5. Article 17 is amended as follows:

- (a) in the second subparagraph of paragraph 1, the words 'Articles 27' are replaced by the words 'Articles 28';
- (b) in paragraph 2, the words 'Articles 27' are replaced by the words 'Articles 28';

6. In Article 18, the words 'Articles 27' are replaced by the words 'Articles 28'.

7. In Article 21, paragraphs 3 and 4 are replaced by the following:

'3. The national competent authorities shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised.

4. The national competent authorities shall draw up an assessment report and make comments on the file as

regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The national competent authorities shall make the assessment report publicly accessible without delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

The public assessment report shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.'

8. The following Article is inserted:

*'Article 21a*

In addition to the provisions laid down in Article 19, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

- (a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;
- (b) to conduct post-authorisation safety studies;
- (c) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX;
- (d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;
- (e) the existence of an adequate pharmacovigilance system;
- (f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The marketing authorisation shall lay down deadlines for the fulfilment of these conditions where necessary.'

9. Article 22 is replaced by the following:

*'Article 22*

In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.

Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.'

10. The following Articles are inserted:

*'Article 22a*

1. After the granting of a marketing authorisation, the national competent authority may impose an obligation on the marketing authorisation holder:

(a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

(b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The national competent authority 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.

3. On the basis of the written observations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

*Article 22b*

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, the Commission may adopt, by means of delegated acts in accordance with Article 121a, and subject to the conditions of Articles 121b and 121c, measures supplementing the provisions in Articles 21a and 22a.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

*Article 22c*

1. The marketing authorisation holder shall incorporate any conditions referred to in Articles 21a, 22 or 22a in his risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 21a, 22 or 22a.'

11. Article 23 is replaced by the following:

*'Article 23*

1. After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Article 8(3), Articles 10, 10a, 10b and 11, or Article 32(5), or Annex I.



In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

4. In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest 7 days after receipt of the request.

12. Article 24 is amended as follows:

(a) in paragraph 2, the second subparagraph is replaced by the following:

'To this end, the marketing authorisation holder shall provide the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with paragraph 1.;

(b) paragraph 3 is replaced by the following:

'3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national

competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with paragraph 2.'

13. The title 'Chapter 4 Mutual recognition and decentralised procedure' is deleted.

14. Article 27 is amended as follows:

(a) paragraphs 1 and 2 are replaced by the following:

'1. A coordination group shall be set up for the following purposes:

(a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;

(b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107k and 107q;

(c) the examination of questions relating to variations of marketing authorisations granted by the Member States, in accordance with Article 35(1).

The Agency shall provide the secretariat of this coordination group.

For the fulfilment of its pharmacovigilance tasks, including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1)(aa) of Regulation (EC) No 726/2004.

2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of 3 years. Member States may appoint an alternate for a renewable period of 3 years. Members of the coordination group may arrange to be accompanied by experts.

Members of the coordination group and experts shall, for the fulfilment of their tasks, rely on the scientific and regulatory resources available to national competent authorities. Each national competent authority shall monitor the level of expertise of the evaluations carried out and facilitate the activities of the nominated coordination group members and experts.

Article 63 of Regulation (EC) No 726/2004 shall apply to the coordination group as regards transparency and the independence of its members.;

(b) the following paragraphs are added:

‘4. The Executive Director of the Agency or his representative and representatives of the Commission shall be entitled to attend all meetings of the coordination group.

5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of national competent authorities, including the consultative bodies concerned with the marketing authorisation.

6. Save where otherwise provided for in this Directive, the Member States represented within the coordination group shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.

7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.’.

15. After Article 27 the following heading is inserted:

‘CHAPTER 4

***Mutual recognition and decentralised procedure***’.

16. Article 31(1) is amended as follows:

(a) the first subparagraph is replaced by the following:

‘The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.’;

(b) the following subparagraphs are inserted after the first subparagraph:

‘Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 107k shall apply.

However, where urgent action is considered necessary, the procedure laid down in Articles 107i to 107k shall apply.’.

17. Article 36 is deleted.

18. Article 59 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (e) is replaced by:

‘(e) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case.’;

(ii) the following subparagraphs are added:

‘For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included “This medicinal product is subject to additional monitoring”. This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a(1), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Article 107a(1).’;

(b) the following paragraph is added:

‘4. By 1 January 2013, the Commission shall present to the European Parliament and the Council an assessment report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals. The Commission shall, if appropriate, and on the basis of the report, and consultation with appropriate stakeholders, present proposals in order to improve the readability, layout and content of these documents.’

19. Article 63(3) is replaced by the following:

‘3. When the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in the official language or languages of the Member State in which the medicinal product is placed on the market.’

20. Title IX is replaced by the following:

‘TITLE IX

## PHARMACOVIGILANCE

### CHAPTER 1

#### **General provisions**

##### *Article 101*

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients’ or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action

concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

##### *Article 102*

The Member States shall:

- (a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority; for these tasks, organisations representing consumers, patients and healthcare professionals may be involved as appropriate;
- (b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;
- (c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;
- (d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;
- (e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number;
- (f) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

For the purposes of point (a) and (e) of the first paragraph the Member States may impose specific obligations on doctors, pharmacists and other health-care professionals.

*Article 103*

A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public.

*Article 104*

1. The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under Article 101(1).

2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

3. As part of the pharmacovigilance system, the marketing authorisation holder shall:

- (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;
- (b) maintain and make available on request a pharmacovigilance system master file;
- (c) operate a risk management system for each medicinal product;
- (d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a;
- (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority and the Agency.

4. Notwithstanding the provisions of paragraph 3, national competent authorities may request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities.

*Article 104a*

1. Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 104(3)(c), not be required to operate a risk management system for each medicinal product.

2. The national competent authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Article 104(3)(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the national competent authority 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 national competent authority 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, the national competent authority shall withdraw or confirm the obligation. Where the national competent authority 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 (a) of Article 21a.

*Article 105*

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the national competent authorities in order to guarantee their independence in the performance of those pharmacovigilance activities.

The first paragraph shall not preclude the national competent authorities from charging fees to marketing authorisation holders for performing those activities by the national competent authorities on the condition that their independence in the performance of those pharmacovigilance activities is strictly guaranteed.

## CHAPTER 2

**Transparency and communications***Article 106*

Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

- (a) public assessment reports, together with a summary thereof;
- (b) summaries of product characteristics and package leaflets;
- (c) summaries of risk management plans for medicinal products authorised in accordance with this Directive;
- (d) the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004;
- (e) information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004.

*Article 106a*

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, he shall be required to inform the national competent authorities, the Agency and the Commission.

The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

2. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

4. When the Agency or national competent authorities make public information referred to in paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

## CHAPTER 3

**Recording, reporting and assessment of pharmacovigilance data**

## Section 1

**Recording and reporting of suspected adverse reactions***Article 107*

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study.

Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as the "Eudravigilance database") information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database.

5. Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.

#### *Article 107a*

1. Each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e).

Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

They shall, within 90 days from the receipt of reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Marketing authorisation holders shall access those reports through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 25 of Regulation (EC) No 726/2004.

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

## Section 2

### **Periodic safety update reports**

#### *Article 107b*

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

- (a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;
- (b) a scientific evaluation of the risk-benefit balance of the medicinal product;
- (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

The periodic safety update reports shall be submitted electronically.

2. The Agency shall make available the reports referred to in paragraph 1 to the national competent authorities, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 25a of Regulation (EC) No 726/2004.

3. By way of derogation from paragraph 1 of this Article, the holders of marketing authorisations for medicinal products referred to in Article 10(1), or Article 10a, and the holders of registrations for medicinal products referred to in Articles 14 or 16a, shall submit periodic safety update reports for such medicinal products in the following cases:

- (a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or
- (b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted. The assessment reports of the requested periodic safety update reports shall be communicated to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 107c(4) and Article 107e.

#### Article 107c

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

The dates of submission according to the specified frequency shall be calculated from the date of the authorisation.

2. Holders of marketing authorisations which were granted before 21 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, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6.

Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

- (a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;
- (b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products which are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.

This harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

- (a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004;
- (b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made public by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

- (a) the date of the first marketing authorisation in the Union of a medicinal product containing that active substance or that combination active substances;
- (b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:

- (a) for reasons relating to public health;
- (b) in order to avoid a duplication of the assessment;
- (c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, shall either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made public by the Agency. The marketing authorisation holders shall accordingly submit an application for a variation of the marketing authorisation.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing

authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect 6 months after the date of such publication.

#### *Article 107d*

The national competent authorities shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

#### *Article 107e*

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and frequency of periodic safety update reports has been established.

The single assessment shall be conducted by either of the following:

- (a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004; or
- (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004.

When selecting the Member State in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 28(1).

2. The Member State or rapporteur, as appropriate, 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 Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.



3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State 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 of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

#### Article 107f

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary.

They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

#### Article 107g

1. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event of a variation, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a modification, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented

within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations 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.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

- (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and
- (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with the centralised procedure provided for in Regulation (EC) No 726/2004 and concerned by the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

### Section 3

#### Signal detection

##### Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures:

- (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a;
- (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.

Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

### Section 4

#### Urgent Union procedure

##### Article 107i

1. A Member State or the Commission, as appropriate, shall initiate the procedure provided for in this section, by

informing the other Member States, the Agency and the Commission when urgent action is considered necessary, as a result of the evaluation of data resulting from pharmacovigilance activities, in any of the following cases:

- (a) it considers suspending or revoking a marketing authorisation;
- (b) it considers prohibiting the supply of a medicinal product;
- (c) it considers refusing the renewal of a marketing authorisation;
- (d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or that he intends to do so;
- (e) it considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary.

The Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether it is common to all products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the procedure of the outcome of this verification, and the procedures laid down in Articles 107j and 107k shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make information that the procedure has been initiated available to marketing authorisation holders.

2. Without prejudice to the provisions of paragraph 1 of this Article, and Articles 107j and 107k, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

3. At any stage of the procedure laid down in Articles 107j to 107k, the Commission may request Member States in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraph 1, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, at any stage of the procedure initiated under this section, take temporary measures immediately in relation to those marketing authorisations.

4. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those which are covered by the information or that it is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.

5. At the time of the information referred to in paragraph 1, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

#### Article 107j

1. Following receipt of the information referred to in Article 107i(1), the Agency shall publicly announce the initiation of the procedure by means of the European medicines web-portal. In parallel, Member States may publicly announce the initiation on their national medicines web-portals.

The announcement shall specify the matter submitted to the Agency in accordance with Article 107i, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter which has been submitted to the Agency in accordance with Article 107i. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and the Reference Member State for the medicinal products concerned.

For the purposes of that assessment, the marketing authorisation holder may submit comments in writing.

Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

In the public hearing, due regard shall be given to the therapeutic effect of the medicinal product.

The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 78 of Regulation (EC) No 726/2004.

Where a marketing authorisation holder or another person intending to submit information has confidential data relevant to the subject matter of the procedure, he may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the information being submitted, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention the divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairman, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

- (a) no further evaluation or action is required at Union level;
- (b) the marketing authorisation holder should conduct further evaluation of data together with the follow-up of the results of that evaluation;
- (c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
- (d) the Member States or marketing authorisation holder should implement risk minimisation measures;

(e) the marketing authorisation should be suspended, revoked or not renewed;

(f) the marketing authorisation should be varied.

For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

Where, in the cases referred to in point (f) of the first subparagraph, it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording should be placed.

#### Article 107k

1. Where the scope of the procedure, as determined in accordance with Article 107i(4), does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, and on the basis of a proposal by its chairman, the coordination group may agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in

Articles 33 and 34. However, by way of derogation from Article 34(1), the procedure referred to in Article 121(2) shall apply.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 107i(4), includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, and on the basis of a proposal by its chairman, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

Where the 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.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

(a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the procedure provided for in this section; and

(b) where the opinion is that regulatory action is necessary, adopt a decision to vary, suspend, revoke or refuse renewal of the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and subject to the procedure provided for in this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States. However, by way of derogation from Article 34(1) of this Directive, the procedure referred to in Article 121(2) thereof shall apply.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. However, by way of derogation from Article 10(2) of that Regulation, the procedure referred to in Article 87(2) thereof shall apply. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

## Section 5

### Publication of assessments

#### Article 107l

The Agency shall make public the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107b to 107k by means of the European medicines web-portal.

## CHAPTER 4

### Supervision of post-authorisation safety studies

#### Article 107m

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a, and which involve the collection of safety data from patients or healthcare professionals.

2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The national competent authority may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned.

Any new information which might influence the evaluation of the risk-benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23.

The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107b.

8. Articles 107n to 107q shall apply exclusively to studies referred to in paragraph 1 which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a.

#### Article 107n

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study according to Article 22a. For such studies, the marketing authorisation holder shall submit a draft protocol to the national competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

- (a) a letter endorsing the draft protocol;
- (b) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:
  - (i) it considers that the conduct of the study promotes the use of a medicinal product;
  - (ii) it considers that the design of the study does not fulfil the study objectives; or
- (c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

3. The study may commence only when the written endorsement from the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement as referred to in paragraph 2(a) has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

#### *Article 107o*

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the national competent authority or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform Member States in which the study is conducted.

#### *Article 107p*

1. Upon completion of the study, a final study report shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the national competent authorities an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Committee.

#### *Article 107q*

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention the divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to

in paragraph 1 and including a timetable for the implementation of the agreed position.

If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the national competent authorities an appropriate application for a variation, including an updated summary of product characteristics and package leaflet within the determined timetable for implementation.

The agreement shall be made public on the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

### CHAPTER 5

#### **Implementation, Delegation and Guidance**

##### *Article 108*

In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Article 8(3), and in Articles 101, 104, 104a, 107, 107a, 107b, 107h, 107n and 107p:

- (a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;
- (b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the national competent authorities and the marketing authorisation holder;

- (c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;
- (d) the minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;
- (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;
- (f) the format and content of electronic periodic safety update reports and risk management plans;
- (g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 121(2).

#### Article 108a

In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall, in cooperation with competent authorities and other interested parties, draw up:

- (a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;
- (b) scientific guidance on post-authorisation efficacy studies.

#### Article 108b

The Commission shall make public a report on the performance of pharmacovigilance tasks by the Member States on 21 July 2015 at the latest and then every 3 years thereafter.

21. Article 111 is amended as follows:

- (a) paragraph 1 is amended as follows:

- (i) the first subparagraph is replaced by the following:

'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.'

- (ii) in the fifth subparagraph, point (d) is replaced by the following:

'(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.'

- (b) paragraph 3 is replaced by the following:

'3. After every inspection 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, or 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.'

- (c) paragraph 7 is replaced by the following:

'7. If the outcome of the inspection as referred to in points (a), (b) and (c) of paragraph 1 or the outcome of an inspection of a distributor of medicinal products or active substances or a manufacturer of excipients 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.'

(d) the following paragraph is added:

'8. If the outcome of the inspection referred to in paragraph 1(d) 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.'

22. Article 116 is replaced by the following:

*'Article 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.

A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 8, 10 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.'

23. Article 117 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (a) is replaced by the following:

'(a) the medicinal product is harmful; or';

(ii) point (c) is replaced by the following:

'(c) the risk-benefit balance is not favourable; or';

(b) the following paragraph is added:

'3. 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.'

24. The following Articles are inserted:

*'Article 121a*

1. The power to adopt the delegated acts referred to in Article 22b shall be conferred on the Commission for a period of 5 years from 20 January 2011. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 121b.

2. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

3. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in Articles 121b and 121c.

*Article 121b*

1. The delegation of powers referred to in Article 22b may be revoked at any time by the European Parliament or by the Council.

2. The institution which has commenced an internal procedure for deciding whether to revoke the delegation of powers shall endeavour to inform the other institution and the Commission within a reasonable time before the final decision is taken, indicating the delegated powers which could be subject to revocation and possible reasons for a revocation.

3. The decision of revocation shall put an end to the delegation of the powers specified in that decision. It shall take effect immediately or at a later date specified therein. It shall not affect the validity of the delegated acts already in force. It shall be published in the *Official Journal of the European Union*.

*Article 121c*

1. The European Parliament or the Council may object to a delegated act within a period of 2 months from the date of notification.



At the initiative of the European Parliament or the Council that period shall be extended by 2 months.

2. If, on expiry of the period referred to in paragraph 1, neither the European Parliament nor the Council has objected to the delegated act, it shall be published in the *Official Journal of the European Union* and shall enter into force on the date stated therein.

The delegated act may be published in the *Official Journal of the European Union* and enter into force before the expiry of that period if the European Parliament and the Council have both informed the Commission of their intention not to raise objections.

3. If either the European Parliament or the Council objects to the delegated act within the period referred to in paragraph 1, it shall not enter into force. The institution which objects shall state the reasons for objecting to the delegated act.'

25. Article 122(2) is replaced by the following:

'2. Upon reasoned request, Member States shall send electronically the reports referred to in Article 111(3) to the competent authorities of another Member State or to the Agency.'

26. Article 123(4) is replaced by the following:

'4. The Agency shall make public annually a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended, whose supply has been prohibited or which have been withdrawn from the market.'

27. In Article 126a, paragraphs 2 and 3 are replaced by the following:

'2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI. Member States may decide that Article 63(1) and (2) shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such a marketing authorisation, a Member State:

- (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned.
- (b) may request the competent authority in that Member State to submit copies of the assessment report referred

to in Article 21(4) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.'

28. Article 127a is replaced by the following:

#### 'Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004, and the Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca), (cb) or (cc) of Article 9(4) thereof, the Commission may adopt a decision addressed to the Member States, in accordance with Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.'

#### Article 2

##### **Transitional provisions**

1. With regard to the obligation on the part of the marketing authorisation holder to maintain and make available on request a pharmacovigilance system master file in respect of one or more medicinal products provided for in Article 104(3)(b) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that that obligation applies to marketing authorisations granted before 21 July 2011 as from either:

a) the date on which those marketing authorisations are renewed; or

b) the expiry of a period of 3 years starting from 21 July 2011,

whichever is earlier.

2. The Member States shall ensure that the procedure provided for in Articles 107m to 107q of Directive 2001/83/EC as amended by this Directive applies only to studies which have commenced after 21 July 2011.

3. With regard to the obligation on the part of the marketing authorisation holder to submit information on suspected adverse reactions electronically to the Eudravigilance database, provided for in Article 107(3) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that this obligation applies as from 6 months after the functionalities of the database are established and have been announced by the Agency.

4. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010<sup>(1)</sup> of the European Parliament and of the Council, marketing authorisation holders shall report, within 15 days of the day on which the holder concerned gained knowledge of the event, all serious suspected adverse reactions that occur in the Union, to the competent authority of the Member State on whose territory the incident occurred and shall report all serious suspected adverse reactions that occur on the territory of a third country to the Agency and, if requested, to the competent authorities of the Member States in which the medicinal product is authorised.

5. Until the Agency can ensure the functionalities of the Eudravigilance database as specified in Article 24 of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010, the competent authority of a Member State may require marketing authorisation holders to report to it all non-serious suspected adverse reactions that occur on the territory of that Member State, within 90 days of the day on which the marketing authorisation holder concerned gained knowledge of the event.

6. During this period, Member States shall ensure that the reports referred to in paragraph 4 that relate to events that occurred in their territory are promptly made available to the Eudravigilance database, and in any case within 15 days of the notification of suspected serious adverse reactions.

7. With regard to the obligation on the part of the marketing authorisation holder to submit periodic safety update reports to the Agency as provided for in Article 107b(1) of Directive 2001/83/EC as amended by this Directive, the national competent authorities shall ensure that this obligation applies as from 12 months after the functionalities of the repository have been established and have been announced by the Agency.

Until the Agency can ensure the functionalities agreed for the repository of the periodic safety update reports, the marketing authorisation holders shall submit the periodic safety reports to all Member States in which the medicinal product has been authorised.

#### Article 3

##### Transposition

1. Member States shall adopt and publish, by 21 July 2012 at the latest, the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith communicate to the Commission the text of those provisions.

They shall apply those provisions from 21 July 2012.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

#### Article 4

##### Entry into force

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

#### Article 5

##### Addressees

This Directive is addressed to the Member States.

Done at Strasbourg, 15 December 2010.

*For the European Parliament*  
The President  
J. BUZEK

*For the Council*  
The President  
O. CHASTEL

<sup>(1)</sup> See page 1 of this Official Journal.