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NOTE

from : General Secretariat of the Council
to : Working Party on Pharmaceuticals and Medical Devices

No. Cion prop. : 17501/08 MI 563 SAN 352 ECO 195 ENT 331 CODEC 1886
17502/08 MI 564 SAN 353 ECO 196 ENT 332 CODEC 1887

No. prev. doc. : 11576/09 MI 261 SAN 184 ECO 98 ENT 154 CODEC 937

Subject : Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
and
Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

1. On 10 December 2009, the Commission submitted to the Council and the European Parliament two proposals aiming to introduce measures that improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use. One of these proposals amends Regulation (EC) 726/2004¹ and the other amends Directive 2001/83/EC².

¹ 17501/08 MI 563 SAN 352 ECO 195 ENT 331 CODEC 1886

² 17502/08 MI 564 SAN 353 ECO 196 ENT 332 CODEC 1887

2. The Working Party on Pharmaceuticals and Medical Devices examined the Pharmacovigilance Proposals at eight meetings during the Czech Presidency, completing a first read-through of both Proposals. Under the Swedish Presidency four meetings have taken place so far, on 20 July, 3 September, 2 October and 6 November 2009. These meetings have concentrated on specific topics, see Point 5 below.
3. The progress so far made was reported to the Council (EPSCO) at its meeting on 1 December 2009³.
4. At this stage, all delegations have a general scrutiny reservation on the entire Proposals. The Danish, Maltese and United Kingdom delegations have parliamentary scrutiny reservations.
5. At the meetings on 20 July, 3 September, 2 October and 6 November 2009, the Working Party has, *inter alia*, covered the following topics in its discussions:
 - the protection of personal data in the Eudravigilance database. This has resulted in tentative agreement on a clarification⁴ of the relation between the proposed new provisions in Directive 2001/83/EC and Regulation (EC) 726/2004 on the one hand and the Community legislation on data protection on the other hand;
 - the composition of the Pharmacovigilance Risk Assessment (Advisory)⁵ Committee (PRAC), where the majority of delegations have underlined that due to the nature of Pharmacovigilance, representatives of all Member States should be fully involved at all levels of the process. As an example, national competent authorities are responsible for diminishing the public health effects of adverse reactions to pharmaceuticals. There is now tentative agreement to change the composition of the committee;

³ See document 16055/09 MI 433 SAN 324 ECO 143 ENT 206 CODEC 1318.

⁴ Recital (20a) of the Regulation and (30a) of the Directive.

⁵ The Presidency has proposed to change the name by deletion of the word "Advisory" (PHV-30 and PHV-32). This change is reflected in the present document. **DELETED**: Reservation as they prefer the Commission proposal.

- the mandate and the role of the PRAC where many delegations felt that it should play a more central role and not act as just an advisory body. This has resulted in tentative agreement on a strengthening of the role of the PRAC in relation to the CMPH and to the CMD, including an obligation for the two latter to explain any differences in opinion compared to the PRAC;
- the interaction of the PRAC with other bodies in the EMEA system, in particular the CMD, the CHMP and the CAT;
- the inclusion into the legislative proposals of a requirement for the Agency, in collaboration with the Member States and the Commission, to draw up functional specifications for the Eudravigilance database which will take account of the role and experience of national competent authorities for pharmacovigilance. The new reporting obligations to Eudravigilance will not apply until these specifications are met and to this end a transitional period is envisaged;
- the legal status of CMD opinions and how they are implemented in Member States. The corresponding redrafting proposals have been included but are under legal scrutiny.

The tentative agreements have been incorporated in the text contained in the present document.

8. This document contains the legal texts of the two Proposals as resulting from the discussions in the Working Party on 6 November 2009. The Proposal amending Regulation (EC) 726/2004 is set out in Annex A and the Proposal amending Directive 2001/83/EC is set out in Annex B. Presidency proposals for additions of text are marked by **bold underline** and deletions of text by **~~bold strikethrough~~**. In cases where there is tentative agreement on the Presidency proposals, these are indicated by underline and ~~strikethrough~~.

Positions on specific provisions expressed by Member States in connection with or in the meetings of the Working Party until 6 November 2009 are set out as footnotes to the legal text in the Annexes. In the cases when a footnote is based on a written contribution, a reference to that document is included (*e.g.* PHV-2). The footnotes do normally not reflect the reasoning behind the position. Texts in footnotes marked with ~~strikethrough~~ will be deleted in the next version of this document, unless the delegations concerned object.

9. In addition, some amendments to Article 111 of Directive 2001/83/EEC that are part of the "Proposal on prevention of Falsified medicinal products"⁶ have been moved to this text for illustrative purposes. They are marked in **bold underline italics**.
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⁶ See documents 17504/08 MI 566 SAN 355 ECO 198 ENT 334 CODEC 1889 and 12610/09 MI 300 SAN 210 ECO 110 ENT 166 CODEC 1033.

2008/0257 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission⁷,

Having regard to the opinion of the European Economic and Social Committee⁸,

Acting in accordance with the procedure laid down in Article 251 of the Treaty⁹,

⁷ OJ C , , p. .

⁸ OJ C , , p. .

⁹ OJ C , , p. .

Whereas:

- (1) 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 Agency¹⁰ creates a Community-wide marketing authorisation procedure (the so-called 'centralised procedure') for certain categories of medicinal products, lays down rules for the pharmacovigilance of those products and establishes the European Medicines Agency (hereinafter referred to as the 'Agency').
- (2) Pharmacovigilance rules are necessary for the protection of public health in order to detect, assess and prevent adverse effects of medicinal products placed on the market of the Community, as the full safety profile of medicinal products can only be known once they have entered the market.
- (3) In the light of the experience acquired and following an assessment by the Commission of the Community system of pharmacovigilance, it has become clear that measures are necessary to improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use.
- (4) The main tasks of the Agency in the area of pharmacovigilance laid down in Regulation (EC) No 726/2004 should be maintained and further developed, in particular as regards the management of the Community pharmacovigilance database and data-processing network (hereinafter referred to as 'the Eudravigilance database') and the coordination of safety announcements by the Member States.
- (5) In order to allow all competent authorities to receive and access, at the same time, pharmacovigilance information for medicinal products for human use authorised in the Community, and share it, the Eudravigilance database should be maintained and strengthened as the single point of receipt of such information. Member States should therefore not impose on marketing authorisation holders any additional reporting requirements. The database should be fully accessible to the Member States, the Agency and the Commission, and accessible to an appropriate extent to marketing authorisation holders and the public.

¹⁰ OJ L 136, 30.4.2004, p. 1.

- (6) In order to increase transparency as regards pharmacovigilance issues, a European medicines safety web-portal should be created and maintained by the Agency.
- (7) In order to ensure the availability of the necessary expertise and resources for pharmacovigilance assessments at Community level, it is appropriate to create a new scientific committee within the Agency, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee. That committee should be composed of independent scientific experts with competence in the safety of medicines including the detection, assessment, minimisation and communication of risk, and the design of post-authorisation safety studies and pharmacovigilance audit.
- (8) The rules on scientific committees of the Agency, as laid down in Regulation (EC) No 726/2004, should apply to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee.
- (9)¹¹ In order to ensure harmonised responses across the Community to safety concerns regarding medicinal products for human use, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee should support the Committee for Medicinal Products for Human Use and the coordination group established by 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 use¹² on any question relating to the pharmacovigilance of medicinal products for human use. However, for the sake of consistency and continuity of the assessments, the final responsibility for the risk-benefit assessment of medicinal products for human use authorised in accordance with this Regulation should remain with the Committee for Medicinal Products for Human Use of the Agency and with the authorities competent for the granting of marketing authorisations.
- (10) In accordance with Directive 2001/83/EC the Agency provides the secretariat to the coordination group . In view of the enlarged mandate of the coordination group in the area of pharmacovigilance, the technical and administrative support by the secretariat of the Agency to the coordination group should be reinforced. Provision should be made for the Agency to ensure appropriate coordination between the coordination group and the Agency's scientific committees.

¹¹ **DELETED**: Reservation on this recital due to questioning of the proposed role for the PRAAC. (PHV-14)

¹² OJ L 311, 28.11.2001, p. 67.

- (11) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the Agency. Provision should be made to allow adequate funding for pharmacovigilance activities through the collection of fees charged to marketing authorisation holders. The management of those collected funds should be under a permanent control of the Management Board in order to guarantee the independence of the Agency.
- (12) To ensure the highest levels of expertise and the functioning of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, rapporteurs providing assessment for Community pharmacovigilance procedures, periodic safety update reports, post-authorisation safety study protocols and risk management systems should receive payment through the Agency.
- (13) Provision should be made for the Agency to collect fees as regards the activities of the coordination group within the Community system of pharmacovigilance, as provided for in Directive 2001/83/EC, and for rapporteurs within the coordination group to be then paid by the Agency.
- (14) In order to ensure the collection of any necessary additional data about the safety of medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission should be empowered to require the marketing authorisation holder to conduct post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and that requirement should be included as a condition of the marketing authorisation.
- (15) Where a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or subject to conditions or restrictions with regard to the safe and effective use of the medicinal product, the medicinal product should be intensively monitored on the market. Patients and healthcare professionals should be encouraged to report all suspect adverse reactions to such medicinal products, and a publicly available list of such medicinal products should be kept up to date by the Agency.

- (16) Experience has shown that there is a need to clarify the responsibilities of marketing authorisation holders for the pharmacovigilance of authorised products. The marketing authorisation holder should be responsible for continuously monitoring the safety of his products, for informing the authorities of any changes that might have an 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 their marketing authorisations, these responsibilities should include providing all information available, including the results of clinical trials or other studies, as well as reporting of the use of the medicinal product which is not in accordance with the summary of the product characteristics. Likewise it is appropriate to ensure that all relevant information collected on the safety of the medicinal product is taken into account when marketing authorisations are being renewed.
- (17) Scientific and medical literature provides an important source of information on suspected adverse reaction case reports. Currently, for active substances included in more than one medicinal product, literature cases are reported in a duplicative way. In order to enhance the efficiency of reporting, provision should be made for the Agency to monitor a defined list of literature for a defined list of active substances used in medicinal products for which there are several marketing authorisations.
- (18) As a result of the submission of all adverse reaction data for medicinal products authorised by the Member States directly to the Eudravigilance database, it is not necessary to provide for different reporting rules for medicinal products for human use authorised in accordance with Regulation (EC) No 726/2004. The rules on adverse reaction recording and reporting laid down in Directive 2001/83/EC should therefore apply to medicinal products for human use authorised in accordance with Regulation (EC) No 726/2004.
- (19) There is a need to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. The procedures of Directive 2001/83/EC should therefore apply for the single assessment of periodic safety update reports for different medicinal products containing the same active substance or combination thereof, including joint assessments of products authorised nationally and through the centralised procedure.

- (20) It is appropriate to strengthen the supervisory role for medicinal products authorised through the centralised procedure by providing that the supervisory authority for pharmacovigilance should be the competent authority of the Member State in which the pharmacovigilance system master file of the marketing authorisation holder is sited.
- (20a) This Regulation 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 data¹³ 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 data¹⁴. In order to detect, assess, understand and prevent adverse reactions, identify and take actions to reduce risks and increase 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 EU data protection legislation. This purpose constitutes a substantial public interest which can be justified if identifiable health data are processed only when necessary and parties involved assess this necessity at every stage of the pharmacovigilance process.¹⁵
- (21) The provisions on the surveillance of medicinal products for human use in Regulation (EC) No 726/2004 constitute specific provisions in 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, and repealing Regulation (EEC) No 339/93¹⁶.
- (22) Regulation (EC) No 726/2004 should therefore be amended accordingly,

¹³ OJ L 281, 23.11.1995, p. 31.

¹⁴ OJ L 8, 12.1.2001, p. 1.

¹⁵ Inspired by recital 12 of Regulation (EC) No 1338/2008, OJ L 354 31.12.2009 p. 70-81.

¹⁶ OJ L 218, 13.8.2008, p. 30.

HAVE ADOPTED THIS REGULATION:

Article 1

Amendments to Regulation (EC) No 726/2004

Regulation (EC) No 726/2004 is amended as follows:

(1) In Article 5(2) the following sentence is added:

“For the fulfilment of its pharmacovigilance tasks, it shall ~~be assisted~~ rely on the scientific assessment and advice of ~~by~~ the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee referred to in Article 56(1)(aa).”¹⁷

(2) Article 9(4) is amended as follows:

(a) the following point (aa) is inserted:

“(aa) a recommendation on the frequency of submission of periodic safety update reports;”

(b) the following points (ca) and (cb) are inserted:

“(ca) details of any measures for the safe use of the medicinal product contained in the risk management system to be imposed as conditions of the marketing authorisation;

(cb) if appropriate, the written requirement to conduct post-authorisation safety studies or to comply with requirements on adverse reaction recording or reporting which are stricter than those referred to in Chapter 3;”

¹⁷ **DELETED**: Replace this sentence by "It shall rely on the assessment and advice of the Risk Assessment and Pharmacovigilance Committee referred to in Article 56(1)(aa)"(PHV-9). This would ensure that the new Committee shall be the only scientific body in charge of pharmacovigilance and risk assessment so as to avoid duplication of roles.
Many delegations: Similar ideas.

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

“(f) the assessment report as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials and the risk management system and the pharmacovigilance system of the medicinal product concerned.”

(3) Article 10 is amended as follows:

(a) Paragraph 1 is replaced by the following`:

"1. Within 15 days after receipt of the opinion referred to in Article 5(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents mentioned in points (a) to (d) of Article 9(4).

Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in points (c), (ca) or (cb) of Article 9(4), it shall lay down deadlines for the fulfilment of the conditions where necessary.

Where the draft decision is not in accordance with the opinion of the Agency, the Commission shall annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to Member States and the applicant."

(b) Paragraph 6 is replaced by the following:

“6. The Agency shall disseminate the documents referred to in points (a) to (d) of Article 9(4), together with any deadlines laid down pursuant to the third subparagraph of paragraph 1 of this Article.”

(4) The following Article 10a is inserted:

“Article 10a

1. After the granting of a marketing authorisation, the Agency may require a marketing authorisation holder to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. The requirement shall be made in writing, provide a detailed justification and include the objectives and timeframe for submission and conduct of the study.
2. The Agency shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within a time limit which it shall specify, if the marketing authorisation holder requests this within 30 days of receipt of the written requirement.
3. On the basis of explanations submitted by the marketing authorisation holder, the Commission shall withdraw or confirm the requirement. Where the Commission confirms the requirement, the marketing authorisation shall be varied to include the requirement as a condition of the marketing authorisation and the risk management system shall be updated accordingly.”

(5) Article 14 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 Agency with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in adverse reactions reports and periodic safety update reports submitted in accordance with Chapter 3, and all variations introduced since the marketing authorisation was granted, at least nine months¹⁸ before the marketing authorisation ceases to be valid in accordance with paragraph 1.”

¹⁸ **DELETED**: Worried that ”9 months before” is too early, will there be enough data for new medicinal products?

(b) Paragraph 3 is replaced by the following:

“3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission decides, on justified grounds relating to pharmacovigilance or insufficient exposure to the product, to proceed with one additional five-year renewal in accordance with paragraph 2.”

(c) Paragraph 8 is replaced by the following:

“8. In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This 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 to Directive 2001/83/EC. Continuation of the authorisation shall be linked to the annual reassessment of these conditions.”

(6) The following Article 14a is inserted:

“Article 14a

1. The marketing authorisation holder shall incorporate any conditions or requirements referred to in points (c), (ca) and (cb) of Article 9(4) or in Articles 10a, 14(7) and (8) in his risk management system.
2. The Agency shall include the medicinal products concerned by paragraph 1 in the list referred to in Article 23. The Agency shall remove a medicinal product from the list when the Commission, on the basis of an opinion of the Agency, concludes that the conditions have been fulfilled and that, following the assessment of any data resulting from the implementation of the conditions or requirements, the risk-benefit balance remains positive.

(7) Article 16 is replaced by the following:

“Article 16

1. After an authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h) of Directive 2001/83/EC, 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. He shall apply for approval of such variations in accordance with this Regulation.
2. The marketing authorisation holder shall forthwith supply to the Agency, to the Commission and to the member States any new information which might entail the amendment of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11, or 32(5) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, he shall forthwith inform the Agency and the Commission of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use 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 not in accordance with the summary of the product characteristics.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the assessment conclusions and recommendations made public by means of the European medicines safety web-portal established in accordance with Article 26.

4. In order that the risk-benefit balance may be continuously assessed, the Agency may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The holder shall submit the copy seven days after the receipt of the request at the latest.”

(8) Article 18 is amended as follows:

(a) Paragraph 1 is replaced by the following:

“1. In the case of medicinal products for human use manufactured within the Community, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 40(1) of Directive 2001/83/EC in respect of the medicinal product concerned.”

(b) In paragraph 2, the first subparagraph is replaced by the following:

“In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC to the importer, unless appropriate agreements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.”

(c) The following paragraph 3 is added:

“3. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is sited.”

(9) Article 19 is amended as follows:

(a) Paragraph 1 is replaced by the following:

“1. Under the coordination of the Agency, the supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements concerning manufacturing and imports laid down in Titles IV and XI of Directive 2001/83/EC.

Under the coordination of the Agency, the supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC.¹⁹”

(b) In paragraph 3, the second subparagraph is replaced by the following:

“The inspection shall be undertaken by inspectors from the Member States who possess the appropriate qualifications; they may be accompanied by a rapporteur or expert appointed by the said Committee. The report of the inspectors shall be made available electronically to the Commission, the Member States and the Agency.”

¹⁹ **DELETED**: Add "They may, as considered necessary, conduct pre-authorisation pharmacovigilance inspections to verify the accuracy and successful implementation of the Pharmacovigilance system as described by the applicant in support of the application". (PHV-19)

(10) Article 20 is amended as follows:

(a) Paragraph 3 is replaced by the following:

“3. Following an opinion by the Agency, the Commission may adopt the necessary provisional measures, which shall be applied immediately.

A final decision in respect of the medicinal product concerned shall be adopted within six months, in accordance with the procedure referred to in Article 87(2).

The Commission may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.”

(b) The following paragraph 8 is added:

“8. By way of derogation from paragraphs 1 to 7 of this Article, where a procedure under Articles 31, 36 or 107i to 107l of Directive 2001/83/EC concerns a range of medicinal products or a therapeutic class, medicinal products authorised in accordance with this Regulation and which belong to that range or class shall only be included in the procedure of Article 31, 36 or of Articles 107i to 107l of the Directive.

- (11) Chapter 3 of Title II is replaced by the following:

“Chapter 3 Pharmacovigilance

Article 21

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

However, holders of marketing authorisations granted before [insert concrete date - date set out in the second paragraph of Article 3 of Regulation (EC) No .../...] shall operate a risk management system as referred to in point (c) of Article 104(3) of that Directive only if paragraphs 2, 3 and 4 of this Article are complied with.

- 2.²⁰ The Agency may require a marketing authorisation holder²¹ to operate a risk management system as referred to in point (c) of Article 104(3) of Directive 2001/83/EC, if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. To this effect, the Agency shall also require 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 requirement shall be made in writing, provide a detailed justification, and include the timeframe for submission of the detailed description of the risk-management system.

²⁰ **DELETED**: Paragraphs 2,3 and 4 should form a separate article.

²¹ **DELETED**: Reservation on the obligation imposed on all authorisation holders to have a risk management system.

3. The Agency shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within a time limit which it shall specify, if the marketing authorisation holder requests this within 30 days of receipt of the written requirement.
4. On the basis of explanations submitted by the marketing authorisation holder, the Commission shall withdraw or confirm the requirement. Where the Commission confirms the requirement, the marketing authorisation shall be varied as appropriate to include measures to be taken in the risk management system as conditions of the marketing authorisation as referred to in point (ca) of Article 9(4).

Article 22

The obligations of marketing authorisation holders laid down in Article 106a(1) of Directive 2001/83/EC, and of the Member States, the Agency and the Commission laid down in paragraphs (2), (3) and (4) of that Article shall apply to safety announcements concerning medicinal products for human use authorised in accordance with this Regulation.

Article 23

The Agency shall establish and make public a list of medicinal products²² for human use under intensive monitoring.

That list shall include the names and active substances of medicinal products authorised pursuant to this Regulation subject to conditions or requirements referred to in points (c), (ca) and (cb) of Article 9(4), or in Articles 10a, 14(7) and 14(8), and of medicinal products authorised pursuant to Directive 2001/83/EC which are referred to in Articles 21a, 22 and 22a thereof, and an electronic link to the product information.

The Agency shall keep the list up to date.

²² **DELETED**: Reservation on the list of medicinal products, its usefulness compared to cost should be reassessed.

Article 24

1. The Agency, in collaboration with the Member States²³ and the Commission, shall set up and maintain a database and data processing network (hereinafter 'the Eudravigilance database') to collate pharmacovigilance information regarding medicinal products authorised in the Community and to allow competent authorities to access the information at the same time and to share it.

The Eudravigilance database shall contain information on adverse reactions in human beings arising from use of the product within the terms of the marketing authorisation as well as from any other use, including overdose, misuse²⁴, abuse, medication errors²⁵ ²⁶, and those occurring in the course of studies with the medicinal product or after occupational exposure.

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

²⁷The Management Board of the Agency shall on the basis of an independent²⁸ audit report confirm and announce when full functionality of the Eudravigilance database is achieved and the system meets the defined functional specifications mentioned in the first subparagraph.

²³ **DELETED**: Make clear that Member States are only responsible for providing data on events that occurred on their territory.

²⁴ **DELETED**: Delete "misuse" as it is not defined.

²⁵ **DELETED**: See suggestion for a definition of "medication error" in PHV-14.

²⁶ **DELETED**: Add "off-label use".

²⁷ **DELETED**: Add in the beginning of this subparagraph "Where there is sufficient evidence that the above functional specifications have been met, the Commission, in agreement with the management Board of the Agency, shall commission an independent audit assessing the functionality of the Eudravigilance database. The report should also take into account the experience of Member States as expressed in a statement issued by the Pharmacovigilance Risk Assessment Committee." (PHV-56)

²⁸ **DELETED**: Replace "of an independent audit" by "of this audit" (PHV-56)

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

The Agency shall ensure that health-care professionals and the public have appropriate levels of access to the Eudravigilance database, with personal data protection being guaranteed.

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

2a. Individual adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically²⁹ upon receipt to the national competent authority of the Member State where the reaction occurred.³⁰

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3.^{32 33} Individual adverse reaction reports held on the Eudravigilance database may be requested by the public. Those reports shall be provided by the Agency or the national competent authority from which they are requested within 90 days, unless disclosure would compromise the anonymity of the subjects of the reports.

²⁹ **DELETED**: Insert the word "immediately" (PHV-56)

³⁰ **DELETED**: Insert "In addition, adverse reaction reports and follow-ups from other countries shall be transmitted to the national competent authority functioning as a Rapporteur or Co-rapporteur for the respective medicinal product or other medicinal products with the same active substance." (PHV-56)

³¹ **DELETED**: -add a new paragraph:

~~"2a. Individual adverse reaction reports submitted to the Eudravigilance database [by marketing authorisation holders] shall be transmitted electronically upon receipt, in the form of a report, to the national competent authority of the Member State where the reaction occurred." (PHV-36)~~

³² **DELETED**: Make a separate article out of this paragraph.

³³ **DELETED**: Questions the need for this paragraph.

*Article 25*³⁴

The Agency, in collaboration with the Member States, shall develop standard web-based structured forms³⁵ for the reporting of suspected adverse reactions by health-care professionals and patients.³⁶

³⁴ **DELETED**: Question the need for this article.

³⁵ **DELETED**: These forms already exist.

³⁶ **DELETED**: Must be possible for a national competent authority to contact a patient or a doctor.

DELETED: These reports should be automatically sent to the Member State where the adverse event took place.

Article 26

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

- (1) the members of the committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the members of the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter ‘the coordination group’), together with their professional qualifications and with the declarations pursuant to Article 63(2) of this Regulation;
- (2) a summary³⁷ of each meeting of the committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the coordination group as regards pharmacovigilance activities;
- (3) risk management systems for medicinal products authorised in accordance with this Regulation;
- (4) the list of medicinal products under intensive monitoring referred to in Article 23 of this Regulation;
- (5) a list of the locations in the Community where pharmacovigilance system master files are sited and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Community;
- (6) information about how to report suspected adverse reactions to medicinal products and standard forms for their web-based reporting by patients and health-care professionals;
- (7) Community reference dates and frequency of submission of periodic safety update reports established in accordance with Article 107c of Directive 2001/83/EC;

³⁷ **DELETED**: Commercially sensitive information should be deleted.

- (8) protocols and public abstracts of results as regards post authorisation safety studies conducted in more than one Member State and referred to in Articles 107o and 107q of Directive 2001/83/EC;
- (9) the initiation of the procedure under Articles 107i to 107l of Directive 2001/83/EC, the substances or products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;
- (10) Assessment conclusions, **recommendations**³⁸, opinions and decisions taken by the committees^{39 40} referred to in points (a) and ~~(aa)~~ of Article 56(1) of this Regulation and the coordination group, the national competent authorities and the Commission in the framework of the procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 of Title IX of Directive 2001/83/EC.

Article 27⁴¹

1. The Agency shall monitor selected⁴² medical literature for reports of suspected adverse reactions to medicinal products for human use containing certain active substances. It shall publish the list of active substances being monitored and the publications subject to this monitoring.
2. The Agency shall enter into the Eudravigilance database relevant information from the selected literature.
3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide⁴³ regarding the conduct of medical literature monitoring and the entry of relevant information into the Eudravigilance database.

³⁸ **DELETED**: Reservation on deletion.

³⁹ Refers only to CHMP.

⁴⁰ **DELETED**: Commercially sensitive information should be deleted.

⁴¹ **DELETED**: Scrutiny reservation on this Article.

⁴² **DELETED**: Clarify the notion of "selected".

⁴³ **DELETED**: Clarification needed on the content of this guide.

Article 28

1. The obligations of marketing authorisation holders and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.
2. The obligations of marketing authorisation holders laid down in Article 107b of Directive 2001/83/EC and the procedures under Article 107b and Article 107c thereof shall apply to the submission of periodic safety update reports, the establishment of Community reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

The rules for the submission of periodic safety update reports laid down in the second subparagraph of Article 107c(2) of that Directive shall apply to holders of marketing authorisations which were granted before [insert concrete date - date set out in the second paragraph of Article 3 of Regulation (EC) No .../...] and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with Article 107c of that Directive.

3. The Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall assess the periodic safety update reports.⁴⁴

It shall prepare an assessment report⁴⁵ within 90 days of receipt of the periodic safety update report and send it to the marketing authorisation holder⁴⁶.

⁴⁴ **DELETED**: "The rapporteur appointed for this purpose by the PRAAC should work closely with the CHMP rapporteur of the product and both should preferably be from the same Member State and/or the same national competent authority." (PHV-44)

⁴⁵ **DELETED**: Replace "assessment report" by "advice" (PHV-31)

⁴⁶ **DELETED**: Add "and the CHMP" (PHV-31)

Within 30 days of receipt of the assessment report⁴⁷, the marketing authorisation holder may submit comments to the Agency.

At its next meeting following the end of the period for comments by the marketing authorisation holder, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall adopt the assessment report⁴⁸ with or without changes and a recommendation⁴⁹, taking into account any comments submitted by the marketing authorisation holder.

4. Within 30 days of receipt of the report⁵⁰ by the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, the Committee for Medicinal Products for Human Use shall consider the report⁵¹ and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned. **Where this opinion of the Committee for Medicinal Products for Human Use is not in accordance with the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.**

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

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

⁴⁷ **DELETED**: Insert "and advice of the PRAAC" (PHV-31)

⁴⁸ **DELETED**: Replace "assessment report" by "advice" (PHV-31)

⁴⁹ **DELETED**: Use the concept "position statement" instead of "recommendation".

⁵⁰ **DELETED**: Replace "report" by "advice" (PHV-31)

⁵¹ **DELETED**: Replace "report" by "advice" (PHV-31)

6. The opinions and decisions referred to in paragraphs ~~3 to 4~~ 4 and 5 of this Article shall be made public by means of the European medicines safety web-portal referred to in Article 26.

Article 28a

1. Regarding medicinal products authorised in accordance with this Regulation, the Agency and marketing authorisation holders shall take the following measures:
- (a) monitor the outcome of risk minimization measures contained in risk management systems and of conditions or requirements referred to in points (c), (ca) and (cb) of Article 9(4) or in Articles 10a, 14(7) and (8) ;
 - (b) assess updates to the risk management system;
 - (c) monitor the data in the Eudravigilance database to determine whether there are new or changed risks or whether there are changes to the risk benefit balance.
2. The Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall perform the initial scrutiny and prioritisation of indications of new or changed risks or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those indications and any subsequent action as regards the marketing authorisation shall be conducted in accordance with Article 28.
3. The Agency and marketing authorisation holders shall inform each other in the event of new or changed risks or changes to the risk benefit balance being detected.

Article 28b

1. For post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which fulfil the criteria set out in Article 107n(1) of Directive 2001/83/EC, Articles 107n(2), 107o to 107q and Article 107r (1) thereof shall apply.

2. Where, in accordance with the procedure referred to in paragraph 1 of this Article, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee ~~makes~~ issues recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation and the Commission shall adopt a decision in accordance with Article 10.⁵²

Article 28c

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

The Agency shall make available all suspected adverse reaction reports that occurred in the Community to the World Health Organization.

2. Information received on abuse of medicinal products including information related to illicit drugs⁵³ shall be exchanged between the Agency and the European Monitoring Centre for Drugs and Drug Addiction.

Article 28d

Upon request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonization and standardization of technical measures in pharmacovigilance.

⁵² **DELETED**: In conjunction with the suggested text on Article 107r of the Directive, the following text could be added at the end of this paragraph : "Where this opinion of the CHMP is not in accordance with the recommendation of the PRAC, the CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences" (PHV-46)

⁵³ The term "illicit drugs" is used in UN Conventions and refers to narcotics.

Article 28e

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

Article 28f

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

Article 29

The Commission shall adopt any amendments which may be necessary to update the provisions of this Chapter to take account of scientific and technical progress.

Those measures, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Article 29a

The Commission shall make public a report on the conduct of pharmacovigilance tasks by the Agency on [insert concrete date - three-years after the date of application set out in the second paragraph of Article 3] at the latest and then every three years thereafter.”

(12) Article 56(1) is amended as follows:

(a) the following point (aa) is inserted:

"(aa) the Pharmacovigilance Risk Assessment ~~Advisory~~⁵⁴ Committee, which shall be responsible for providing advice to the Committee for Medicinal Products for Human Use and the coordination group on any question⁵⁵ relating to the pharmacovigilance of medicinal products for human use;"

(b) point (f) is replaced by the following:

"(f) a Secretariat, which shall provide technical, scientific and administrative support for the committees and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group and ensure appropriate coordination between it and the committees."

(13) Article 57 is amended as follows:

(a) in paragraph 1, points (c) to (f) are replaced by the following:

"(c) coordination of the supervision of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;

(d) ensuring the collation and dissemination of information on adverse reactions to medicinal products authorised in the Community by means of a database permanently accessible to all Member States;

⁵⁴ **DELETED**: Reservation on the change of the name.

⁵⁵ **DELETED**: What is the role of this committee in relation to the Committee on Advanced Therapies (Art. 8 of Regulation 1394/2007)? If two advisory committees were to reach different conclusions on the same issue problems could be created for the CHMP.

- (e) assisting Member States with the rapid communication of information concerning pharmacovigilance to health-care professionals and coordinating the safety announcements of the national competent authorities;
 - (f) distributing appropriate pharmacovigilance information to the general public, in particular by setting up and maintaining a European medicines safety web-portal;”
- (b) In paragraph 2, the following subparagraph is inserted after the first subparagraph:
- “For the purposes of the database, the Agency shall establish a list of all medicinal products authorised in the Community. To this effect the following measures shall be taken:
- (a) the Agency shall, by *-/- (insert date - six-months after the entry into force of the amending regulation)* at the latest, make public a format for the electronic submission of medicinal product information;
 - (b) marketing authorisation holders shall, by *-/- (insert date - eighteen months after the entry into force of the amending regulation)* at the latest, electronically submit to the Agency information for all medicinal products authorised or registered in the Community, using the format referred to in point (a);
 - (c) from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new authorisations granted in the Community, using the format referred to in point (a).”

(14) The following Article 61a is inserted:

"Article 61a^{56 57}

1. The Pharmacovigilance Risk Assessment ~~Advisory~~⁵⁸ Committee⁵⁹ shall be composed⁶⁰ of the following:

- (a) ~~one ten~~ members and ~~one ten~~ alternates appointed by each Member State, after consultation⁶⁴ of the Management Board, ~~on the basis of proposals by the national competent authorities;~~
- (b) five members and five alternates⁶² appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament.

63

A Member State may delegate its tasks in the Pharmacovigilance Risk Assessment Committee to another Member State. Any Member State may represent a maximum of one other Member State.⁶⁴

56 **DELETED**: Reservation on this Article. (PHV-5)

57 **DELETED**: Align the provisions on the Pharmacovigilance Risk Assessment Committee with those for the CAT and the Paediatrics committee.

58 **DELETED**: Reservation on the change of the name.

59 **DELETED**: Change the name to "Risk Assessment and Pharmacovigilance Committee". (PHV-9)

60 **DELETED**: Will there also be co-opted members. What about their voting rights? Cion: The system of co-opted members does not apply to this committee, instead the Commission appoints some members.

61 **DELETED**: Clarify what is meant by consultation. **DELETED**: clarify skills and competences needed and delegation of tasks.

62 **DELETED**: Delete "and five alternates". (PHV-4 and PHV-9)

63 **DELETED**: Add a point (c) with the following wording : "One representative of patients organisations". (PHV-9)

64 **DELETED**: The right to be represented should not be restricted.

The alternates⁶⁵ shall represent and vote for the members in their absence.

~~The Commission may adapt the number of members and alternates in the light of technical and scientific needs. Those measures, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).~~

2. The members and alternates of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance and risk assessment of medicinal products for human use, in such a way as to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, ~~the Executive Director of the Agency shall assist~~ Member States shall liaise⁶⁶ with the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.

⁶⁵ **DELETED**: Insert provisions that allow alternates to become rapporteurs.

⁶⁶ **DELETED**: Considers this liaising as redundant since paragraph 1 provides for consultation.

3. The members and alternates of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall be appointed for a term of three years, which may be prolonged once⁶⁷ and thereafter renewed following the procedures referred to in paragraph 1 (a) and (b).⁶⁸ The Committee shall elect its Chairman among its members for a term of three years, which may be prolonged once.
4. Paragraphs (3), (4), (6), (7) and (8) of Article 61 shall apply to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee.
5. ~~Members and alternates of the Pharmacovigilance Risk Assessment Advisory Committee may not seek or take instructions from any national competent authority, organisation or person. They shall carry out the duties assigned to them objectively and impartially.~~

⁶⁷ **DELETED**: Why only once? Cion: The intention of the provision is that a term in office may be prolonged for another three years through a simple procedure. After that, a member can be reappointed on the basis of a complete procedure for nomination.

⁶⁸ **DELETED**: Add "At meetings of the Committee for Advanced Therapies, they may be accompanied by experts". These experts should be able to vote. Cion: Right to be accompanied by experts follows from Article 61(3).

6.⁶⁹ ~~Representatives of the national competent authorities shall be entitled to attend all meetings of the Pharmacovigilance Risk Assessment Advisory Committee to facilitate appropriate coordination between the tasks of the Agency and the work of national competent authorities. They may provide clarification or information if invited to do so but shall not seek to influence discussions.~~

4a. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all the aspects of the risk management of the use of medicines including detection, assessment, minimisation and communication related to the risk, **the design**⁷⁰ of post-authorisation safety studies and pharmacovigilance audit.”

⁶⁹ **DELETED**: Delete this paragraph only as part of package of changes that gives all Member States full representation in the committee.

⁷⁰ **DELETED**: Add "and evaluation"

(15) Article 62 is amended as follows:

(a) Paragraph 1 is amended as follows:

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

“Where, in accordance with this Regulation, any of the committees referred to in Article 56(1) is required to evaluate a medicinal product, it shall appoint one of its members to act as rapporteur⁷¹ for the coordination of the evaluation. The Committee concerned may appoint a second member to act as co-rapporteur.”

(ii) the fourth subparagraph is replaced by the following:

“If there is a request for re-examination of one of its opinions where this possibility is foreseen in the Community legislation, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion. The applicant may request that the Committee consults a scientific advisory group in connection with the re-examination.”

(b) in paragraph 2, the first subparagraph is replaced by the following:

“Member States shall transmit to the Agency the names of national experts with proven experience in the evaluation of medicinal products who would be available to serve on working parties or scientific advisory groups of any of the committees referred to in Article 56(1), together with an indication of their qualifications and specific areas of expertise.”

⁷¹ **DELETED**: How will the Rapporteur of the Pharmacovigilance Committee interact with the Rapporteur of CHMP? Are they the same person? **DELETED**: Pharmacovigilance Rapporteur must come from same MS as the one making the assessment.

(c) In paragraph 3, the following subparagraph is added:

“The first and second subparagraph shall apply also to the work of rapporteurs in the coordination group as regards the fulfilment of its tasks in accordance with Articles 107c, 107e, 107g, 107l and 107r of Directive 2001/83/EC.”

(16) Article 64(2) is amended as follows:

(a) Point (b) is replaced by the following:

“(b) for managing all the Agency resources necessary for conducting the activities of the committees referred to in Article 56(1), including making available appropriate scientific and technical support to those committees, and for making available appropriate technical support to the coordination group;”

(b) Point (d) is replaced by the following:

“(d) for ensuring appropriate coordination between the committees referred to in Article 56(1) and, where necessary, between the committees and the coordination group;”

(17) In Article 66(g), the figure "67" is replaced by the figure "68".

(18) Article 67 is amended as follows:

(a) In paragraph 3, the first subparagraph is replaced by the following:

“The Agency's revenue shall consist of a contribution from the Community and fees paid by undertakings for obtaining and maintaining Community marketing authorisations and for other services provided by the Agency or the coordination group as regards the fulfilment of its tasks in accordance with in accordance with Articles 107c, 107e, 107g, 107l and 107r of Directive 2001/83/EC.”

(b) Paragraph 4 is replaced by the following:

“4. Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the collection of fees to be paid by marketing authorisation holders for the carrying out of these activities by the Agency.”

(19) Article 82(3) is replaced by the following:

“3. Without prejudice to the unique, Community nature of the content of the documents referred to in points (a) to (d) of Article 9(4) and in points (a) to (e) of Article 34(4), this Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product covered by a single authorisation.”

(20) In Article 83(6), the second sentence is replaced by the following:

“Article 28(1) and (2) shall apply *mutatis mutandis*.”

Article 2

Transitional provisions

1. The requirement for the inclusion of a summary of the essential information necessary to use the medicine safely and effectively in the summary of the product characteristics and the package leaflet provided for in point 3a of Article 11 and in point (aa) of Article 59(1) of Directive 2001/83/EC as amended by Directive .../.../EC, which applies to medicinal products authorised pursuant to Regulation (EC) No 726/2004 by virtue of its Article 9(4)(a) and (d), shall apply to a marketing authorisation granted before the date set out in the second paragraph of Article 3 of this Regulation from renewal of that authorisation or from the expiry of a period of three years starting from that date, whichever is the earliest.

2. The requirement for 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 point (b) of Article 104(3) of Directive 2001/83/EC as amended by Directive .../.../EC, which applies to medicinal products authorised pursuant to Regulation (EC) No 726/2004 by virtue of Article 21 of Regulation (EC) No 726/2004 as amended by this Regulation, shall apply to marketing authorisations granted before the date set out in the second paragraph of Article 3 of this Regulation or from the expiry of a period of three years starting from that date.
3. The procedure under Articles 107n to 107r of Directive 2001/83/EC as amended by Directive .../.../EC, which apply by virtue of Article 28b of Regulation (EC) No 726/2004 as amended by this Regulation, shall apply only to studies which have commenced after the date set out in the second paragraph of Article 3 of this Regulation.

Article 3

Entry into force and application

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

It shall apply from [18 months from the entry into force].

Done at Brussels,

For the European Parliament
The President

For the Council
The President

2008/0260 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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 establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission⁷²,

Having regard to the opinion of the European Economic and Social Committee⁷³,

Acting in accordance with the procedure laid down in Article 251 of the Treaty⁷⁴,

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 use⁷⁵ lays down harmonised rules for the authorisation, supervision and pharmacovigilance of medicinal products within the Community.

⁷² OJ C , , p. .

⁷³ OJ C , , p. .

⁷⁴ OJ C , , p. .

⁷⁵ OJ L 311, 28.11.2001, p. 67.

- (2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse effects of medicinal products placed on the market of the Community, as the full safety profile of medicinal products can only be known once they have entered the market.
- (3) In the light of the experience acquired and following an assessment by the Commission of the Community system of pharmacovigilance, it has become clear that measures are necessary to improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use.
- (4) While taking into account the fact that the regulation of medicinal products should be fundamentally aimed at safeguarding public health, this aim should be achieved by means that do not impede the free movement of safe medicinal products within the Community. It has emerged from the assessment of the Community system of pharmacovigilance that divergent Member State action on safety issues of medicinal products is creating barriers to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Community level should be strengthened and rationalised.
- (5) For the sake of clarity, the definition of adverse reaction should be amended to ensure that it not only covers noxious and unintended effects derived from the authorised use of a medicinal product at the normal doses, but also medication errors and uses outside the authorised summary of the product characteristics, including the misuse and abuse of the product.
- (6) 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 permanently accessible for inspection. The competent authorities should undertake the supervision of those systems. A summary of the pharmacovigilance system should be therefore submitted with the marketing authorisation application and include a reference to the site where the Pharmacovigilance System Master File for the medicinal product concerned is maintained and accessible for inspection.

- (7) The planning of pharmacovigilance for each individual medicinal product by the marketing authorisation holder should take place in the context of a risk management system and should be proportionate to the identified risks, potential risks, and the need for additional information on the medicinal product. It should also be foreseen that any key measures contained in a risk management system are included in the marketing authorisation as conditions.
- (8) In order to ensure the collection of any necessary additional data about the safety of authorised medicinal products, competent authorities should be empowered to require post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and this requirement should be included as a condition of the marketing authorisation.
- (9) Where a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or where there are conditions or restrictions with regard to the safe and effective use of the medicinal product, the medicinal product should be intensively monitored on the market. Patients and healthcare professionals should be encouraged to report all suspect adverse reactions to such medicinal products, and a publicly available list of such medicinal products should be maintained 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 Agency⁷⁶ (hereinafter referred to as the ‘Agency’).
- (10) In order to make it possible for the healthcare professionals and patients to identify easily the most relevant information about the medicines they use, the summary of the product characteristics and the package leaflet should include a concise section on the key information about the medicinal product and information how to minimize its risks and maximize its benefits.

⁷⁶ OJ L 136, 30.4.2004, p. 1.

- (11) Experience has shown that the responsibilities of marketing authorisation holders for the pharmacovigilance of authorised products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of his products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is maintained up to date. As medicinal products could be used outside the terms of their marketing authorisations, these responsibilities should include providing all information available, including the results of clinical trials or other studies, as well as reporting of the use of the medicinal product, which is not in accordance with the summary of the product characteristics. Likewise it is appropriate to ensure that the renewal of marketing authorisations should consider all relevant information collected on the safety of the medicinal product.
- (12) 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 adoption of opinions, transparency, independence and professional secrecy of its members, and the need for cooperation between Community and national bodies.
- (13) With a view to ensuring that the same level of scientific expertise in the area of pharmacovigilance decision-making at both Community and national level, when fulfilling pharmacovigilance tasks the coordination group should be able to rely on the advice of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee of the Agency.
- (14) In order to avoid duplication of work, a single opinion should be adopted by the coordination group for pharmacovigilance assessments concerning products authorised in more than one Member State. The agreement within the coordination group should suffice for pharmacovigilance measures to be implemented throughout the Community. Where no agreement is found in the coordination group, the Commission should be authorised to adopt a decision to that effect, addressed to the Member States.

- (15) A single assessment should also be conducted in the case of pharmacovigilance issues which concern products authorised by the Member States and products authorised in accordance with Regulation (EC) No 726/2004. In such cases, the Commission should adopt harmonised measures for all products concerned on the basis of a Community assessment.
- (16) Member States should operate a pharmacovigilance system to collect information useful in the surveillance of medicinal products including information on suspected adverse drug reactions, on misuse, abuse and medication errors, and ensure its quality through the follow up of suspected adverse drug reaction cases.
- (17) 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.
- (18) 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 Community pharmacovigilance database and data-processing network referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 (hereinafter ‘the Eudravigilance database’).
- (19) In order to increase the level of transparency on the processes of pharmacovigilance, the Member States should create and maintain medicines safety web-portals. To the same end, the marketing authorisation holders should provide the authorities with prior warning about safety announcements and the authorities should provide each other with such a warning.
- (20) Community rules on pharmacovigilance should continue to rely on the crucial safety monitoring role of healthcare professionals, and should take account of the fact that patients are also well placed to report adverse reactions to medicines. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make available to them methods for such reporting.

- (21) As a result of the submission of all 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.
- (22) Requirements for periodic safety update reports should be proportional 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 necessary for generic, well-established use, informed consent, homeopathic, or traditional use registered herbal medicinal products. However, in the interest of public health the authorities should require periodic safety update reports for such products when there is a need to assess their risk or review the adequacy of product information.
- (23) There is a need to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. Provision should be made for a single assessment of periodic safety update reports for medicinal products authorised in more than one Member State. Moreover, procedures should be established to set single frequency and submission dates of periodic safety update reports for all products containing the same active substance or combination thereof.
- (24) 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 Community procedure leading to a harmonised result.

- (25) The Member States should automatically submit certain safety issues related to medicinal products to the Agency thereby triggering a Community assessment of the issue. Therefore it is appropriate to establish rules to ensure an assessment procedure by the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, and rules for the subsequent follow-up as regards the terms of the marketing authorisations with a view to the adoption of harmonised measures across the Community. As this procedure is triggered on the basis of a set of binding criteria, it should take precedence over other procedures which could also be used to address safety issues, such as those referred to in Articles 31 and 36 of Directive 2001/83/EC.
- (26) It is necessary to introduce harmonised guiding principles and regulatory supervision of post-authorisation safety studies that are non-interventional, that are initiated, managed or financed by the marketing authorisation holder, that involve the collection of data from patients or healthcare professionals thus falling outside 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 use⁷⁷. Supervision of such studies should be the responsibility of the national competent authority for studies to be conducted in one Member State and of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee for studies to be conducted in more than one Member State. Provision should also be made for the subsequent follow-up, if appropriate, as regards the terms of the marketing authorisations with a view to the adoption of harmonised measures across the Community.

⁷⁷ OJ L 121, 1.5.2001, p. 34.

- (27) In order to enforce the provisions related to the pharmacovigilance, the Member States should ensure that effective, proportionate and dissuasive penalties are applied to marketing authorisation holders for non-compliance with pharmacovigilance obligations.
- (28) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the national competent authorities. It should be possible to ensure adequate funding for pharmacovigilance activities through the collection of fees. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence.
- (29) It should be possible for Member States to allow, 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 products or of products placed on the market or shortages thereof.

(30) Since the objective of this directive of improving the safety of medicines placed on the market in the Community in a harmonised way across the Member States cannot be sufficiently achieved by the Member States and can be better achieved at Community level, the Community may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. 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.

(30a)⁷⁸ 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 data⁷⁹ 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 data⁸⁰. In order to detect, assess, understand and prevent adverse reactions, identify and take actions to reduce risks and increase 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 EU data protection legislation. This purpose constitutes a substantial public interest which can be justified if identifiable health data are processed only when necessary and parties involved assess this necessity at every stage of the pharmacovigilance process.⁸¹

⁷⁸ Inspired by recital 12 of Regulation (EC) No 1338/2008, OJ L 354 31.12.2009, p. 70-81.

⁷⁹ OJ L 281, 23.11.1995, p. 31.

⁸⁰ OJ L 8, 12.1.2001, p. 1.

⁸¹ **DELETED**: Recitals are not transposed into national law. It is therefore desirable also to include provisions on data protection in the enacting terms. (Compare footnote on Article 107m). Cion: Community law on data protection applies anyway.

- (31) The provisions on the surveillance of medicinal products for human use in Directive 2001/83/EC constitute specific provisions in 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, and repealing Regulation (EEC) No 339/93⁸².
- (31a) In accordance with point 34 of the Interinstitutional Agreement on better law-making⁸³, Member States are encouraged to draw up, for themselves and in the interests of the Community, their own tables illustrating, as far as possible, the correlation between this Directive and the transposition measures, and to make them public.
- (32) Directive 2001/83/EC should therefore be amended accordingly,

⁸² OJ L 218, 13.8.2008, p. 30.

⁸³ 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 amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

“(11) Adverse reaction⁸⁴: A response to a medicinal product which is noxious and unintended.”^{85 86 87 88},

⁸⁴ **DELETED**: Use concept "Therapeutic use-related adverse reaction" instead. (PHV-2)

⁸⁵ **DELETED**: Replace this definition by "Adverse reaction: A noxious and unintended response associated to the use of a medicinal product for the prophylaxis, diagnosis or therapy of disease, or for the restoration, correction or modification of physiological function and for which foreseeable risk prevention or correction actions may come to be considered."(PHV-3)

DELETED: Support.

⁸⁶ **DELETED**: Leave definition now in force unchanged. **DELETED**: Find other ways to create legal basis for including separately "medication errors" and "misuse" in Eudragilance.

⁸⁷ **DELETED**: Replace the proposed definition by "Adverse reaction: A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man in accordance with the summary of product characteristics for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function" and "Misuse of medicinal product: Use of medicinal products which is not in accordance with the summary of product characteristics, including medication errors, and is accompanied by harmful physical or psychological effects". (PHV-6) **DELETED**: Support. **DELETED**: This definition of "Misuse" covers also off-label use.

⁸⁸ **DELETED**: The problem with the definition now in force is the part "at normal doses in man" that should be replaced by "at any dose", which would lead to better reporting and thus facilitate tracing of causal connections. The definition suggested here is too inexact.

DELETED: Support. **DELETED**: In principle prefers the definition now in force, but sees problem with limitation to "normal use" - adverse reactions in off-label use must be reported.

(b) point 14 is replaced by the following:

“(14) Suspected adverse reaction^{89 90}: An adverse reaction in respect of which a causal relationship between the event and the medicinal product cannot be excluded.”⁹¹;

(c) point 15 is replaced by the following:

“(15) Post-authorisation safety study: Any study⁹² with an authorised medicinal product conducted with the⁹³ aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile⁹⁴ of the medicinal product, or of measuring the effectiveness of risk management⁹⁵ measures.”;

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⁸⁹ **DELETED**: Is there really a need for a definition of suspected adverse reaction? Introduce separate definition for "medication error" instead. **DELETED**: Support for a definition of "medication error". **DELETED**: Recalled the U.S. FDA definition of medication error. (PHV-7). Presidency also provided definitions.(PHV-8)

⁹⁰ **DELETED**: Delete this definition and introduce a definition for medication error as follows: "A medication error is any non intentional and inappropriate event (incident) which could have or did lead to an adverse effect, while the medication is in the control of a healthcare professional or a patient." (PHV-9) **DELETED**: Support this text.

⁹¹ **DELETED**: Effects of this definition must be scrutinised. "Reaction" already implicitly indicates a causal relation between the event and the medicinal product.

⁹² **DELETED**: "Any study" is too broad.

⁹³ **DELETED**: "... with the *primary* aim ...". A change in line with **DELETED** suggestion for Article 107n.

⁹⁴ **DELETED**: "confirming the safety profile" could be misunderstood - delete.

⁹⁵ **DELETED**: Need for workable definition of "risk management system" in order to take action when risks are detected.

⁹⁶ **DELETED**: Add the following definition: "A medication error is any preventable event relating to administration of a medicinal product, that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer". (PHV-14)

⁹⁷ **DELETED**: Add the following two definitions: (PHV-49)

"Off-label use accompanied by harmful effects means use of a medicinal product which is not in accordance with the summary of product characteristics and which is accompanied by harmful physical or psychological effects"

"Medication error is the administration of any medication incorrectly, i.e. dosage, selection of drug, selection of resident, time or method of administration, omission of prescribed medication, or the administration of a medication without a valid order, and which is accompanied by harmful physical or psychological effects".

DELETED: Against these definitions, especially for off-label use.

(d) The following points 28b, 28c and 28d 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 interventions.

(28c) Pharmacovigilance system: a system utilized by marketing authorisation holders 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.

(28d) Pharmacovigilance system master file: A detailed description of the pharmacovigilance system utilized 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 system⁹⁸ which shall include the following elements:

- proof that the applicant has the services of a qualified person responsible for pharmacovigilance;
- the Member State where the qualified person resides⁹⁹;
- the contact details for 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 site where the pharmacovigilance system master file for the medicinal product is maintained.”;

(b) the following point (iaa) is inserted:

“(iaa) A detailed description of the risk-management system^{100 101} which the applicant will introduce for the medicinal product concerned.”

⁹⁸ **DELETED**: Suggests a European database containing Pharmacovigilance systems that should be updated by the Reference Member State and the Rapporteur.

⁹⁹ **DELETED**: Why not the Member State where the qualified person works? **DELETED**: Support.

¹⁰⁰ **DELETED**: The risk management system should be proportionate to the risks with the product, including the possibility of no pharmacovigilance system for certain products.

¹⁰¹ **DELETED**: Distinguish between "risk management system" and "risk management plan".

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

“(l) Copies of the following:

- any authorisation obtained in another Member State^{102 103}, including a summary of the data contained in periodic safety reports and adverse reactions reports, or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;²
- copies of¹⁰⁴ 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. Copies of 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 authorization, whether in the Community or in a third country, and the reasons for such a decision.”

(d) point (n) is deleted.

¹⁰² **DELETED**: Move "or in a third country" so that it follows after "another Member State".

¹⁰³ **DELETED**: Suggests rewording “Any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, including a summary of the data contained in the periodic safety reports and adverse reaction reports, together with a list of those Member States in which an application for an authorization submitted in accordance with this Directive is under examination.”

¹⁰⁴ **DELETED**: Delete "copies of ". (PHV-5)

(e) the following subparagraphs are added:

“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 point (l) of the first subparagraph shall be updated¹⁰⁵ on a regular basis¹⁰⁶.”

3. Article 11¹⁰⁷ is amended as follows:

(a) the following point 3a is inserted:¹⁰⁸

“(3a) a summary of the essential information¹⁰⁹ necessary to use the medicine safely and effectively;

(b) the following subparagraph is added:

“For the purposes of point (3a) of the first subparagraph, for medicinal products included on the list¹¹⁰ referred to in Article 23 of Regulation (EC) No 726/2004, the summary shall include the statement: “This medicinal product is under intensive monitoring. All¹¹¹ suspected adverse reactions should be reported to <name and web-address of the national competent authority>¹¹².”

¹⁰⁵ **DELETED**: Is the updating limited to point (l)? **DELETED**: Support.

¹⁰⁶ **DELETED**: "regular basis" is unclear, it should be a fixed time period (i.e. six months).

¹⁰⁷ **DELETED**: Questions the usefulness of including a reference to the intensive monitoring in the SPC. (PHV-5)

¹⁰⁸ **DELETED**: Opposes insertion of point (3a) as its implementation seems difficult. (PHV-9)

¹⁰⁹ **DELETED**: The entire Summary of Product Characteristic SPC should be read, therefore a section with only "essential information" should not be introduced. **DELETED**: Scrutiny reservation.

¹¹⁰ **DELETED**: Doubts and questions on management of the list.

¹¹¹ **DELETED**: Prefer that only serious events be reported.

¹¹² **DELETED**: Replace this subparagraph with: "The summary of the product characteristics shall include the statement: “Any suspected adverse reactions should be reported to....” (to be completed in accordance with the national spontaneous reporting system)".(PHV-9)

DELETED: Support.

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

“1. Articles 3(1) and (2), 4(4), 6(1), 12, 17(1), 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, 111(1) and (3), 112, 116, 117, 118, 122, 123, 125, 126, second subparagraph, and 127 of this Directive as well as Commission Directive 2003/94/EC(*) 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 figure ‘27’ is replaced by the figure ‘28’;

(b) In paragraph 2, the figure ‘27’ is replaced by the figure ‘28’;

6. In Article 18, the figure ‘27’ is replaced by the figure ‘28’.

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

“3. The national competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for their fulfilment^{113 114}, for each medicinal product which they have authorised.

¹¹³ **DELETED**: Delete "together with any deadlines for their fulfilment".

¹¹⁴ **DELETED**: Add "where appropriate".

4. The national competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials and 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 of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The national competent authorities shall make publicly accessible without delay the assessment report, 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.”

8. The following Article 21a is inserted:

“Article 21a

A marketing authorisation may be granted subject to one or more of the following conditions:

- (1) to take certain measures for the safe use of the medicinal product contained in the risk management system;
- (2) to conduct post-authorisation safety studies;
- (3) to comply with requirements on adverse reaction¹¹⁵ recording or reporting which are stricter than those referred to in Title IX;
- (4) any other conditions or restrictions with regard to the safe and effective use of the medicinal product.

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The marketing authorisation shall lay down deadlines¹¹⁷ for the fulfilment of the conditions where necessary. “

¹¹⁵ **DELETED**: Prefers "suspected adverse reaction".

¹¹⁶ **DELETED**: Add "(5) the adequacy of the Pharmacovigilance system".

¹¹⁷ **Cion**: Explained that these deadlines are the same as those in Article 21 paragraph 3.

9. Article 22 is replaced by the following:

“Article 22

In exceptional circumstances¹¹⁸ and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

This 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 authorisation shall be linked to the annual reassessment¹¹⁹ of these conditions.”

10. The following Articles 22a and 22b are inserted:

“Article 22a

1. After the granting of a marketing authorisation, the national competent authority may¹²⁰ require a marketing authorisation holder to conduct a post-authorisation safety study if there are concerns about the risks¹²¹ of an authorised medicinal product. The requirement shall be made in writing, provide a detailed justification and include the objectives and timeframe for submission and conduct of the study.

¹¹⁸ **DELETED**: Risk that "in exceptional circumstances" is too loose a condition - could be misused.

¹¹⁹ **DELETED**: Annual reassessment could overlap with periodic reporting, prefers provisions on "special reporting".

¹²⁰ **DELETED**: All new products must be subject to intensive monitoring

¹²¹ **DELETED**: Prefers the term "safety hazards" which is used in Article 1 point 15.

2. The national competent authority shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement¹²² within a time limit which it shall specify, if the marketing authorisation holder requests this within 30-days of receipt of the written requirement.
3. On the basis of explanations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the requirement. Where the national competent authority confirms the requirement, the marketing authorisation shall be varied¹²³ to include the requirement as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 22b

1. The marketing authorisation holder shall be required to incorporate any conditions or requirements 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 or requirements pursuant to Articles 21a, 22 or 22a.

The Agency shall include the medicinal products concerned in the list referred to in Article 23 of Regulation (EC) No 726/2004. The Agency shall remove a medicinal product from the list when the national competent authority concludes that the conditions or requirements have been fulfilled and that, following the assessment of any data resulting from the implementation of the conditions or requirements, the risk-benefit balance remains positive.”

¹²² **DELETED**: Need for rewording - a Marketing Authorisation Holder cannot provide explanation on a requirement he was not the author of; to this aim "explanations" could be replaced by "objections".

¹²³ **DELETED**: What is the procedure for variation - shall the applicant submit an application? (PHV-5)

11. Article 23 is replaced by the following:

“Article 23

1. After an 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 supply to the national competent authority any new information which might entail the amendment of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11, or 32(5), or Annex I.

In particular, he 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 for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use 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 not in accordance with the summary of the product characteristics.

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

4. In order that the risk-benefit balance may be continuously assessed, the national competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

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

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 adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and all variations introduced since the marketing authorisation was granted, at least nine 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 or to insufficient exposure¹²⁴ to the product, to proceed with one additional five-year renewal in accordance with paragraph 2.”

13. The title "Chapter 4 Mutual recognition and decentralised procedure" is deleted¹²⁵.

¹²⁴ In reply to an explanation that "insufficient exposure" means that there are not enough data on the safety profile of the product, **DELETED** pointed out that there are some very safe products that are seldom used and for which an additional five year period is unnecessary.

¹²⁵ **DELETED**: What is the effect for purely national authorisations of moving Article 27 from the chapter on mutual recognition to the chapter on procedures for marketing authorisation. Cion: There is no change in the competence of the CMD.

14. Article 27 is amended as follows:¹²⁶

(a) Paragraph 1 is 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, 107l and 107r;¹²⁷
- (c) the examination of questions related to the variations to the terms 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, the coordination group shall ~~be assisted by~~ rely on¹²⁸ the scientific assessment and advice of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee referred to in Article 56(1)(aa) of Regulation (EC) No 726/2004.”

¹²⁶ **DELETED**: General scrutiny reservation on provisions concerning CMD. According to Articles 107g and 107l the opinions of the coordination group will be binding, therefore provisions on the powers of the coordination group should be set out in the Regulation and not in the Directive.

¹²⁷ **DELETED**: Replace this subparagraph by "the examination of any question relating to the risk/benefit ratio of a drug by relying on the opinion of the Risk Assessment and Pharmacovigilance Committee".(PHV-9) **DELETED**: Support. **DELETED**: Positive scrutiny reservation.

¹²⁸ **DELETED**: Reservation, suggests "take into account " instead of "rely on". **DELETED**: "rely on" is too strong - "base itself on the scientific assessment" would be better. **DELETED** Prefer "rely on".

(b) In paragraph 2, the following subparagraphs are added:

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

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

(c) The following paragraphs 4, 5, 6 and 7 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.

6.¹²⁹ Save where otherwise provided for in this Directive, **the Member States within** the coordination group shall use **its their** best endeavours to ~~take decisions~~ reach a position¹³⁰ by consensus **on the action to be taken**. If such a consensus cannot be reached, the position of the majority¹³¹ of **members the Member States within the coordination group** shall prevail.

¹²⁹ **DELETED**: Suggests the following text for this paragraph:

~~"Save where otherwise provided for in this Directive, the Member States 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 within the coordination group shall prevail."~~ (PHV-38)

¹³⁰ **DELETED**: "position" is not the right word, maybe "opinion". **DELETED**: reservation on the changes to this article.

¹³¹ **DELETED**: clarify the meaning of "majority".

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.”

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15. After Article 27 the following is inserted:

“Chapter 4 Mutual recognition and decentralised procedure”

¹³² **DELETED**: Add the following paragraph: “If the coordination group proposes to disagree with the draft opinion of the Pharmacovigilance Risk Assessment Committee, it shall not reach a final position without first notifying that committee of the reasons for its view and affording that committee an opportunity to review the draft opinion it gave in the light of those reasons. The coordination group shall take account of any revised draft opinion from the Pharmacovigilance Risk Assessment Committee before reaching its final position.”
(AFM-35)

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

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

“The Member States or the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community 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 a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary.”¹³³

(b) the following subparagraph is inserted after the first subparagraph:¹³⁴

“However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i¹³⁵ to 107l shall apply.”

17. In Article 36(1) the following subparagraph is added:¹³⁶

“However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107l shall apply.”

¹³³ **DELETED**: There is need for further consideration whether the effect of Article 107g (2), making the CMD opinions binding, is desired and whether it complies with the mandate of the CMD.

¹³⁴ **DELETED**: Suggests the deletion of this proposed subparagraph and the insertion, as third subparagraph in Article 31, of the following text : "Where the matter relates to the protection of public health and safety issues, the procedure laid down in Articles 107i to 107l shall apply" (PHV-47 and PHV-58).

¹³⁵ **DELETED**: There are many criteria listed in Article 107i(1), so when does paragraph (a) apply? **Cion**: Article 107i is for severe cases, Article 31 is for less severe cases.

¹³⁶ **DELETED**: Suggests the deletion of Article 36 (PHV-47 and PHV-58).

18. Article 59(1) is amended as follows:^{137 138}

(a) the following point (aa) is inserted:

“(aa) a summary of the essential information necessary to use the medicine safely and effectively;”^{139 140}

(b) the following second and third subparagraphs are added:

“The information referred to in point (aa) of the first subparagraph shall be presented in a box surrounded by a black border. Any new or amended text shall for a period of 1-year be presented in bold text and preceded by the following symbol ****** and text "New information".

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included "This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority>".”

¹³⁷ **DELETED**: Against specific summary of the essential information - the leaflet as a whole is needed to give the necessary essential information; **DELETED**: Support. **DELETED**: Similar ideas.

¹³⁸ **DELETED**: Delete points (a) and (b) and replace them with the following text: "The package leaflets shall include the statement: “Any suspected adverse reactions should be reported to ...” (to be completed in accordance with the national spontaneous reporting system)". (PHV-9) **DELETED**: Support.

¹³⁹ **DELETED**: Against any form of summary. **DELETED**: Opposed at this stage.

¹⁴⁰ **DELETED**: Agree with Cion proposal.

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

"3. When the product is not intended to be delivered directly to the patient¹⁴¹, or when the product is necessary to address severe availability problems, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars¹⁴² should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State in which the product is placed on the market."¹⁴³

20. In Article 65, the following point (g) is added:¹⁴⁴

“(g) the summary of the essential information necessary to use the medicine safely and effectively provided for in Article 11(3a) and Article 59(1)(aa).”

¹⁴¹ **DELETED**: Replace " not intended to be delivered directly to the patient" by "reserved for use in public health institutions only". (PHV-2)

¹⁴² **DELETED**: Replace the text starting with 'that certain particulars ...' by "referred to in paragraphs 1 and 2 of this article". (PHV-2)

¹⁴³ In order to increase transparency in the application of Article 63(3), **DELETED** also suggests to add the following classification in Article 70(2) under Title VI "Classification of medicinal products":

"(d) medicinal products, because of their pharmaceutical characteristics or novelty or in the interest of public health, reserved for use in public health institutions only.". (PHV-2)

¹⁴⁴ **DELETED**: Delete point (g).(PHV-9); **DELETED**: Agree that it is superfluous.

21. 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 Community pharmacovigilance activities.

The pharmacovigilance system shall be used to collect¹⁴⁵ information on the risks of medicinal products as regards patients' or public health. That information shall particularly refer to adverse reactions in human beings,¹⁴⁶ arising from use of the product within the terms of the marketing authorisation as well as from any other use, including¹⁴⁷ overdose, misuse¹⁴⁸, abuse, medication errors¹⁴⁹, and those occurring in the course of studies with the medicinal product or after occupational exposure.

¹⁴⁵ **DELETED**: Replace the rest of this sentence with "all information on undesirable effects".

¹⁴⁶ **DELETED**: Delete the rest of this sentence since examples could be misleading.

DELETED: Replace rest of sentence with "whatever the conditions of use".

¹⁴⁷ **DELETED**: use "adverse clinical consequences" instead of giving a list of examples.

¹⁴⁸ **DELETED**: Delete "misuse"; **DELETED**: Replace by "off-label use"; **DELETED**: Add "off-label use"; **DELETED**: "misuse" is important concept and should remain in text. Could consider to include "off-label use".

¹⁴⁹ **DELETED**: A definition of "medication error" is needed; **DELETED**: Definitions of "medication error" exist in national legislations but it would be useful to have a definition at European level.

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 as necessary. They shall perform a regular audit¹⁵⁰ of their pharmacovigilance system and report the results¹⁵¹¹⁵² to the Commission on [insert concrete date - two-years after the date of transposition referred to in Article 3(1)] at the latest and then every two years thereafter.
3. Each Member State shall designate a competent authority for the conduct of pharmacovigilance tasks.
4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonization and standardization of technical measures in pharmacovigilance.

Article 102

The Member States shall:

- (1) take all appropriate measures to encourage¹⁵³ doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority or the marketing authorisation holder;
- (2) ensure that adverse reaction¹⁵⁴ reports¹⁵⁵ contain the highest quality¹⁵⁶ ¹⁵⁷information possible;

¹⁵⁰ **DELETED**: Clarify the contents of "regular audit". In favour of a centralised audit, led by Cion in consultation with the MS on the PhV system relating to data collection and transmission of ADR reports only. (PHV-18)

¹⁵¹ **DELETED**: Suggests that the Commission in co-operation with the respective Member State shall report on the state of the national pharmacovigilance system.

¹⁵² **DELETED**: Clarify the reporting obligations better.

¹⁵³ **DELETED**: Replace "to encourage" by "to oblige"; **DELETED**: asked for specific examples of encouragement measures.

¹⁵⁴ **DELETED**: Change to "*suspected* adverse reaction".(PHV-11)

¹⁵⁵ **DELETED**: These reports should not concern individual cases, they must be epidemiological reports.

¹⁵⁶ **DELETED**: Replace "highest quality" by "accurate and verifiable". **DELETED**: Reservation.

DELETED: Impossible for Member States to ensure quality as information comes from third

- (3) through the methods of collecting information and where necessary through the follow up of adverse reaction¹⁵⁸ reports, ensure that any biological¹⁵⁹ medicinal product prescribed, dispensed, or sold in their territory which is the subject of an adverse reaction report is identifiable;
- (4) 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 (1) of the first paragraph the Member States may impose specific requirements on doctors, pharmacists and other health-care professionals in respect of the reporting of suspected serious or unexpected adverse reactions.

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.

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 be required to operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the system under Article 101(1).
2. The marketing authorisation holder shall by means of the system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

parties.

¹⁵⁷ **DELETED**: Supports **DELETED**, and wants to add "for proper evaluation" after "information".

¹⁵⁸ **DELETED**: Change to "*suspected* adverse reaction".(PHV-11)

¹⁵⁹ **DELETED**: The notion of "biological products" varies between Member States; **DELETED**: Delete "biological".

The marketing authorisation holder shall be required to 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 followed.

3. As part of the pharmacovigilance system, the marketing authorisation holder shall be required to:
 - (a) have permanently and continuously¹⁶⁰ 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 minimization measures which are contained in the risk management plan or which are laid down as conditions or requirements in the marketing authorisation pursuant to Articles 21a, 22 or 22a;
 - (e) assess updates to the risk management system and monitor pharmacovigilance data to determine whether there are new or changed risks 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 in the Community and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details¹⁶¹ of the qualified person to the competent authority and the Agency.¹⁶²

¹⁶⁰ **DELETED**: Clarify "permanently and continuously". Does the person have to be an employee?

¹⁶¹ **DELETED**: Add "CV or qualifications". Qualification of a medical doctor or a pharmacist needed.

¹⁶² **DELETED**: Add at the end of this paragraph "This should not preclude the nomination of a person responsible for pharmacovigilance at national level, in order to ensure compliance with pharmacovigilance activities"(PHV-11). **DELETED**: support. **DELETED**: Scrutiny reservation.

*Article 104a*¹⁶³

1. By way of derogation from point (c) of Article 104(3), holders of marketing authorisations granted before [insert concrete date - date set out in the second subparagraph of Article 3(1) of Directive .../.../EC] shall be required to operate a risk management system¹⁶⁴ only if paragraphs 2, 3 and 4 of this Article are complied with.
2. The national competent authority may require a marketing authorisation holder to operate a risk management system, as referred to in point (c) of Article 104(3), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. To this effect, the national competent authority shall also require¹⁶⁵ 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 requirement shall be made in writing, provide a detailed justification, and 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 present¹⁶⁶ explanations on the requirement within a time limit which it shall specify, if the marketing authorisation holder requests this within 30 days of receipt of the written requirement.

¹⁶³ **DELETED**: Clarify the overall aim of this Article. Better to always require a risk management system and allow exemptions than the approach chosen here. **DELETED**: Support

¹⁶⁴ **DELETED**: Will the risk management system be compulsory for new products but not for old?

¹⁶⁵ **DELETED**: Marketing Authorisation Holder must be obliged to submit description of Risk Management System automatically, without requirement from NCA

¹⁶⁶ **DELETED**: Add "written".(PHV-10)

4. On the basis of ¹⁶⁷ explanations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the requirement¹⁶⁸. Where the national competent authority confirms the requirement,¹⁶⁹ the marketing authorisation shall be varied as appropriate to include measures of the risk management system as conditions of the marketing authorisation as referred to in point 1 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.

The first paragraph shall not preclude the collection of fees to be paid by marketing authorisation holders for the carrying out of those activities by the national competent authorities.

¹⁶⁷ **DELETED**: Add "written".(PHV-10)

¹⁶⁸ **DELETED**: Add a time limit, i.e. "within 30 days".(PHV-10)

¹⁶⁹ **DELETED**: Add the following text "a new timeframe for the submission of the requested detailed description of the risk-management system shall be taken into account, if necessary. Further, ...".(PHV-10)

CHAPTER 2

Transparency and communications

*Article 106*¹⁷⁰

Each Member State shall set up and maintain a national medicines safety web-portal¹⁷¹ which shall be linked to the European medicines safety web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines safety web-portals, the Member States shall make public at least the following^{172 173}:

- (1) risk management systems for medicinal products authorised in accordance with this Directive;
- (2)¹⁷⁴ the list of medicinal products under intensive monitoring referred to in Article 23 of Regulation (EC) No 726/2004;

¹⁷⁰ **DELETED**: Considers the text of this Article as too detailed and suggests to replace by "Each Member State shall ensure that relevant information on drug safety is publicly available, providing means for the electronic reporting of suspected adverse drug reactions by healthcare professionals and patients. The minimum information to be publicly available should be defined on the guidelines referred to in Article 108 of this Directive."(PHV-11)

¹⁷¹ **DELETED**: Suggests to use EMEA web-portal for pharmacovigilance and national web-portals that link to EMEA. **DELETED**: Requires that the information is provided in a language understood by all users of the EMEA web-portal.

¹⁷² **DELETED**: MS should decide what information should be made available and how to do it.

¹⁷³ **DELETED**: A portal including also SPCs, leaflets and assessment reports would be more useful.

¹⁷⁴ **DELETED**: Delete this point.

- (3)¹⁷⁵ web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients based on the forms referred to in Article 25 of Regulation (EC) No 726/2004.¹⁷⁶

*Article 106a*¹⁷⁷

1. As soon as the marketing authorisation holder has the intention to make a public announcement relating to information on pharmacovigilance concerns to the use of a product, and in any event¹⁷⁸ before the public announcement is made, he shall be required to inform the Member State competent authorities¹⁷⁹, the Agency and the Commission.

The marketing authorisation holder shall be required to 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 twenty-four hours prior to a public announcement relating to information on pharmacovigilance concerns.

¹⁷⁵ **DELETED**: This point needs rewording - provisions are needed on what shall be reported rather than how. **DELETED**: Keep existing system.

¹⁷⁶ **DELETED**: Suggests that for MS whose database is Eudravigilance an on-line reporting form be made available on the website of EMEA. (PHV-18)

¹⁷⁷ **DELETED**: Scrutiny reservation, holds that the concept in the present Article 104(9) "prior or simultaneous notification" should be kept.

¹⁷⁸ **DELETED**: Add "*at least 24 hours* before..."(PHV-11) **DELETED**: Support.

¹⁷⁹ **DELETED**: Add "electronically".

- 3.¹⁸⁰ 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 common safety messages and the timetables for their distribution. The Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall, at the request of the Agency, provide advice on those safety announcements.

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

¹⁸⁰ **DELETED**: Replace the two paragraphs of point 3 by this text: "For active substances contained in medicinal products authorised in more than one Member State, Member States shall make all reasonable efforts to agree on common safety messages and the timetables for their distribution."(PHV-11)

CHAPTER 3

Recording, reporting and assessment of pharmacovigilance data

Section 1

Recording and reporting of adverse reactions

Article 107

- 1.¹⁸¹ Marketing authorisation holders shall be required to record all suspected adverse reactions in the Community or in third countries which are brought to their attention, whether reported spontaneously by patients or¹⁸² healthcare professionals or occurring in the context of a post-authorisation safety¹⁸³ study.

Marketing authorisation holders shall be required to ensure that those reports are accessible at a single point within the Community.

By way of derogation to 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/EC¹⁸⁴.

¹⁸¹ **DELETED**: Relation between 107(1) and 107a(1) leads to a risk of duplication regarding the information received from MAH and MS. What will the rules be for information received from healthcare professionals and patients? **DELETED**: Support, reports by healthcare professionals and patients directly to the EMEA.

¹⁸² **DELETED**: Delete "patients or" and add as a last sentence "Patient reports coming from a verifiable source should also be recorded." (PHV-17). **DELETED**: Against.

¹⁸³ **DELETED**: Replace "safety study" by "study undertaken within the EU or in third countries". Alternatively, delete from "whether reported ..." until the end of the sentence.

¹⁸⁴ **DELETED**: Delete this sentence. (AFM-14) **DELETED**: Support.

- 2.¹⁸⁵ The marketing authorisation holder may not refuse reports of suspected adverse reactions received electronically from patients and health-care professionals.
3. Marketing authorisation holders shall be required to submit electronically to¹⁸⁶ the database and¹⁸⁷ data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as ‘the Eudravigilance database’)¹⁸⁸ ¹⁸⁹ information on all serious suspected adverse reactions that occur in the Community and in third countries¹⁹⁰ within 15 days following the receipt of the report or, in the absence of a report, following¹⁹¹ the day on which the holder concerned gained knowledge¹⁹² of the event.

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¹⁸⁵ **DELETED**: Delete this paragraph. (PHV-17)

¹⁸⁶ **DELETED**: Add "both".(PHV-21)

¹⁸⁷ **DELETED**: Replace "to the database and" by "information on serious suspected adverse reactions that occur in the Community to the Member State on whose territory the incident occurred, unless otherwise specified by the Member State, by means of the" (PHV-17)

¹⁸⁸ **DELETED**: Insert "and the national competent authorities,". (PHV-21). **DELETED**: support, but proposes an optional system where MAH can be required by MS to notify them of adverse reactions occurring on their territory. **DELETED**: support

¹⁸⁹ **DELETED**: Support the Commission on one central database. **DELETED**: Stress importance that national competent authorities are informed about notifications and direct transmissions to the Eudravigilance database.

¹⁹⁰ **DELETED**: Delete "(hereinafter referred to as ‘the Eudravigilance database’) information on all serious suspected adverse reactions that occur in the Community and in third countries" (PHV-17)

¹⁹¹ **DELETED**: Delete "the receipt of the report or, in the absence of a report, following"(PHV-22).

DELETED: Support.

¹⁹² **DELETED**: Count 15 days from the day when the MAH gained knowledge.

¹⁹³ **DELETED**: Add the following subparagraph: " Marketing authorisation holders shall be required to submit electronically information on serious suspected adverse reactions that occur in third countries to the database referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as "the Eudravigilance database') within 15 days following the receipt of the report or; in the absence of a report, following the day on which the holder concerned gained knowledge of the event." (PHV-17)

Marketing authorisation holders shall be required to submit electronically to the Eudragilance database information on all non-serious suspected adverse reactions¹⁹⁴ that occur in the Community¹⁹⁵, within 90¹⁹⁶ days following¹⁹⁷ the receipt of the report or, in the absence of a report, following the day on which the holder concerned gained knowledge of the event.¹⁹⁸

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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 Eudragilance database the suspected adverse reactions recorded in the listed medical literature²⁰⁰, but they shall monitor all other medical literature and report any suspected adverse reactions.^{201 202}

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- 194 **DELETED**: Suggests to replace "non-serious suspected adverse reactions" with "suspected adverse reactions confirmed as non-serious". (PHV-19) **DELETED**: A guidance document could clarify what a "non-serious adverse reaction" is since it is difficult to clarify just by changing the wording. **DELETED**: Not necessary since "serious adverse reactions" are defined in the directive.
- 195 **DELETED**: Add: "and in third countries".(PHV-22) **DELETED**: Support.
- 196 **DELETED**: 30 days.
- 197 **DELETED**: Delete "the receipt of the report or, in the absence of a report, following".(PHV-22)
- 198 **DELETED**: Delete this subparagraph. (PHV-17) **DELETED**: Delete this subparagraph.
- 199 **DELETED**: Add a new subparagraph :
"Marketing authorisation holders can be required by Member States to notify them of adverse reactions occurred in their territory within the same deadlines as mentioned in the two previous subparagraphs." (PHV-22)
- 200 **DELETED**: Delete the rest of the sentence.
- 201 **DELETED**: Rewording needed. Sounds like MAH don't have to report adverse reactions already known in medical literature.
- 202 **DELETED**: Delete this subparagraph. (PHV-17)
- 203 **DELETED**: Add the following subparagraph:
"The Agency, in collaboration with Member States, shall make provisions in order to avoid replication of literature reports sent by marketing authorisation holders, by means of the procedure laid down in chapter 5." (PHV-41)

4. Member States^{205 206} shall access²⁰⁷ reports on adverse reactions through the Eudravigilance database^{208 209} and shall²¹⁰ assess the quality^{211 212} of the data received from marketing authorisation holders²¹³. They²¹⁴ shall, as appropriate, involve patients and health-care professionals in the²¹⁵ follow up of any reports they receive and ²¹⁶request follow up of such reports to be conducted by the marketing authorisation holders²¹⁷. The marketing authorisation holders²¹⁸ shall be required to report any follow up information received to the Eudravigilance database²¹⁹.

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- 204 **DELETED**: To mirror changes suggested to paragraph 2a of Article 24 of the Regulation, the following paragraph should be inserted :
 "3a. Individual adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically immediately upon receipt to the national competent authority of the Member State where the reaction occurred. In addition, adverse reaction reports and follow-ups from other countries shall be transmitted to the national competent authority functioning as Reference Member State for the respective medicinal product or other medicinal products with the same active substance."
 (PHV-56)
- 205 **DELETED**: Add " and marketing authorisation holders" (PHV-22)
- 206 **DELETED**: Make clear that it is the Member State where the event occurred. **DELETED**: Support.
- 207 **DELETED**: Replace "shall access reports" by "shall have access to reports" (PHV-56)
- 208 **DELETED**: Concern about the reliability and functionality of the database. **DELETED**: Similar concerns.
- 209 **DELETED**: Replace "database and shall" by "database. Member States shall". (PHV-22)
- 210 **DELETED**: Delete "access reports on adverse reactions through the Eudravigilance database and shall" (PHV-17)
- 211 **DELETED**: What is meant by "quality"? Will there be a scientific evaluation of the report?
- 212 **DELETED**: Questions on "quality of data". Guidelines to be drafted under 108(2)? How should notification occur? **DELETED**: Support.
- 213 **DELETED**: It must be made clear who has the responsibility. **DELETED**: similar concerns
- 214 **DELETED**: Replace "They" by "Member States". (PHV-22)
- 215 **DELETED**: Add "validation and". (PHV-20)
- 216 **DELETED**: Add "may".
- 217 **DELETED**: Delete "by the marketing authorisation holders" (PHV-22). **DELETED**: support
- 218 **DELETED**: Replace "The marketing authorisation holders" by "Member States and marketing authorisation holders". (PHV-22)
- 219 **DELETED**: Delete "to the Eudravigilance database". (PHV-17) Suggests to amend this paragraph as follows: "Member States shall collaborate in the detection of duplicates. For this purpose, Member States may, as appropriate, involve patients and health-care professionals (rest unchanged)" (PHV-41). **DELETED**: Support.

Article 107a

1. The Member States shall record all suspected adverse reactions that occur in their territory which are brought to their attention from healthcare professionals and patients.

Member States shall ensure that reports of such reactions are submitted by means of the national medicines safety web-portals^{220 221 222 223}.

- 2.²²⁴ Member States shall, within 15 days²²⁵ following the receipt of the reports referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

Marketing authorisation holders shall access those reports through the Eudravigilance database.²²⁶

²²⁰ **DELETED**: How should the national safety web-portals be set up and what room for manoeuvre do MS have?

²²¹ **DELETED**: Are the national safety web-portals the only means of reporting or just an alternative? The content of the web-portals should be further clarified.

²²² **DELETED**: What obligations do national competent authorities have except for reporting of adverse reactions? Ensuring data quality? Special requirements how to store reports?

²²³ **DELETED**: Delete this subparagraph. (PHV-17)

²²⁴ **DELETED**: Replace paragraph 2 with the following text and add a new paragraph 2a :
"2. Member States shall submit electronically to the Eudravigilance database all serious reports received, within 15 days following the receipt of the reports, and all non-serious reports received, within 90 days following the receipt of the reports. (PHV-41)
~~2a. Member States shall have full and permanent access to the Eudravigilance database."~~
(PHV-17)

²²⁵ **DELETED**: Insert "for suspected serious adverse reactions and within 90 days for suspected non-serious adverse reactions".(PHV-21) **DELETED**: Support.

²²⁶ **DELETED**: This subparagraph should become paragraph 3 and be amended as follows:
"Marketing authorisation holders shall access the reports mentioned in paragraph 2 through the Eudravigilance database." (PHV-41)

3. The Member States shall ensure that reports of medication errors^{227 228 229} brought to their attention in the framework of suspected adverse reaction reporting for medicinal products are made available to the Eudragilance database and to any authorities 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 the authorities responsible for patient safety within that Member State.

Section 2

Periodic safety update reports²³⁰

Article 107b^{231 232}

1. Marketing authorisation holders shall be required to submit to the Agency²³³ periodic safety update reports containing:
- (a) summaries of data relevant to the benefits and risks of the medicinal product;
 - (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.

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²²⁷ **DELETED**: Need for a definition of "medication errors". **DELETED**: Support.

²²⁸ **DELETED**: Medication errors must be kept separate from other adverse reactions in the database.

DELETED: Support.

²²⁹ **DELETED**: What will happen to the information on medication errors? Possibility of important legal consequences for the (reporting) medical professional has to be taken into account.

DELETED: Similar concerns.

²³⁰ **DELETED**: Has tabled a comprehensive new text on the Periodic Safety Update Reports, see PHV-53

²³¹ **DELETED**: Scrutiny reservation on the article. No value added of a centralised system here.

²³² **DELETED**: Discrepancy between article 107b and 107c. Need for simplification.

²³³ **DELETED**: Add: "and the national competent authority" **DELETED**: Support.

²³⁴ **DELETED**: Insert "(d) an estimate of the patients' exposure 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 distribute the reports referred to in paragraph 1 to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, the Committee for Medicinal Products for Human Use and the coordination group.
3. By way of derogation from paragraph 1 of this Article, holders of marketing authorisations for medicinal products referred to in Articles 10²³⁵, 10a²³⁶ or 10c, and holders of registrations for medicinal products referred to in Articles 14 or 16a, shall be required to submit periodic safety update reports for such products only 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) where a Community reference date and the corresponding frequency of submission of periodic safety update reports have been determined in accordance with paragraphs 3 and 4 of Article 107c, subject to the conditions laid down in Article 107c(5)²³⁷.

*Article 107c*²³⁸

1. The frequency²³⁹ of submission of the periodic safety update reports shall be specified in the marketing authorisation.²⁴⁰

It shall be counted from the date of the authorisation.

²³⁵ **DELETED**: Doubts about the derogation of generics since they constitute a large proportion of the market. If original is no longer on the market, no PSUR will be available. **DELETED**: Support. **DELETED**: No PSUR should be needed or generics which have been on the market for more than 10 years. **DELETED**: maintain PSUR on generics.

²³⁶ **DELETED**: No reason to exclude homeopathic and traditional herbal medicines. **DELETED**: Support waiver for homeopathic and traditional products.

²³⁷ **DELETED**: Replace "subject to the conditions laid down in Article 107c(5)" by "when CMD(h) or CHMP finds it necessary, or". Also add a new point (c) "upon request whenever a Member State finds it necessary after the granting of a marketing authorisation" (PHV-50)

²³⁸ **DELETED**: In conjunction with the changes proposed for Article 107b, it is suggested that Article 107c be deleted (PHV-50)

²³⁹ **DELETED**: What are the obligations of the Member State that issued the Marketing Authorisation if CMD agrees to a change of the frequency? (PHV-14)

²⁴⁰ **DELETED**: a general derogation should be possible for certain pharmaceuticals.

2. Holders of marketing authorisations which were granted before [insert concrete date - date set out in the second subparagraph of Article 3(1)], 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 3, 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 product has not yet been placed on the market, at least every six months after authorisation and until the placing on the market;
- (b) where a product has been placed on the market, at least every six months during the first two years following the initial placing on the market, once a year for the following two years and at three-yearly intervals thereafter.²⁴¹
3. Where products that are subject to different marketing authorisations contain the same active substance or combination thereof, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended to provide for a single frequency for the submission of the reports relating to all such products and to provide for a Community reference date from which the frequency is counted.^{242 243}

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

²⁴¹ **DELETED**: Need for simplification. Reports every six months replaced by annual reports and annual reports replaced by reports every three years after the first renewal of marketing authorisation. **DELETED**: Support.

²⁴² **DELETED**: Who or what triggers the determination of the frequency? If it is the MAH, how is it triggered?

²⁴³ **DELETED**: Amend the second part of point 3 as follows : "... paragraphs 1 and 2 may be amended and harmonised to provide for a single assessment in the context of a PSUR work-sharing procedure and to provide for a Community reference date from which the frequency is determined" (PHV-54)

- (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 procedure of Regulation (EC) No 726/2004;
 - (b) the coordination group, in other cases than those referred to in point (a).
4. For the purposes of paragraph 3, the Community reference date for products containing the same active substance or combination thereof shall be one of the following:
- (a) the date of the first authorisation in the Community of a medicinal product containing that active substance or combination;
 - (b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for medicinal product containing that active substance or combination.
5. When establishing Community reference dates and the frequency of submission of periodic safety update reports, or subsequently, the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, may require that periodic safety update reports are also submitted for medicinal products referred to in Article 107b(3), under the following conditions:
- (a) the obligation to submit the reports shall apply for a specific period determined by the Committee or the coordination group, as appropriate; and
 - (b) ²⁴⁴the obligation shall be based on one of the following grounds relating to the protection or promotion of public health:
 - (i) evidence is available that product information relating to the safe use of the medicinal products concerned is out of date²⁴⁵;
 - (ii) a need to update warnings in product information based on new information has been identified.

²⁴⁴ **DELETED**: The conditions listed under (i) and (ii) are no reasons for submitting PSURs.

²⁴⁵ **DELETED**: What does "out of date" mean?

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 Community reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:
- (a) for reasons related to public health;
 - (b) in order to avoid duplication of assessment;
 - (c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified.

7. The Agency shall make public a list of Community reference dates and frequency of submission of periodic safety update reports by means of the European medicines safety 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 3, 4, 5 and 6 shall take effect six months after the date of such publication.

*Article 107d*²⁴⁶

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

²⁴⁶ **DELETED**: Does this article relate to purely nationally authorised products? Shall all MS have access to all PSURs?

Article 107e²⁴⁷

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 3 to 6 of Article 107c, for all medicinal products containing the same active substance or combination thereof and for which a Community reference date and frequency of periodic safety update reports has been established.

The assessment shall be conducted by either of the following:

- (a) a Member State appointed²⁴⁸ by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the procedure of Regulation (EC) No 726/2004;
- (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the procedure 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 90 days of receipt of the periodic safety update report and send it to the marketing authorisation holder and the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee.

Within 30 days of receipt of the assessment report, the marketing authorisation holder may submit comments to the Agency. The Agency shall make such comments available to the Member State or rapporteur and to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee.

²⁴⁷ ~~DELETED~~: Need for simplification. Political signals lost due to long case handling procedures. ~~DELETED~~: Agrees with need for simplification.

²⁴⁸ ~~DELETED~~: Replace "appointed" with "selected"

3. At its next meeting following the end of the period for comments by the marketing authorisation holder referred to in paragraph 2, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall adopt the assessment report with or without changes, taking into account any comments submitted in accordance with that paragraph.

Article 107f²⁴⁹

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the terms of 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 concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, consider the report and adopt an opinion²⁵⁰ on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion²⁵¹.

²⁴⁹ **DELETED**: Need for clarification as regarding the difference between the articles 107f and 107g. Why broader flexibility in 107f compared to 107g? **DELETED**: Similar concerns

²⁵⁰ **DELETED**: Concerns that the opinion of the coordination group would be binding on the MSs, without the possibility to refer the matter to the CHMP. It is critical that the coordination group would base their decisions on the recommendations of the PRAAC and implement rather than re-discuss the PRAAC decision. (PHV-19)

²⁵¹ **DELETED**: What is the meaning of the phrase: “timetable for the implementation of the opinion”? (PHV-14)

2. If ~~the opinion of~~ within the coordination group, the Member States reach agreement on the action to be taken ~~is adopted~~ by consensus, the chairman shall record the agreement and send it to inform the marketing authorisation holder ~~accordingly and the Member States~~. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned ~~as necessary to comply with the opinion within the determined in accordance with the implementation~~ time table determined in the agreement. ~~for implementation, and~~ ~~They~~ shall inform the Commission and the coordination group accordingly.²⁵²

If an ~~opinion agreement~~ by consensus cannot be reached adopted, the position of the majority of the Member States within the coordination group opinion²⁵³ shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

3. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the procedure 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 ~~Advisory~~ Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned.²⁵⁴

²⁵² **DELETED**: Suggests to replace this subparagraph by "If within the coordination group the Member States reach agreement on the action to be taken by consensus, the chairman shall record the agreement and shall 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 authorisation concerned in accordance with the implementation timetable determined in the agreement. They shall inform the Commission and the coordination group accordingly. (PHV-38)

²⁵³ **DELETED**: Replace "If an opinion by consensus cannot be adopted, the majority opinion" by: "If an agreement by consensus cannot be reached, the position of the majority of the Member States within the coordination group" (PHV-38).

²⁵⁴ **DELETED**: Why are timetables not mentioned in this paragraph?

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 under this section; and
 - (b) where the opinion states that regulatory action is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and concerned by the procedure under 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.

Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, the Agency and national competent authorities shall take the following measures:
 - (a) monitor the outcome of risk minimization measures contained in risk management systems and of conditions or requirements 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 or changed risks or whether there are changes to the risk benefit balance.²⁵⁵

Member States shall ensure that the marketing authorisation holders also take the measures set out in points (a), (b) and (c).

²⁵⁵ **DELETED**: Clarification needed as regarding who will perform this monitoring. Will the work be divided between the Agency and the MS?

2. The Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall perform the initial scrutiny and prioritisation of indications of new or changing risks or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those indications and any subsequent action as regards the marketing authorisation shall be conducted in accordance with Articles 107d to 107g.
- 3.²⁵⁶ The Agency and national competent authorities shall inform each other and the marketing authorisation holder in the event of new or changed risks 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 or changed risks or changes to the risk benefit balance being detected.

²⁵⁶ **DELETED**: Reservation on this paragraph.

Section 3
Community procedure²⁵⁷

*Article 107i*²⁵⁸

1. A Member State shall²⁵⁹ initiate the procedure under this section²⁶⁰, by informing the other Member States, the Agency and the Commission, in any of the following cases:
 - (a) it considers suspending or revoking of a marketing authorisation²⁶¹;
 - (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 withdrawn²⁶² a marketing authorisation, or that he intends to do so;
 - (e) it considers that new contraindications, a reduction in the recommended dose, or a restriction to the indications is necessary^{263 264};

²⁵⁷ **DELETED**: Has tabled a comprehensive new text on the Community procedure, see PHV-47 and PHV-58.

²⁵⁸ In reply to a question, the Cion representative explained that this procedure normally takes precedence over the procedure in Article 31 and that this procedure applies also to “purely national authorisations” even if the product is authorised in one MS only.

²⁵⁹ **DELETED**: Add "for safety reasons" in order to restrict application accordingly.

DELETED: Replace "shall" by "may".

²⁶⁰ **DELETED**: Suggests to replace first part of sentence by „Member States shall initiate the procedure under this section *in relation to a marketing authorization issued in accordance with Chapter 4, ...*”

²⁶¹ **DELETED**: This indent has potentially a very broad application. Are Pharmacovigilance rules always the best way to handle all these cases? **DELETED**: Similar question. Quality defects are not reasons for Pharmacovigilance action.

²⁶² **DELETED**: Is it legally possible for a Marketing authorisation holder to withdraw a Marketing Authorisation?

²⁶³ **DELETED**: This should be voluntary. **DELETED**: Delete both (d) and (e).

²⁶⁴ **DELETED**: Add "to ensure that the risk-benefit of the product remains positive".(PHV-19)

- (f) it has conducted a pharmacovigilance inspection²⁶⁵ and found serious deficiencies²⁶⁶.
2. The information referred to in paragraph 1 may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the issue relates to more medicinal products than those which are covered by the information or that it is common to all products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly²⁶⁷.

Where the scope of the procedure initiated under this section concerns a range of 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.

3. At the time of the information referred to in paragraph 1, the Member State shall make available to the Agency all relevant scientific information available to it and any assessment by the Member State.

Article 107j

1. After initiation of the procedure under this section, where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation or prohibit the use of a medicinal product. It shall inform the Agency, the Commission and the other Member States not later than the following working day.

²⁶⁵ **DELETED**: This procedure does not provide for immediate action which is needed if serious deficiencies are found in an inspection.

²⁶⁶ **DELETED**: Add "which could result in a change in the risk-benefit of a product".(PHV-19)

²⁶⁷ **DELETED**: Add "but will limit the procedure to the specific risk under evaluation".(PHV-19)

2. At any stage of the procedure under this section, the Commission²⁶⁸ may request the Member States in which the product is authorised to take temporary measures immediately.²⁶⁹
3. Where the scope of the procedure, as determined in accordance with Article 107i(2), concerns a range of products or therapeutic class which 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.

*Article 107k*²⁷⁰

- 1.²⁷¹ Following the information referred to in Article 107i(1), the Agency²⁷² shall publicly announce the initiation of the procedure²⁷³ by means of the European medicines safety web-portal.

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

²⁶⁸ **DELETED**: Under what circumstances does this provision apply - today CHMP must give opinion? What procedure will be used to adopt temporary measures?

²⁶⁹ **Cion**: Explained that this provision allows the Commission to take necessary action while waiting for the CHMP opinion to be adopted.

²⁷⁰ **DELETED**: Reservation on the entire procedure - simplification needed.

²⁷¹ **DELETED**: Delete this paragraph. (PHV-14). **DELETED**: Support.

²⁷² **DELETED**: Insert "relayed by the Member States"

²⁷³ **DELETED**: Doubts whether it is appropriate to announce publicly the start of the procedure. It could cause unnecessary worries. **DELETED**: Scrutiny reservation for the same reasons.

2.²⁷⁴ The Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall assess the matter which has been submitted. For the purposes of that assessment, it may hold a public hearing^{275 276}.

Public hearings²⁷⁷ shall be announced by means of the European medicines safety web-portal. The announcement shall include information on how marketing authorisation holders and the public can participate.

The Agency shall provide the opportunity, to all those who request it, to participate in the hearing either in person²⁷⁸ or through the use of web-based technology²⁷⁹.

Where a marketing authorisation holder or another person intending to submit information has commercially confidential data relevant to the issue of the procedure, he may request to present those data to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee in a non-public hearing.

²⁷⁴ **DELETED**: Delete the second, third and fourth subparagraph of this paragraph. (PHV-14)

²⁷⁵ **DELETED**: What is the reason for holding a public hearing? **DELETED**: Similar questions. Presidency: Add at the end "... or make it possible for the public to send comments in writing" (PHV-52).

²⁷⁶ **DELETED**: Concerns about the impact of public hearings.

²⁷⁷ Presidency: Add "and initiatives for written comments" (PHV-52).

²⁷⁸ **DELETED**: Clarification needed on what is meant by "in person".

²⁷⁹ **DELETED**: Replace "either in person or through the use of web-based technology" by "by means of submitting written comments".

Presidency: Add "In case of a written procedure, the Agency shall provide information on how to submit comments." (PHV-52)

3. Within 60 days of the information submitted, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee shall **make a recommendation**²⁸⁰, stating the reasons on which it is based. The recommendation shall ~~be~~ **include** any or a combination of the following:
- (a) no further evaluation or action is required at Community 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 study²⁸¹ together with the follow up evaluation of the results of that study;
 - (d) the Member States or marketing authorisation holders should implement risk minimisation measures;
 - (e) the marketing authorisation should be suspended, revoked²⁸² or not renewed;²⁸³
 - (f) the marketing authorisation should be varied²⁸⁴.

For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures **recommended**²⁸⁵ and any conditions or restrictions to which the marketing authorisation should be made subject.

280 **DELETED**: What is the legal status of this recommendation. Who is the recipient? (PHV-14)

281 **DELETED**: Specify objective and scope of this study.

282 **DELETED**: How could the revocation be withdrawn?

283 **DELETED**: Replace the text of point (e) by the following text : "a re-evaluation of the benefit-risk balance of the marketing authorisation should be performed in order to maintain, suspend, revoke or not renew this marketing authorisation".

284 **DELETED**: Add "for safety reasons"

285 **DELETED**: Replace "recommended" by "established" or "agreed".

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 suggest²⁸⁶ the wording of such changed or added information and where such wording should be placed in the summary of the product characteristics, labelling or package leaflet.

Article 107l

1. Where the scope of the procedure, as determined in accordance with Article 107i(2), does not include any marketing authorisation granted in accordance with the procedure of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, consider the recommendation and adopt an opinion²⁸⁷ on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned, including a timetable for the implementation of the opinion. Where this opinion of the coordination group is not in accordance²⁸⁸ with the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall annex to its opinion a detailed explanation of the scientific grounds for the differences.

²⁸⁶ **DELETED**: Replace "suggest" by "propose".

²⁸⁷ **DELETED**: If new data become available during the course of the coordination group's consideration of the PRAAC recommendation, the matter should be referred back to the PRAAC for re-examination. (PHV-20)

²⁸⁸ **DELETED**: The coordination group should adopt its opinion in accordance with the recommendation of the PRAAC unless a different decision can be justified on the basis of public health (PHV-20)

2. If ~~the opinion of~~ within the coordination group, the Member States reach agreement on the action to be taken ~~is adopted~~ by consensus, the chairman shall record the agreement and send it to inform the marketing authorisation holder ~~accordingly and the Member States~~. The Member States shall ^{289 290} adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned ~~as necessary to comply with the opinion within the determined~~ in accordance with the implementation time table determined in the agreement. ~~for implementation, and t~~They shall inform the Commission and the coordination group.^{291 292}

If an ~~opinion agreement~~ by consensus cannot be reached adopted, the position of the majority of the Member States within the coordination group opinion²⁹³ 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)²⁹⁴ shall apply.

²⁸⁹ **DELETED**: What is the legal basis for making the opinion binding for Member States? (PHV-14)

²⁹⁰ **DELETED**: Is there a potential conflict with the provisions in Art. 107j(1) (If a Member State acts on a recommendation that is not endorsed by CMD. (PHV-14)

²⁹¹ **DELETED**: Add the following sentence "The marketing authorisation holder shall submit to the National Competent Authorities an updated SPC and **DELETED** within the determined timetable for implementation" (PHV- 55 REV 1).

²⁹² **DELETED**: Replace this subparagraph by "If within the coordination group the Member States reach agreement on the action to be taken by consensus, the chairman shall record the agreement and shall 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. They shall inform the Commission and the coordination group accordingly." (PHV-38).

²⁹³ **DELETED**: Replace " If an opinion by consensus cannot be adopted, the majority opinion" by " If an agreement by consensus cannot be reached, the position of the majority of the Member States within the coordination group ". (PHV-38)

²⁹⁴ **DELETED**: Cases, in which the procedure will pass through the Standing Committee, will result in high work load at national level. Also the question of time for informing a political hierarchy needs to be taken in account. (PHV-15)

3. Where the scope of the procedure, as determined in accordance with Article 107i(2), includes at least one marketing authorisation granted in accordance with the procedure 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 ~~Advisory~~ 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 this opinion of the Committee for Medicinal Products for Human Use is not in accordance with the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall annex to its opinion a detailed explanation of the scientific grounds for the differences.
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 under 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 concerned by the procedure under 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 4

Publication of assessments

*Article 107m*²⁹⁵

The Agency²⁹⁶ shall make public the ~~recommendations~~, opinions and decisions referred to in Articles 107b to 107l by means of the European medicines safety web-portal.²⁹⁷

²⁹⁵ **DELETED**: Reservation.

²⁹⁶ **DELETED**: Insert "along with Member States". **DELETED**: Insert "relayed by the Member States".

²⁹⁷ **DELETED**: Add "ensuring the protection of personal data and commercial confidential information".

CHAPTER 4

Supervision of post-authorisation safety studies ²⁹⁸

Article 107n ^{299 300}

1. This Chapter shall apply to non-interventional post-authorisation safety studies which are initiated, managed or financed³⁰¹ by the marketing authorisation holder³⁰², voluntarily or³⁰³ following a requirement in accordance with Articles 21a or 22a, and which involve the collection³⁰⁴ of data from patients or health-care professionals^{305 306}.
2. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

²⁹⁸ **DELETED**: Has requested that all studies be stored centrally in a database.

²⁹⁹ **DELETED**: Reservation; would like to see some reference to the Directive on clinical trials.

³⁰⁰ **DELETED**: Provide that ethical committees must be involved. **DELETED**: Support.

³⁰¹ **DELETED**: Clarification of "financed" needed, does it mean funded in full?

³⁰² **DELETED**: The possibility must be provided for the safety studies to be conducted jointly, as a single company may not be able to conduct such a study. Make clear that this provision applies also to studies that are made on request of Competent Authorities or the EMEA.

³⁰³ **DELETED**: Delete "voluntarily or" (PHV-45 and PHV-46)

³⁰⁴ **DELETED**: ~~Direct or indirect~~ "collection"?

³⁰⁵ **DELETED**: It should also be possible to collect data *inter alia* from health insurance funds. Wants a conference to Volume IXa.

³⁰⁶ **DELETED**: Delete the last phrase "and ... professionals" and add a new sentence: "For other non-interventional post-authorisation safety studies initiated, managed or financed by the marketing authorisation holder, competent authorities should receive the protocol and be informed about the initiation of the study and, without delay, about any result that may impact the benefit-risk balance".

Article 107o³⁰⁷

1. Before a study is conducted, the marketing authorisation holder shall be required to submit a draft protocol to the national competent authority³⁰⁸, for studies to be conducted in only one Member State³⁰⁹, and to the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee, for studies to be conducted in more than one Member State.³¹⁰
2. Within 60 days³¹¹ of the submission of the draft protocol the national competent authority³¹² or the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³¹³, as appropriate, may issue
 - (a) a letter of objection, which shall be based on detailed grounds, in any of the following cases:
 - (i) it considers that the study is a clinical trial falling under the scope of Directive 2001/20/EC;
 - (ii) it considers that the conduct of the study promotes the use of a medicinal product,³¹⁴

³⁰⁷ **DELETED**: The provisions in this article will overburden the CHMP.

³⁰⁸ **DELETED**: Replace the rest of this paragraph by "... authority, if the product is authorised according to Directive 2001/83/EC and the study is to be conducted in that Member State, or to the CHMP for studies to be conducted if the product is authorised according to Regulation 726/2004 (PHV-45). **DELETED**: Replace the same part of the text by "... authority and, for studies to be conducted in more than one Member State, to the Pharmacovigilance Risk Assessment Committee" (PHV-46).

³⁰⁹ **DELETED**: Suggests that, in principle, all post-authorisation safety studies should be notified to and reviewed by the PRAAC, even where a study is approved by a national competent authority for conduct in one MS only. (PHV-27)

³¹⁰ **DELETED**: Draft protocols for studies relating to more than one country should be submitted to the NCA as well.

³¹¹ **DELETED**: Workload, particularly for PRAAC, will be heavy and the 60-day deadline very tight. **DELETED**: Compare time limits in Directive 2001/20/EC.

³¹² **DELETED**: Most active ingredients are used in many Member States. Therefore all competent authorities must be given an opportunity to object.

³¹³ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

³¹⁴ **DELETED**: Delete point (ii) (PHV-46).

- (iii) it considers that the design of the study does not fulfil the study objectives; or

- (b) a recommendation³¹⁵ on the draft protocol.
3. After the expiry of the period referred to in paragraph 2 the marketing authorisation holder may commence the study³¹⁶. However,³¹⁷ where a letter of objection referred to in point (a) of paragraph 2 has been issued, the study may commence only with the written approval from the national competent authority or the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³¹⁸, as appropriate^{319 320}.

Where a recommendation referred to in point (b) of paragraph 2 has been issued, the marketing authorisation holder shall take that recommendation into account before commencing the study^{321 322}.

³¹⁵ **DELETED**: Replace "a recommendation on" by "an approval of". (AFM-45)

³¹⁶ **DELETED**: Add "if no objection or recommendation has been issued by the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate" (PHV-28). **DELETED**: Add "when specific Member State requirements are fulfilled, including the approval of the Ethics Committee" (PHV-46).

³¹⁷ **DELETED**: Delete the word "However" and make this sentence a new subparagraph.(PHV-28)

³¹⁸ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

³¹⁹ **DELETED**: What happens if PRAAC and Competent Authority do not agree?

³²⁰ **DELETED**: Written approval from the national competent authority or the PRAAC should always be required.

³²¹ **DELETED**: Insert "and shall accordingly notify the national competent authority or the Pharmacovigilance Risk Assessment Committee, as appropriate".(PHV-28)

³²² **DELETED**: Delete this subparagraph. (PHV-45)

Article 107p

1. After a study has been commenced, major amendments³²³ to the protocol shall be submitted³²⁴ to the national competent authority or³²⁵ the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³²⁶, as appropriate.
2. During the conduct of a study, the marketing authorisation holder shall continuously monitor the data generated and its implications for the risk-benefit balance³²⁷ of the medicinal product concerned.

Any new information which might influence the risk-benefit balance of the medicinal product shall be communicated to the national competent authority³²⁸ in accordance with Article 23.

3. Payments³²⁹ to healthcare professionals for participating in the studies shall be restricted to compensation of time and expenses incurred.

³²³ **DELETED**: Clarify the exact meaning of "major amendments". **DELETED**: should be defined in a specific guideline about studies to be included in Article 108 (7).

³²⁴ **DELETED**: Insert "defined in accordance with appropriate guidelines, made"(PHV-28)

³²⁴ **DELETED**: Provide a time-limit for the submission of these amendments.

³²⁵ **DELETED**: Replace "or" by "and to" (PHV-46)

³²⁶ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

³²⁷ **DELETED**: What if the risk-benefit balance becomes unfavourable?

³²⁸ **DELETED**: Insert "or to the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate,"(PHV-28)

³²⁹ **DELETED**: Who is in charge of controlling payments? **DELETED**: same question.

Article 107q

1. Upon completion of the study, final study reports shall be submitted to the national competent authority or³³⁰ the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³³¹ within 12 months of the last patient visit³³² unless a written waiver has been given by the national competent authority or the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³³³, as appropriate.
2. The marketing authorisation holder shall consider whether the results of the study have an impact on the terms of the marketing authorisation and shall if necessary submit to the national competent authorities an application to vary the marketing authorisation.
3. ³³⁴The marketing authorisation holder shall electronically submit³³⁵ an abstract of the study results to the national competent authority or³³⁶ the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³³⁷.

For studies conducted in more than one Member State, the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³³⁸ may³³⁹ decide that the abstract is made public

³³⁰ **DELETED**: Replace "or" by "and to" (PHV-46)

³³¹ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

DELETED: Suggests "... when conducted in more than one Member State, within 12 months of the end of data collection, unless ..." (PHV-46)

³³² **DELETED**: There is no such thing as a "last patient visit", replace it by "last data collected" or equivalent expression.

³³³ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

³³⁴ **DELETED**: Suggests as a starting phrase "Together with the final study report, the marketing authorisation holder ..." (PHV-46)

³³⁵ **DELETED**: Within the same deadline as in paragraph 1.

³³⁶ **DELETED**: Replace "or" by "and to" (PHV-46)

³³⁷ **DELETED**: Suggests to replace the reference to the PRAC by a reference to the CHMP. (PHV-45)

DELETED: Add at the end "when conducted in more than on Member State" (PHV_46)

³³⁸ **DELETED**: Replace " For studies conducted in more than one Member State, the Pharmacovigilance Risk Assessment Committee" by "National competent authorities or the CHMP". (PHV-45)

³³⁹ **DELETED**: Change to "must" or "should".

by means of the European medicines safety web-portal³⁴⁰, after deletion of any information of a commercially confidential nature.

³⁴⁰ **DELETED**: Add "and national web-portals" (PHV-46)

*Article 107r*³⁴²

1. Based on the results of the study and after consultation of the marketing authorisation holder,³⁴³ the Pharmacovigilance Risk Assessment ~~Advisory~~ Committee³⁴⁴ may make³⁴⁵ recommendations concerning the terms of the marketing authorisation, stating the reasons on which they are based. Those recommendations shall be made public by means of the European medicines safety web-portal³⁴⁶.
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 coordination group shall adopt an opinion^{347 348} on the matter taking into account³⁴⁹ the recommendation referred to in paragraph 1 and including a timetable for the implementation of the opinion.³⁵⁰

341 **DELETED**: Add a new paragraph "4. The national competent authority or the CHMP may decide to vary, suspend or revoke a marketing authorisation in accordance with the results of the study conducted. The procedure as laid down in art 36-36b shall apply." (PHV-45)

342 **DELETED**: Delete this article. (PHV-45)

343 **DELETED**: Insert "the national competent authority or" (PHV-28)

344 **DELETED**: Insert ", as appropriate,"(PHV-28)

345 **DELETED**: What is the trigger of this procedure? What will be the next procedure? Standing Committee? **DELETED**: same question. Cion: yes, any remaining problem will be handled in the Standing Committee.

346 **DELETED**: Add "and national web-portals" (PHV-46)

347 **DELETED**: Will such opinions also be made public as is the case for corresponding recommendations?

348 **DELETED**: Replace " the coordination group shall adopt an opinion" by "the Member States within the coordination group shall reach a position" (PHV-38)

349 **DELETED**: Replace "taking into account" by "relying on" (PHV-46)

350 **DELETED**: Add "Where this opinion of the coordination group is not in accordance with the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall annex to its opinion a detailed explanation of the scientific grounds for the differences." (PHV-46)

If the opinion of the coordination group is adopted by consensus, the chairman shall record the agreement and inform the marketing authorisation holder accordingly. The Member States shall vary, suspend or revoke the marketing authorisation concerned as necessary to comply with the opinion within the determined time table for implementation, and they shall inform the Commission and the coordination group.^{351 352}

If an opinion by consensus cannot be adopted, the majority opinion³⁵³ shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

³⁵¹ **DELETED**: Replace this subparagraph by " If within the coordination group the Member States reach agreement on the action to be taken by consensus, the chairman shall record the agreement and shall 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. They shall inform the Commission and the coordination group accordingly." (PHV-38)

³⁵² **DELETED**: Add at the end " ... of any deviation from the agreed timetable" (PVH-46).

³⁵³ **DELETED**: Replace "If an opinion by consensus cannot be adopted, the majority opinion" by " If an agreement by consensus cannot be reached, the position of the majority of the Member States within the coordination group" (PHV-38).

CHAPTER 5

Guidelines, adaptation and review

Article 108

Following consultation with the Agency, Member States and interested parties, the Commission shall adopt and make public guidelines on good pharmacovigilance practice for medicinal products authorised in accordance with Article 6(1) in the following areas:

- (1) the establishment and operation of the pharmacovigilance system by the marketing authorisation holder and the content and maintenance of the pharmacovigilance system master file;
- (2) quality assurance and quality control by the marketing authorisation holder, the national competent authorities and the Agency of their performance of pharmacovigilance activities.
- (3) the use of internationally agreed terminologies, formats and standards for the conduct of pharmacovigilance³⁵⁴;
- (4) the methodology for the monitoring of data in the Eudravigilance database to determine whether there are new or changed risks;
- (5) the format of electronic³⁵⁵ reporting of adverse reactions by Member States and marketing authorisation holders;
- (6) the format of electronic periodic safety update reports;
- (7) the format of protocols, abstracts and final study reports for the post-authorisation safety studies;

³⁵⁴ **DELETED**: Add "activities".(PHV-28)

³⁵⁵ **DELETED**: Delete "electronic", format should always be the same.

(8) the procedures and formats for pharmacovigilance communications.

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Those guidelines shall take account of international harmonisation work carried out in the field of pharmacovigilance and shall where necessary be revised to take account of technical and scientific progress.

Article 108a

The Commission shall adopt any amendments which may be necessary to update the provisions of this Title to take account of scientific and technical progress.

Those measures, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

Article 108b

The Commission shall make public a report on the conduct of pharmacovigilance tasks by the Member States on [insert concrete date: three-years after the date of transposition referred to in Article 3(1)] at the latest and then every three years thereafter.”

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DELETED: Add one more area where guidelines are needed as follows:

"(9) standards for data quality harmonization on electronic reporting of adverse reactions and procedures for cooperation between the Agency and the national competent authorities in the monitoring of data quality." (PHV-31)

22. Article 111 is amended as follows:

(a) paragraph 1 is shall be amended as follows:

(i) the first subparagraph is shall be replaced by the following:

“Under the coordination of the Agency^{357 358}, the competent authority of the Member State concerned³⁵⁹ shall ensure that the legal requirements governing medicinal products are complied with, by means of repeated inspections, and if necessary unannounced inspections, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples.^{360 361}”

(ia)³⁶² the second subparagraph shall be replaced by the following:

“The competent authority may carry out repeated and/or unannounced inspections at the premises of manufacturers, distributors or importers of active substances used as starting materials, at the premises of marketing authorisation holders, at the premises of traders or at the premises of manufacturers or importers or distributors of excipients, whenever it considers that there are grounds for suspecting non-compliance with the legal requirements or guidelines. These inspections may also be carried out at the request of a Member State, the Commission or the Agency.”

³⁵⁷ **DELETED**: Add wording that clarifies that inspections by the national competent authorities of a Member State of installations on the territory of that Member State are not subject to this coordination.

³⁵⁸ **DELETED**: Delete "Under the coordination of the Agency"(PHV-29) (PHV-26).

DELETED: Support.

³⁵⁹ **DELETED**: Replace the beginning of this subparagraph by the following text:

"The competent authority of the Member State concerned, either by itself or under the coordination of the Agency, shall ensure that ... (rest unchanged)"(PHV-25).

³⁶⁰ **DELETED**: Add "Where appropriate, inspections shall be coordinated by the Agency, in cooperation with the Member States."(PHV-29)

³⁶¹ **DELETED**: Add "To assist with coordination of inspections in third countries, Member States shall exchange information on planned inspections with the Agency." (PHV-26).

DELETED: Support. Cion: This would narrow the field of action of the EMEA.

³⁶² This change to Article 111 is a Presidency proposal discussed in connection with the "Proposal on prevention of Falsified medicinal products". It is included here only in order to provide a full picture of the changes to this Article and should not be discussed as part of the "Pharmacovigilance Proposal".

(ii) In the fifth subparagraph point (d) ~~is~~ **shall be** replaced by the following:

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

(iii)³⁶³ **the following sixth subparagraph shall be added:**

‘Inspections shall be carried out in accordance with the guidelines referred to in Article 111a.’

(b)³⁶⁴ Paragraph 3 is replaced by the following:

“3. After every inspection as referred to in paragraph 1, the competent authority shall report on whether the manufacturer, importer or ~~wholesaler~~ **wholesale distributor** complies with the principles and guidelines of good manufacturing practice and good distribution practices referred to in Articles 47 and 84, or on whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those reports to the manufacturer, importer, marketing authorisation holder, or **to the** wholesale distributor who has undergone the inspection.

Before adopting the report, the competent authority shall give the manufacturer, importer, marketing authorisation holder, or wholesale distributor concerned the opportunity to submit their comments.”

³⁶³ This change to Article 111 is part of the "Proposal on prevention of Falsified medicinal products". It is included here only in order to provide a full picture of the changes to this Article and should not be discussed as part of the "Pharmacovigilance Proposal".

³⁶⁴ This change to Article 111 is part both of the "Pharmacovigilance Proposal" and of the "Proposal on prevention of Falsified medicinal products".

(b1)³⁶⁵

Paragraphs 5 and 6 shall be replaced by the following:

'(5) Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice or good distribution practices shall be issued to the manufacturer, importer, or wholesale distributor if the outcome of the inspection shows that the person complies with the principles and guidelines of good manufacturing practice or good distribution practices as provided for by Community legislation.

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

(6) Member States shall enter the certificates of good manufacturing practice and good distribution practices which they issue in a Community database managed by the Agency on behalf of the Community.

³⁶⁵ This change to Article 111 is part of the "Proposal on prevention of Falsified medicinal products". It is included here only in order to provide a full picture of the changes to this Article and should not be discussed as part of the "Pharmacovigilance Proposal".

(c) Paragraph 7 **is shall be** replaced by the following³⁶⁶:

“7. If the outcome of the inspection as referred to in points (a), (b) and (c)³⁶⁷ of paragraph 1 **or the outcome of an inspection of a distributor of medicinal products or active substances used as starting materials** is that the **manufacturer inspected entity**^{368 369} 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 Community legislation, the information shall be entered in the Community database as referred to in paragraph 6.”

(d) The following paragraph 8 **is shall be** added:

“8. If the outcome of the inspection as 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 his 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.”

³⁶⁶ The changes to Article 111(7) are part both of the "Pharmacovigilance Proposal" and of the "Proposal on prevention of Falsified medicinal products".

³⁶⁷ The limitation to points a, b and c is connected with the introduction of paragraph 8 that deals with inspections referred to in paragraph 1(d).

³⁶⁸ In the original, the "Pharmacovigilance Proposal" refers to "manufacturer". In order to cover "good distribution practices", introduced by the "Proposal on prevention of Falsified medicinal products", it is suggested to replace "manufacturer" by "inspected entity".

³⁶⁹ **DELETED**: Instead of "responsible person" insert "inspected entity" in line with a similar change in the "Proposal on prevention of Falsified medicinal products".

23. Article 116 is replaced by the following:

“Article 116

The competent authorities shall suspend, revoke, withdraw³⁷⁰ or vary a marketing authorisation if the view is taken that the product is harmful or that it lacks therapeutic efficacy³⁷¹, or that the risk-benefit balance is not positive, 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.³⁷²

An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10 to 11 are incorrect or have not been amended in accordance with Article 23, or where any conditions or requirements referred to in Articles 21a, 22 or 22a have not been fulfilled³⁷³ or where the controls referred to in Article 112 have not been carried out.”

24. Article 117 is amended as follows:

(a) paragraph 1 is amended as follows:

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

“(a) the medicinal product is harmful; or³⁷⁴”

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

“(c) the risk-benefit balance is not favourable; or³⁷⁵ “

³⁷⁰ **DELETED**: Problem with binding nature of a CMD opinion that forces withdrawal. What to do if that is the only product on the market in a Member State?

³⁷¹ **DELETED**: Delete "or that it lacks therapeutic efficacy" as this is difficult to establish.

³⁷² **DELETED**: Has a medicinal product ever been recalled because of lack of therapeutic efficacy?

³⁷³ **DELETED**: Align to the changes suggested by **DELETED** for Articles 21a and 22.

³⁷⁴ **DELETED**: Prefer current wording.

³⁷⁵ **DELETED**: Prefer current wording.

(b) The following paragraph 3 is added:

“3. The competent authority may prohibit the supply of the product to new patients.”^{376 377}

25. In Article 122(2) the following subparagraph is added:

“The Member States shall send electronically all inspection reports 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 which are prohibited³⁷⁸ in the Community.”³⁷⁹

27. In Article 126a³⁸⁰, 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 Title V, with the exception of Article 63(1) and (2), and Titles VI, VIII, IX and XI.³⁸¹

³⁷⁶ **DELETED**: Reservation;**DELETED**: methodologically unsound, why should a product continue to be administered if its risk-benefit balance is unfavourable. PL: What if two MS have a different approach to a product?

³⁷⁷ It was suggested to make this provision transitional.

³⁷⁸ It was discussed to replace "prohibited" by "refused, suspended, or withdrawn from the market".

³⁷⁹ **DELETED**: Instead of "prohibited in the Community" insert "referred to in paragraph 1".

DELETED: Support **DELETED** suggestion, and made reference to similar existing list for veterinary products.

³⁸⁰ **DELETED**: Cion should prepare a report based on Article 126a(5). Article 126a should not be changed until such a report gives the possibility to evaluate the effects of the application of this Article. **DELETED**: Shares SI concerns.

³⁸¹ **DELETED**: Delete "with the exception of Article 63(1) and (2) and Titles" and insert as a second sentence "Member States may decide that Article 63(1) and (2) of Title V shall not apply to medicinal products authorised under the first paragraph." (PHV-24)

DELETED Positive scrutiny reservation on this suggestion.

3. Before granting such an authorisation a Member State³⁸² shall notify the marketing authorization holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant an authorisation under this Article in respect of the 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 Scientific Committee³⁸³ in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca) or (cb) 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."

³⁸² **DELETED**: The rest of this sentence becomes point (a) and the following point (b) is inserted:

"(b) may request the competent authority in that State to furnish a copy of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the said medicinal product. If so requested, the competent authority in that 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 said medicinal product."(PHV-24)

³⁸³ In reply to a question, the Commission representative explained that this is a reference to the CHMP.

Article 2
Transitional provisions

1. With regard to the requirement for the inclusion of a summary of the essential information necessary to use the medicine safely and effectively in the summary of the product characteristics and the package leaflet provided for in point 3a of Article 11 and in point (aa) of Article 59(1) of Directive 2001/83/EC³⁸⁴ as amended by this Directive, the Member States shall ensure that the requirement applies to a marketing authorisation granted before the date set out in the second subparagraph of Article 3(1) of this Directive from renewal of that authorisation or from the expiry of a period of three years starting from that date, whichever is the earliest.
2. With regard to the requirement for 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 point (b) of Article 104(3) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that that requirement applies to marketing authorisations granted before the date set out in the second subparagraph of Article 3(1) of this Directive or from the expiry of a period of three years starting from that date.
3. The Member States shall ensure that the procedure under Articles 107n to 107r of Directive 2001/83/EC as amended by this Directive applies only to studies which have commenced after the date set out in the second subparagraph of Article 3(1) of this Directive.

³⁸⁴ **DELETED** Reservation, linked to its reservations on Article 11 and 59.

Article 2a

Transitional provision (new)

- 1. With regard to the requirements for the marketing authorisation holder to submit information on suspected adverse reactions electronically to the Eudravigilance database, provided for in point 3 of Article 107 of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that these requirements apply 6 months after the functionalities of the database are established and have been announced by the Agency.**

- 2. Until the Agency can ensure these functionalities of the Eudravigilance database marketing authorisation holders shall be required to, within 15 days following the receipt of a report or, in the absence of a report, following the day on which the holder concerned gained knowledge of the event³⁸⁵, report all serious suspected adverse reactions that occur in the Community, to the competent authority of the Member State on whose territory the incident occurred and all serious suspected adverse reactions that occur on the territory of a third country to the Agency and the competent authorities of the Member States in which the medicinal product is authorised.**

³⁸⁵ **DELETED**: Replace "following the day on which the holder concerned gained knowledge of the event" by "of any other comparable information". (PHV-56)

- 3. Until the Agency can ensure these functionalities of the Eudravigilance database marketing authorisation holders shall also be required to, within 90 days following the receipt of a report or, in the absence of a report, following the day on which the holder concerned gained knowledge of the event, report all non-serious suspected adverse reactions that occur in the Community, to the competent authority of the Member State on whose territory the incident occurred and all non-serious suspected adverse reactions that occur on the territory of a third country to the Agency and the competent authorities of the Member States in which the medicinal product is authorised.**³⁸⁶
- 4. During this transitional period, Member States shall ensure that reports mentioned in paragraphs 2 and 3³⁸⁷ are made available promptly to the Eudravigilance database, and in any case within 15 days after the notification of serious adverse reactions and within 90 days after the notification of non-serious adverse reactions³⁸⁸, at the latest.**

³⁸⁶ **DELETED**: Suggest deletion of this paragraph, as exchange of reports on non-serious suspected adverse reactions will not be possible to deal with during the transitional period.

DELETED Support for this paragraph.

³⁸⁷ **DELETED**: Replace "paragraphs 2 and 3" by "paragraph 2 that occurred on their territory". (PHV-56)

³⁸⁸ **DELETED**: Delete "and within 90 days after the notification of non-serious adverse reactions ". (PHV-56)

Article 3
Transposition

1. Member States shall adopt and publish, by [18³⁸⁹ months from the entry into force] 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 ~~and a correlation table between those provisions and this Directive~~.

They shall apply those provisions from [18 months from the entry into force].

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 twentieth day after that of its publication in the *Official Journal of the European Union*.

Article 5
Addressees

This Directive is addressed to the Member States.

³⁸⁹ **DELETED**: Replace "18 months" by "24 months".

Done at Brussels,

For the European Parliament
The President

For the Council
The President
