SUBSIDIARY LEGISLATION 458.35

PHARMACOVIGILANCE REGULATIONS

30th October, 2012

LEGAL NOTICE 369 of 2012.

Citation, purpose and scope.

1. (1) The title of these regulations is the Pharmacovigilance Regulations.

(2) These regulations implement the provisions of Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the community code relating to medicinal products for human use.

(3) These regulations shall apply to authorised medicinal products for human use and any pharmacovigilance activity connected therewith.

Interpretation.

2. For the purpose of these regulations:

"the Act" means the Medicines Act; Cap. 458.

"adverse reaction" means a response to a medicinal product which is noxious and unintended;

"the Agency" means the European Medicines Agency established by Regulation (EC) No 2004/726;

"the Authority" means the Medicines Authority established under article 4 of the Act; Cap. 458.

"the Commission" means the Commission in accordance with Council Decision 1999/468/EC of the 28th June, 1999;

"the Community" means the European Union and the European Economic Area;

"Member State" means a State which is a member of the Community;

"serious adverse reaction" means an adverse reaction which results in death, or is life threatening, or requires in-patient hospitalisation or the prolongation of existing hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

"periodic safety update reports" means the periodical reports containing the records referred to in regulation 31;

"pharmacovigilance system" means a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in these regulations and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance;

"pharmacovigilance system master file" means a detailed description of the pharmacovigilance system used by the marketing

authorisation holder with respect to one or more authorised medicinal products;

"post-authorisation safety study" means any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures;

"risk-benefit balance" means an evaluation of the positive therapeutic effects of the medicinal product in relation to any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;

"risk management system" means a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions;

"risk management plan" means a detailed description of the risk management system;

"unexpected adverse reaction" means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

Setting up of pharmacovigilance system.

3. (1) The Authority shall set up and operate a pharmacovigilance system for the fulfilment of its pharmacovigilance tasks and its participation in Community pharmacovigilance activities. The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

(2) By means of the pharmacovigilance system referred to in sub-regulation (1), the Authority shall evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. A regular audit of its pharmacovigilance system shall be carried out and the results reported to the Commission on the 21st September, 2013 at the latest and then every two years thereafter.

(3) The suitable information collected within this system shall be communicated by the Authority to the other Member States and the Agency. The information shall be recorded in the database referred to in point (l) of the second subparagraph of Article 57(1) of Regulation (EC) No 726/2004 and shall be permanently accessible to all Member States and without delay to the public.

(4) It shall be the duty of doctors and other healthcare professionals to immediately report to the Authority any suspected adverse reaction to a medicinal product in Malta.

(5) The Authority shall facilitate patient reporting through the

provision of alternative reporting formats in addition to web-based formats as well as take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. The Authority shall also ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary.

(6) The Authority shall ensure through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, and the batch number.

(7) The Authority shall also take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in these regulations is subject to effective, proportionate and dissuasive penalties.

Power to delegate.

4. The Authority may delegate any of the tasks entrusted to it under these regulations to another Member State subject to a written agreement of the latter.

Information to the Commission.

5. The Authority 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.

Duty of the marketing authorisation holder.

6. (1) The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system provided for under regulation 3.

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

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

(4) As part of the pharmacovigilance system, the marketing authorisation holder shall:

(*a*) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;

(*b*) maintain and make available on request a pharmacovigilance system master file;

(*c*) operate a risk management system for each medicinal product;

(*d*) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation;

(*e*) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products:

Provided that the qualified person referred to in paragraph (*a*) shall reside and operate in the European Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the Authority and the Agency.

(5) Notwithstanding the provisions of sub-regulation (3), the Authority may request the nomination of a contact person for pharmacovigilance issues at national level reporting to the qualified person responsible for pharmacovigilance activities.

Derogation.

7. Without prejudice to regulation 6(2), (3) and (4), holders of marketing authorisations granted before the 21st July, 2012 shall, by way of derogation from regulation 6(4)(*c*), not be required to operate a risk management system for each medicinal product.

The Authority may impose obligation.

8. The Authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in regulation 6(4)(*c*), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, the Authority shall also oblige the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned. The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the detailed description of the risk-management system.

Opportunity to file written observations.

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

Authority may withdraw or confirm obligation.

10. On the basis of the written observations submitted by the marketing authorisation holder, the Authority shall withdraw or confirm the obligation. Where the Authority confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation.

Management of funds intended for activities connected with pharmacovigilance

11. 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 Authority in order to guarantee their independence in the performance of those pharmacovigilance activities.

Authority not precluded from charging fees.

12. Regulation 11 shall not preclude the Authority from charging fees to marketing authorisation holders for performing those activities by the Authority on the condition that its independence in the performance of those pharmacovigilance activities is strictly guaranteed.

Transparency and communications.

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

(*a*) public assessment reports, together with a summary thereof;

(*b*) summaries of product characteristics and package leaflets;

(*c*) summaries of risk management plans for medicinal products authorised in accordance with Directive 2001/83/EC as amended;

(*d*) the list of medicinal products referred to in Article 23 of Regulation (EC) No 726/2004;

(*e*) information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004.

Public announcements.

14. (1) A marketing authorisation holder shall inform the Authority, the Agency and the Commission if it intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product. The marketing authorisation holder shall inform the authorities at the same time or before the public announcement is made. The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

(2) Unless urgent public announcements are required for the protection of public health, the Authority, the Agency and the Commission shall inform each other not less than twenty-four hours prior to the making of a public announcement relating to information on pharmacovigilance concerns.

(3) For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public. Under the coordination of the Agency, the Authority shall make all reasonable efforts to agree

on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution.

(4) When the Agency or the Authority make public information referred to in sub-regulations (2) and (3), any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

Recording, reporting and assessment of pharmacovigilance data.

15. Marketing authorisation holders shall record all suspected adverse reactions in the Community or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study. Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Community:

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

Electronic reports of adverse reactions.

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

Eudravigilance database.

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

Non-serious suspected adverse reactions.

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

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

Procedures to obtain data.

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

Collaboration with Agency and Member States.

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

Recording suspected adverse reactions.

21. The Authority shall record all suspected adverse reactions that occur in its territory which are brought to its attention from healthcare professionals and patients. The Authority shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with the provisions of regulation 3(5) and (6).

Submission of reports.

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

Report follow-up.

23. For reports submitted by a marketing authorisation holder, where the suspected adverse reaction occurred in Malta, the Authority may involve the marketing authorisation holder in the follow-up of the reports.

Detection of duplicates.

24. The Authority shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

Reports of serious suspected adverse reactions.

25. (1) The Authority shall, within fifteen days following the receipt of the reports of serious suspected adverse reactions referred to in regulation 21, submit the reports electronically to the Eudravigilance database.

(2) The Authority shall, within ninety days from the receipt of reports referred to in regulation 21, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Access to reports through Eudravigilance database.

26. Marketing authorisation holders shall access such reports as are referred to in regulation 25 through the Eudravigilance database.

Reactions arising from an error.

27. The Authority shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to its attention are made available to the Eudravigilance database.

Additional obligations may not be imposed.

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

Periodic safety update reports.

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

(*a*) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(*b*) a scientific evaluation of the risk-benefit balance of the medicinal product;

(*c*) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing

authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

(2) The evaluation referred to in sub-regulation (1)(b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

(3) The periodic safety update reports shall be submitted electronically.

Agency to make reports available.

30. The Agency shall make available the reports referred to in regulation 29 to the Authority, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 25a of Regulation (EC) No 726/2004.

When reports are to be submitted.

31. (1) By way of derogation from regulation 29, the holders of marketing authorisations for medicinal products referred to in Directive 2001/83/EC, Article 10(1), or Directive 2001/83/EC, Article 10a, and the holders of registrations for medicinal products referred to in Directive 2001/83/EC, Article 14, or Directive 2001/83/EC, Article 16a, shall submit periodic safety update reports for such medicinal products in the following cases:

(*a*) where such obligation has been laid down as a condition in the marketing authorisation; or

(*b*) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

(2) The assessment reports of the requested periodic safety update reports shall be communicated to the Agency's Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 107c(4) and Article 107e of Directive 2001/83/EC.

Frequency and dates of submission.

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

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

Authorisations granted before the 21st July 2012.

33. (1) Holders of marketing authorisations which were granted before the 21st July, 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with sub-regulation (2) until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or

determined in accordance with regulations 35, 36 or 37.

(2) Periodic safety update reports shall be submitted to the Authority immediately upon request or in accordance with the following:

(*a*) where a medicinal product has not yet been placed on the market, at least every six months following authorisation and until the placing on the market;

(*b*) where a medicinal 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.

Medicinal products authorised only in one Member State.

34. Regulation 33 shall also apply to medicinal products which are authorised only in one Member State and for which regulation 35 does not apply.

Harmonised frequency for submission of reports.

35. (1) Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of regulations 32 and 33 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Community reference date from which the submission dates are calculated.

(2) This harmonised frequency for the submission of the reports and the Community reference date may be determined, after consultation of the Agency's Pharmacovigilance Risk Assessment Committee, by one of the following:

(*a*) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004;

(*b*) the coordination group, in other cases than those referred to in paragraph (*a*).

(3) The harmonised frequency for the submission of the reports determined pursuant to the sub-regulations (1) and (2) shall be made public by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

Community reference date.

36. For the purposes of regulation 35, the Community reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

(*a*) the date of the first marketing authorisation in the Community of a medicinal product containing that active substance or that combination active substances;

(*b*) if the date referred to in paragraph (*a*) cannot be ascertained, the earliest of the known dates of the marketing authorisations for medicinal products containing that active substance or that combination of active substances.

Marketing authorisation holders may submit requests.

37. (1) Marketing authorisation holders shall be allowed to submit requests to the Agency's Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine the Community reference dates or to change the frequency of submission of periodic safety update reports on one of the following grounds:

(*a*) for reasons relating to public health;

(*b*) in order to avoid a duplication of the assessment;

(*c*) in order to achieve international harmonisation.

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

Publication of reference dates and reports.

38. 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 web-portal.

Effective date of changes.

39. 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 regulations 35, 36 and 37 shall take effect six months after the date of such publication.

Assessment by the Authority of periodic safety update reports.

40. The Authority shall, when it is a reference member state or a rapporteur at the Agency's Pharmacovigilance Risk Assessment committee, assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

Single assessment of periodic safety update reports.

41. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 107c of Directive 2001/83/EC, for all medicinal products containing the same active substance or the same combination of active substances and for which a Community reference date and frequency of periodic safety update reports has been established.

Conducting the single assessment.

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

(*a*) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of

Regulation (EC) No 726/2004; or

(*b*) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004.

Assessment report.

43. The Member State or rapporteur, as appropriate, shall prepare an assessment report within sixty days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Submission of comments.

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

Rapporteur to update assessment report.

45. Following the receipt of the comments referred to in regulation 44, the rapporteur or Member State shall within fifteen days update the assessment report taking into account any comments submitted, and forward it to the Agency's Pharmacovigilance Risk Assessment Committee. The Agency's Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

Authority to consider necessity of any action.

46. Following the assessment of periodic safety update reports, the Authority shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary. The Licensing Authority as established under article 3 of the Act, shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Coordination group to consider the report.

47. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) of Directive 2001/83/EC as amended, which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

Deliberations of the coordination group.

48. (1) If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary,

suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

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

(3) If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34 of Directive 2001/83/EC as amended.

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

Adoption of an opinion on marketing authorisations.

49. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 107e(1) of Directive 2001/83/EC as amended which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within thirty days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

Detailed explanation of scientific grounds.

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

Decisions to be adopted by the Commission.

51. (1) On the basis of the opinion of the Agency's Committee for Medicinal Products for Human Use referred to in regulation 50, the Commission shall:

(*a*) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for herein; and

(*b*) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the

marketing authorisations granted in accordance with the centralised procedure provided for in Regulation (EC) No 726/2004 and concerned by the procedure provided for herein.

(2) Articles 33 and 34 of Directive 2001/83/EC as amended shall apply to the adoption of the decision referred to in sub-regulation (1)(*a*) and to its implementation by the Member States.

Decision on measures relating to marketing authorisations.

52. Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in regulation 51(1)(*b*). 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 as amended.

Signal detection.

53. Regarding medicinal products authorised in accordance with Directive 2001/83/EC as amended, the Authority in collaboration with the Agency shall take the following measures:

(*a*) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a of Directive 2001/83/EC as amended;

(*b*) assess updates to the risk management system;

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

Analysis and prioritisation of risk signals.

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

Mutual information about risks.

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

Duties of the Authority on information about risks.

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

Urgent Community procedure.

57. (1) The Authority or the Commission, as appropriate, shall initiate the procedure provided for herein, by informing the other Member States, the Agency and the Commission when urgent action is considered necessary, as a result of the evaluation of data resulting from pharmacovigilance activities, in any of the following cases:

(*a*) it considers suspending or revoking a marketing authorisation;

(*b*) it considers prohibiting the supply of a medicinal product;

(*c*) it considers refusing the renewal of a marketing authorisation;

(*d*) it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or that he intends to do so;

(*e*) it considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary:

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

(2) Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the procedure of the outcome of this verification, and the procedures laid down in Articles 107j and 107k of Directive 2001/83/EC as amended shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make information that the procedure has been initiated available to marketing authorisation holders.

(3) (*a*) Without prejudice to the provisions of sub-regulation (1), and Articles 107j and 107k of Directive 2001/83/EC as amended, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

(*b*) At any stage of the procedure laid down in Articles 107j to 107k of Directive 2001/83/EC as amended, the Commission may request Member States in which the medicinal product is authorised to take temporary measures immediately.

(4) (*a*) Where the scope of the procedure, as determined in accordance with sub-regulation (1), includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission may, at any stage of the procedure initiated hereunder, take temporary measures immediately in relation to those marketing authorisations.

(*b*) The information referred to in this regulation may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

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

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

Supervision of post-authorisation safety studies.

58. (1) This regulation applies to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC as amended, and which involve the collection of safety data from patients or healthcare professionals.

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

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

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

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

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

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

(*b*) Any new information which might influence the evaluation of the risk- benefit balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 23 of Directive 2001/83/EC as amended.

(*c*) The obligation laid down in sub-regulation (2) is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in regulation 29.

(8) Regulations 59 to 62 shall apply exclusively to studies referred to in sub-regulation (1) which are conducted pursuant to an

obligation imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC as amended.

Submission of draft protocol.

59. (1) Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State (e.g. Malta) that requests the study according to Article 22a of Directive 2001/83/EC. For such studies, the marketing authorisation holder shall submit a draft protocol to the Authority.

(2) Within sixty days of the submission of the draft protocol the Authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

(*a*) a letter endorsing the draft protocol;

(*b*) a letter of objection, which shall set out in detail the grounds for the objection, in any of the following cases:

(i) it considers that the conduct of the study promotes the use of a medicinal product;

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

(*c*) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

(3) (*a*) The study may commence only when the written endorsement from the Authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

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

Authorisation of amendments.

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

Finalisation of the study.

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

Pharmacovigilance Risk Assessment Committee, as appropriate.

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

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

Recommendations to vary, suspend, withdraw marketing authorisations.

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

(2) (*a*) 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 Directive 2001/83/EC as amended, the Member States represented within the coordination group shall agree a position on the matter taking into account the recommendation referred to in sub-regulation (1) and including a timetable for the implementation of the agreed position.

(*b*) If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States.

(*c*) 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.

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

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

(*f*) If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 33 and 34 of Directive 2001/83/EC as amended.

(*g*) Where the agreement reached by the Member States

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