Our Ref: 04/2012

CONSULTATION DOCUMENT ON IMPLEMENTATION 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.

Objectives and Scope

Medicinal products contribute considerably to the health of EU citizens. The discovery, development and effective use of medicinal products improve quality of life, reduce the length of time spent in hospital and save lives. Medicinal products can, however, also have adverse effects and adverse drug reactions present an important public health burden in the Community. It is estimated that 5% of all hospital admissions are due to an adverse drug reaction, 5% of all hospital patients suffer an adverse drug reaction and adverse drug reactions are the fifth most common cause of hospital death.

Some adverse reactions will only be detected after a medicine has been authorised and the full safety profile of medicinal products can only be known once they have entered the market. Pharmacovigilance rules are therefore necessary for the protection of public health in order to prevent, detect and assess adverse effects of medicinal products. Community rules so far adopted have made a major contribution to the achievement of the objective that medicinal products authorised to be placed on the Community market are continuously monitored as regards their safety. However, 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 new measures are necessary to improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use. As from the 21 July 2012, this directive is amending directive 2001/83/EC on the community code relating to medicinal products for human use and all provisions apply.

Main Changes

The Directive is directly applicable to all Member States as from the 12 July 2012.

Major changes compared to Directive 2001/83/EC:

• Providing for clear roles and responsibilities for the key responsible parties and clear obligations against which they perform their roles;
• Rationalising EU decision-making on drug safety issues in order to deliver measures that are equally and fully implemented for all relevant products and across the Community with a view to preventing unnecessary patient exposure to risks;
• Strengthening medicines safety transparency and communication to increase the understanding and trust of patients and health professionals in the safety of medicines and improve the penetration of key warnings;
• Strengthening companies' pharmacovigilance systems, allowing companies to improve their systems constantly while reducing administrative burden;

• Ensuring the proactive and proportionate collection of high quality data relevant to the safety of medicines through risk management and structured data collection in the form of post authorisation safety studies, together with rationalised single case and periodic reporting of suspected adverse reactions;
• Involving stakeholders in pharmacovigilance including through direct patient reporting of suspected adverse reactions and inclusion of patients and heath-care professionals in decision-making.
• Simplification of the current Community pharmacovigilance procedures with consequent efficiency gains for both the pharmaceutical industry and medicines regulators.

DIRECTIVE 2010/84/EU:

Comments

Your comments on the proposed Legal Notices are invited.

Comments are to reach the Medicines Authority in writing or via email consultations.medicinesauthority@gov.mt by the **29th May 2012.**

Should any further information be required kindly contact the Medicines Authority using the following contact details:

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Minister of Health, the Elderly and Community Care

L.N. of 2012

MEDICINES ACT, 2003
(CAP. 458)

Pharmacovigilance Regulations, 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, 2003, the Minister of Health, the Elderly and Community Care has made the following regulations:-

Citation and Commencement

1. The title of these regulations is the Pharmacovigilance Regulations, 2012.

2. The 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 enter into force on 21th July 2012.

Scope

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

Interpretation

5. For the purposes of these regulations

"abuse of medicinal products" means persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects;

"the Act" means the Medicines Act, 2003;

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

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

"the Authority" the Medicines Authority established under article 4 of the Act;

"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" refers to 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 Report" refers to the periodical reports containing the records referred to in regulation 32 of these regulations;

"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" refers to an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics;

Setting up of pharmacovigilance system

6. 1 (a) 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.

(b) By means of the pharmacovigilance system referred to in regulation 6 1(a), 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 21 September 2013 at the latest and then every 2 years thereafter.

(c) 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.

(d) 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.

(e) 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. It 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;

(f) 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;

(g) 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

7. A Member State may delegate any of the tasks entrusted to it under this regulation to another Member State subject to a written agreement of the latter.

8. 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.

Duty of the marketing authorisation holder

9. 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 6 (1) of these regulations.

2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to regulation 9 (1) of these regulations, to 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.

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

5. Notwithstanding the provisions of paragraph 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.

10. Without prejudice to Regulation 9 sub paragraphs 2, 3 and 4, holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Regulation 9 sub paragraphs 3 (c) are not be required to operate a risk management system for each medicinal product.

11. The Authority may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Regulation 9 (3)(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.

12. 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 30 days of receipt of the written notification of the obligation.

13. 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.

The management of funds intended for activities connected with pharmacovigilance

14. 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.

15. Regulation 14 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

16. 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.

17. 1 A marketing authorisation holder shall to 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 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public. Under the coordination of the Agency, the 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 paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

Recording, reporting and assessment of pharmacovigilance data

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

19. 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.

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

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

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

22. 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.

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

24. 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.

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

26. 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.

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

28. The Authority shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in regulation 24 of these regulations, submit the reports electronically to the Eudravigilance database.

The Authority shall, within 90 days from the receipt of reports referred to in regulation 24 of these regulations, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

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

30. 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.

31. 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

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

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

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

(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

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

The periodic safety update reports shall be submitted electronically.

33. The Agency shall make available the reports referred to in Regulation 32 of these regulations 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.

34. By way of derogation from Regulation 32 of these regulations, 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, Articles 14 or Directive 2001/83/EC, 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. 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.

35. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.
The dates of submission according to the specified frequency shall be calculated from the date of the authorisation.

36. Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with Regulations 38, 39 or 40 of these regulations.

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 6 months following authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2 years and at three- yearly intervals thereafter.

37. Regulation 36 of these regulations shall also apply to medicinal products which are authorised only in one Member State and for which Regulation 38 of these regulations does not apply.

38. 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 35 and 36 of these regulations 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 the Community reference date from which the submission dates are calculated.

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 point (a).

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

39. For the purposes of regulation 38 of these regulations, 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 point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

40. 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 periodic safety update reports on one of the following grounds:

(a) for reasons relating to public health;

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

(c) in order to achieve international harmonisation.

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

41. 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.

42. 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 38, 39 and 40 shall take effect 6 months after the date of such publication.

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

44. 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.

45. 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.

46. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

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

48. Following the receipt of the comments referred to in Regulation 47 of these regulations, the rapporteur or Member State shall within 15 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.

49. 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.

50. 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.

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

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

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

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.

52. 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 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

53. 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.

54. On the basis of the opinion of the Agency's Committee for Medicinal Products for Human Use referred to in Regulation 53, the Commission shall:

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

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

Articles 33 and 34 of Directive 2001/83/EC as amended 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.

55. 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 Directive 2001/83/EC as amended.

Signal Detection

56. 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.

57. 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.

58. 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.

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

Urgent Union Procedure

60. 1. A Member State or the Commission, as appropriate, shall initiate the procedure provided for in this section, by informing the other Member States, the Agency and the Commission when urgent action is considered necessary, as a result of the evaluation of data resulting from pharmacovigilance activities, in any of the following cases:

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

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

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. Without prejudice to the provisions of paragraph 1 of this Regulation, 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.

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. Where the scope of the procedure, as determined in accordance with paragraph 1, includes medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission

may, at any stage of the procedure initiated under this section, take temporary measures immediately in relation to those marketing authorisations.

The information referred to in Regulation 60 may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

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 Regulation 60 subparagraph 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

61. 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 12 months of the end of data collection.

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

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

The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of

the periodic safety update reports as laid down in Regulation 32 of these regulations.

8. Regulation 62 to 65 shall apply exclusively to studies referred to in Regulation 61 (1) which are conducted pursuant to an obligation imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC as amended.

62. 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 (for eg 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 60 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. The study may commence only when the written endorsement from the Authority or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement as referred to in Regulation 62 subparagraph 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

63. 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

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

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

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

Recommendations to vary, suspend, withdraw marketing authorisations

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

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to 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 Regulation 65 subparagraph 1 of these regulations and including a timetable for the implementation of the agreed position.

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

The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

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

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

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

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.

Repeals L.N. 61 of 2006

66. The Pharmacovigilance Regulations, 2006 are hereby being repealed.

Minister of Health, the Elderly and Community Care

L.N. of 2012

MEDICINES ACT
(CAP. 458)

Medicines (Marketing Authorisation) (Amendment) Regulations, 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, the Minister of Health, the Elderly and Community Care, after consultation with the Licensing Authority, has made the following regulations:-

Title and Scope

1. (1) The title of these regulations is the Medicines (Marketing Authorisation) (Amendment) Regulations, 2012 and they shall be read and construed as one with the Medicines (Marketing Authorisation) Regulations, 2007, hereinafter referred to as "the principal regulations".

(2) The scope of these regulations is to transpose amendments to Directive 2001/83/EC on the Community code relating to medicinal products for human use, brought about by Directive 2010/84/EU, as regards pharmacovigilance and Directive 2011/62/EU, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

2. These regulations shall enter into force on 21th July 2012.

Amends Regulation 2 of the principal regulations.

3. In sub-regulation (1) of regulation 2 of the principal regulations, there shall be added the following definitions:

"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 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;

Amends Regulation 4 of the principal regulations

4. The following shall be added to Regulation 4(2)(b):

The authority may decide that regulations 10 (1) and (2) of the Medicinal Products (Labelling and Packaging Regulations) and Article 63(1) and (2) of Directive 2001/83/EC shall not apply to medicinal products authorised under paragraph (a) of these regulations.

Amends regulation 5 of the principal regulations.

5. For regulation 5 of the principal regulations, there shall be substituted the following:

"5. (1) A marketing authorisation may only be granted or renewed if the general conditions applicable to authorisations and the conditions set out under Directive 2001/83/EC on the Community Code relating to medicinal products for human use and subsequent amendments thereto, are fulfilled as follows:

(*a*) an application for marketing authorisation shall be made to the Licensing Authority which shall refer such application to the Authority for processing;

(*b*) a marketing authorisation may only be granted to an applicant established in the Community;

(*c*) the application shall be accompanied by the following documents and particulars to be submitted in accordance with Annex I:

(i) the name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer;

(ii) the name of the medicinal product;

(iii) qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organisation, where an INN for the medicinal product exists, or a reference to the relevant chemical name;

(iv) evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged;

(v) a description of the manufacturing method;

(vi) therapeutic indications, contra-indications and adverse reactions;

(vii) posology, pharmaceutical form, method and route of administration and expected shelf life;

(viii) reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment;

(ix) description of the control methods employed by the manufacturer;

(x) a written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting

audits, in accordance with Regulation 5 of the Good Manufacturing Practice in respect of Medicinal Products, Active Substances and Investigational Medicinal Products for Human Use Regulations.(S.L. 458.42) The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice;

(xi) results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests, clinical trials.

(xii) a summary of the applicant's pharmacovigilance system which shall include the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his/her tasks,
- the contact details of the qualified person,
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX,
- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept;

(xiii) the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof of the risk-management system which the applicant will introduce.

(xiv) a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of the Clinical Trials Regulations and of Directive 2001/20/EC of the European Parliament and of the Council of the 4th 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 on human use;

(xv) a summary, in accordance with Regulation 8, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in the Medicinal Products (Labelling and Packaging) Regulations, and of the immediate packaging of the medicinal product, containing the details provided for in those Regulations, together with a package leaflet in accordance with those same Regulations;

(xvi) a document showing that the manufacturer is authorised in his own country to produce medicinal products;

(xvii) copies of the following:

- any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with the provisions of Directive 2001/83/EC, as amended, is under examination.
- the summary of the product characteristics proposed by the applicant in accordance with Regulation 8 or approved by the competent authorities of the Member State in accordance with Regulation 16 and the package leaflet proposed in accordance with the Medicinal Products (Labelling and Packaging)

Regulations, or as approved by the competent authorities of the Member State in accordance with the Medicinal Products (Labelling and Packaging) Regulations.

- details of any decision to refuse authorisation, whether in the Community or in a third country, and the reasons for such a decision;

(xv) a copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, accompanied by a copy of the relevant Agency opinion;

(2) The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in sub-Regulation 1(c)(x) shall be accompanied by detailed summaries in accordance with Regulation 9.

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

(4) The information in sub-Regulation (1) shall be updated where and when appropriate."

Amends Regulation 8 of the principle regulations

6. For Regulation 8 of the principal regulations, the following sub-paragraphs shall be added:

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

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system. Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of article 107a(1) of Directive 2001/83/EC as amended.

Amends Regulation 16(b) of the principle regulations

7. For Regulation 16(b) of the principal regulations, sub-paragraphs (iii) and (iv) shall be substituted by the following:

(iii) The Authority shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Article 23 of the Medicines Act

together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised.

(iv) The Authority shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

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

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

Following sub-paragraph 16(b) a new sub-paragraph shall be inserted:

16(c) In addition to the provisions laid down in Regulation 15 of of these regulations, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(i) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(ii) to conduct post-authorisation safety studies;

(iii) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX of Directive 2001/83/EC;

(iv) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

(v) the existence of an adequate pharmacovigilance system;

(vi) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Regulation 17 of these regulations, while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC as amended.

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

Amends Regulation 17 of the principle Regulations

8. For Regulation 17 of the principal Regulations shall be substituted the following:

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

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

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

9. Following Regulation 17(a), there shall be added the following:

17(b) After the granting of a marketing authorisation, the Licensing Authority may impose an obligation on the marketing authorisation holder:

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

(ii) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the guidelines or Regulations published by the Commission pursuant to Article 22b of Directive 2001/83/EC.

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

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 30 days of receipt of the written notification of the obligation.

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

17(c) (iii) The Authority shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with Articles 21a, 22 and 22a of Directive 2001/83/EC as amended, together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised.

(iv) The Authority shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk

management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The marketing authorisation holder shall incorporate any conditions referred to in Regulations 16(b), 17(a) and 17(b) in his risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Regulations 16(b), 17(a) or 17(b).

Amends Regulation 18 of the prinicipal Regulations

(10) Regulation 18 shall be replaced by the following:

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

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

2. The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in Regulation 5(1)(c), Regulation 7 and Regulation 8 of the principal Regulations, or Article 32(5), or Annex I of Directive 2001/83/EC.

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

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

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

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

(5) After a marketing authorisation has been granted, the holder of the authorisation shall inform the Authority of the date of actual marketing of the medicinal product for human use in Malta, taking into account the various presentations authorised.
The holder shall also notify the Authority if the product ceases to be placed on the market in Malta, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

(6) Upon request by the Authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide it with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.

Amends Regulation 19 of the principral Regulations

(11) Regulation 19 shall be replaced by the following:

(1) Without prejudice to sub-Regulations (5) and (6), a marketing authorisation shall be valid for five years.

(2) The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the Authority.

(3) To this end, the marketing authorisation holder shall provide the Authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX of Directive 2001/83/EC, and information on all variations introduced since the marketing authorisation was granted, at least 9 months before the marketing authorisation ceases to be valid in accordance with sub-Regulation (1).

(4) Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national competent authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to proceed with one additional five-year renewal in accordance with sub-Regulation (2).

(5) Any authorisation granted by the Authority which within three years of its granting is not followed by the actual placing on the market of the authorised product in Malta shall cease to be valid.

(6) When an authorised product previously placed on the market in Malta is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.

(7) The Authority may, in exceptional circumstances and on public health grounds grant exemptions from sub-Regulations (4) and (5) provided that such exemptions are duly justified.

Amends Regulation 23 of the principal Regulations

12 (a) Regulation 23 sub-paragraph (4) shall be replaced by the following:

(4) The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC before any decision is reached on an application for a marketing authorisation or on the suspension or revocation

of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.";

Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) of Directive 2001/83/EC may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32 of Directive 2001/83/EC. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Regulation 65 of the Pharmacovigilance Regulations, 2012 shall apply.

However, where urgent action is considered necessary, the procedure laid down in Regulations 60 and 65 of the Pharmacovigilance Regulations, 2012 shall apply.

Amends Regulation 24 of the prinicipal Regulations

Regulation 24 sub-paragraph 2 of the principal Regulations is deleted.

Coming into force

12. The above amendments to these regulations shall come into force on the 21 July 2012 except for Regulation 5(1)(x) which sall come into force on 2 January 2013.

Minister of Health, the Elderly and
Community Care

L.N. of 2012.

MEDICINES ACT, 2003
(ACT NO. III OF 2003)

Herbal Medicinal Products (Amendment) Regulations 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, 2003, the Minister of Health, the Elderly and Community Care has made the following regulations:-

Title and scope.

(1) (1) The title of these regulations is the Herbal Medicinal Products (Amendment) Regulations, 2012 and shall be read and construed as one with the Herbal Medicinal Products Regulations, 2005 and the Medicines (Marketing Authorisation) Regulations, 2007. (S.L. 458.34)

(2) The 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.

Amends Regulation 9 of the Herbal Medicinal Product Regulations

(2) For Regulation 9(1) of the Herbal Medicinal Products Regulations, there shall be substituted the following:

9. (1) (a) Articles 2(a), 2(b), 28 (1), (2) and (6), 102, 104(a)(1) and 110 (4) of the Medicines Act (Chapter 458 of the Laws of Malta)

(b) Regulations 4(1)(a), (b), Regulation 9, Regulation 12, 15(1), 15(2), Regulation 18(1), (2) and (3), Regulations 19, 20, 26, 27, 28, 29, 30 of the Medicines (Marketing Authorisation) Regulations, (S.L. 458.34)

(c) Good manufacturing practice in respect of medicinal and investigational medicinal products for human use Regulations, (S.L. 458.42)

(d) Manufacture and Importation of Medicinal Products for Human use Regulations, (S.L. 458.36)

(e) Pharmacovigilance Regulations, (S.L. 458.35)

shall apply, by analogy, to traditional use registration granted under these regulations.

(3) The amendments to these regulations shall come into force on the 21 July 2012.

Minister of Health, the Elderly and Community Care

L.N. of 2012

MEDICINES ACT
(CAP. 458)

Pharmacovigilance Inspections Regulations, 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, the Minister of Health, the Elderly and Community Care, after consultation with the Licensing Authority, has made the following regulations:-

Title and Scope

4. (1) The title of these regulations is the Pharmacovigilance Inspections Regulations, 2012 and they shall apply to authorised medicinal products for human use, their marketing authorisation holder and any pharmacovigilance activity connected therewith.

(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 inspections, Directive 2001/83/EC on the community code relating to medicinal products for human use.

5. These regulations shall enter into force on 21st July 2012.

Interpretation

6. For the purpose of these regulations:

"Authority" means the Medicines Authority set up in terms of article 4 of the Medicines Act, 2003;

"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;

Transposed Articles

4. The Authority shall have a right to inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities described in Title IX of Directive 2001/83/EC.

5. After every inspection, the Authority shall report on whether the inspected entity complies with the requirements laid down in Title IX of Directive 2001/83/EC. The Authority shall communicate the content of the report to the inspected entity. Before adopting the report, the Authority shall give the inspected entity concerned the opportunity to submit comments.

6. If the outcome of the inspection 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 of Directive 2001/83/EC, then the Authority shall inform other EU Member States, the European Medicines Agency and the European Commission with that outcome.

Minister of Health, the Elderly and Community Care

L.N. of 2012.

MEDICINES ACT, 2003
(ACT NO. III OF 2003)

Medicinal Products (Labelling and Packaging) (Amendment) Regulations, 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, 2003, the Minister of Health, the Elderly and Community Care has made the following regulations:-

Title, and scope.

1. (1) The title of these regulations is the Medicinal Products (Labelling and Packaging) (Amendment) Regulations, 2012 and they shall be read and construed as one with the Medicinal Products (Labelling and Packaging) Regulations, 2005. (L.N.393 of 2005)

(2) The scope of these regulations is to transpose amendments to Directive 2001/83/EC on the Community code relating to medicinal products for human use, brought about by Directive 2010/84/EU, as regards pharmacovigilance and Directive 2011/62/EU, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

Amendments to Regulation 3 of the principal regulations

(3) To Regulation 3, following sub-regulation (n), the following shall be added:

(o) for medicinal products other than radiopharmaceuticals referred to in Regulation 3a (p), safety features enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:

i. verify the authenticity of the medicinal product, and
ii. identify individual packs,

as well as a device allowing verification of whether the outer packaging has been tampered with;

(p) Medicinal products subject to prescription shall bear the safety features referred to in regulation 3(o), unless they have been listed in accordance with the procedure pursuant to article 54a of Directive 2001/83/EC.
Medicinal products not subject to prescription shall not bear the safety features referred to in regulation 3(o), unless, by way of exception, they have been listed in accordance with the procedure pursuant to article 54a of Directive 2001/83/EC, after having been assessed to be at risk of falsification.

(q) The Licensing Authority may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in Regulation 3(o) to any medicinal product subject to prescription or subject to reimbursement.

(r) The Licensing Authority may, for the purposes of reimbursement, pharmacovigilance and pharmacoepidemiology, use the information contained in the repositories system as may be established by the Commission referred to in Article 54a

of Directive 2001/83/EC;

(s) The Licensing Authority may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in Regulation 3(o) to any medicinal product.

Amends Regulation 5 of the principle regulations

(4) Following Regulation 5, there shall be added a new Regulation 5a

5a Notwithstanding Regulation 8 (2) second paragraph, the Licensing Authority may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

. the price of the medicinal product,
. the reimbursement conditions of social security organizations,
. the legal status for supply to the patient
. authenticity and identification in accordance with regulation 3.

Amends Regulation 7 of the principle regulations

(5) Regulation 7(1) (e) shall be replaced by the following:

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

(6) To Regulation 7(1), following sub-article (h), there shall be added the following:

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

For all medicinal products, a standardized text shall be included, expressly asking patients to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Regulations 24 and 25 of the Pharmacovigilance Regulations (S.L. 458.35), and specifying the different ways of reporting available (electronic reporting, postal address and/or others) in compliance with the second subparagraph of Regulation 25 of the Pharmacovigilance Regulations (S.L. 458.35) .

Amends Regulation 10 of the principle regulations

(5) Regulation 10(3) shall be replaced by the following:

When the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant

an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in the official language or languages of the Member State in which the medicinal product is placed on the market;

Coming into force

(5) The above amendments to these Regulations shall come into force on the 21 July 2012 except for Regulation 3 which shall come into force on 2 January 2013.