PART XI
PHARMACOVIGILANCE
Chapter 1

General Provisions

Article 133

1. EOF applies a pharmacovigilance system in order to fulfil its pharmacovigilance competences and participate in the pharmacovigilance activities of the European Union.

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. EOF, shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on 21 September 2013 at the latest and then every 2 years thereafter. 3. EOF is the competent authority for pharmacovigilance in Greece.

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

Article 134

EOF:

1. a) takes all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions. .
   In order to achieve these objectives, EOF may co-operate, as appropriate for these tasks, with organisations representing consumers, patients and healthcare professionals as well as professional associations in the health sector.; b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats; c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports; d) ensures that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number; 2.

For the purposes of point (a) and (e) of the first paragraph, EOF may impose specific obligations on physicians, pharmacists and other health-care professionals with its decisions, which are published in the Government Gazette.

3. It proceeds with any action necessary so that the sanctions of par. 5A of article 19 of the l.d. 96/1973, as today in force and as set out in article 175 par. 2 of this decision are imposed to physicians, pharmacists or other healthcare professionals who do not communicate the suspected serious or unexpected adverse reactions,.

Article 135

EOF may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter. In reverse, EOF may accept, by written agreement thereof, the delegation to it of the said duties by another competent authority. EOF may be represented by only one Member State or may represent no more than one other Member State respectively. In case it transfers its pharmacovigilance duties, EOF shall inform the Commission, the Agency and all other Member States of the delegation in writing. EOF and the Agency shall make that information public.

Article 136

1. The marketing authorisation holder shall operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to that described in article 133, paragraph 1.

2. The marketing authorisation holder shall by means of the pharmacovigilance system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary. The marketing authorisation holder shall perform a regular audit of his pharmacovigilance system. He shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed

3. As part of the pharmacovigilance system, the marketing authorisation holder shall: a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance; b) maintain and make available on request a pharmacovigilance system master file c) operate a risk management system for each medicinal product d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 34, 35 or 36;

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 Article 136 par.3 (a) 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 EOF and the European Medicines Agency.

4. Notwithstanding the provisions of paragraph 3, the qualified person referred to in article 136 par. 3 (a) appoints a contact person for pharmacovigilance issues in Greece reporting to the qualified person responsible for pharmacovigilance activities and must meet the following criteria:

a) have exceptional knowledge of Greek and English languages.

b) have a degree, certificate or other title of studies granted after the completion of University cycle of studies or other studies, which is recognised as equivalent in Greece with a minimum term of four years in theoretical and practical courses in one of the following scientific sectors: pharmaceutics, medicine, dentistry, biology, biochemistry and chemistry, veterinary, nursing degree granted from a university.

In case of newly-entered scientists who have completed two or more University cycle of studies, of a term less than four years each, at least one of those cycles must concern an object that relates to the pharmaceutical field. In this case, the degree, certificate or other title that certifies the completion of the University cycle of studies in at least one of the above scientific sectors, it is considered adequate to meet the condition of term, provided that the degrees, certificates or other titles that certify the completion of two cycles of studies, are recognised as equivalent in Greece.

If some degrees, certificates or other titles do not meet the criteria set out above, the qualified person of article 136 paragraph 3(a) certifies in writing and on his/her responsibility to EOF that the nominated contact person has adequate knowledge in the field of pharmacovigilance.

c) must have at least a two-year experience in practice, in the field of pharmacovigilance.

d) must not be part of, nor referr to in terms of hierarchy, in sales or promotional departments.

The persons who at the date this ministerial decision enters into force, already hold the position of contact persons for pharmacovigilance issues in Greece, are excluded from the requirements of the above criteria (b) and (c).

Article 137

1. Without prejudice to paragraphs 2,3 and 4 of this article and notwithstanding the provisions of article 136 paragraph 3(c), the marketing authorisation holders are not required to operate a risk management system for each medicinal product whose marketing authorisation was granted before July 21, 2012.

2. EOF may impose an obligation on a marketing authorisation holder to operate a risk management system, as referred to in Article 136, paragrapgh 3(c), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. In that context, EOF 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. and is further obliged to comply with any suggestion or remark of EOF on the said system.

The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the detailed description of the risk-management system.
3. The national competent authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation. In case the marketing authorisation holder requests from EOF in writing, within 30 days of receipt of the written notification of the obligation referred to in the preceding paragraph, to present written observations, EOF grants the marketing authorisation holder this possibility, determining in parallel the deadline for the submission of the written observations. If the deadline for the submission of the written remarks elapses without action, the obligation of the marketing authorisation holder is finalised.
4. On the basis of the written observations submitted by the marketing authorisation holder, EOF shall withdraw or confirm the obligation... Once EOF confirms the obligation or such obligation is finalised due to the fact that the deadline for the submission of the written remarks elapsed without action, , the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in point 34(a) of this Ministerial decision, ,

Article 138

Any marketing authorisation holder who does not perform or does not duly perform its pharmacovigilance obligations, is subjected to the sanctions of paragraph 5A of article 19 of the l.d. 96/1973, which was supplemented by paragraph 4 of article 33 of law 3316/1983, for obstructing EOF's activities, as these are set out in article 175, paragraph 2 hereof.

Article 139

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 EOF in order to guarantee their independence in the performance of those pharmacovigilance activities. In order for the activities set out in the first clause to be conducted by EOF, charges that will be borne by the marketing authorisation holders are enacted by a similar to this, Joint Ministerial Decision.

CHAPTER 2
Transparency and communication

Article 140

EOF 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, EOF shall make publicly available at least the following:

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

b) summaries of product characteristics and package leaflets;

c) summaries of risk management plans for medicinal products authorised in accordance with this Ministerial Decision

d) the list of medicinal products, as referred to in article 23 of the Regulation (EC) 726/2004.

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

Article 141

1. In case the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, he shall be required to inform EOF, the European Medicines Agency and the European Commission before the public announcement is made and in case of emergency at, in parallel therewith. The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

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

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

EOF, in co-operation with the competent Authorities of other Member States, under the co-ordination of the European Medicines Agency and taking into account any advices of the Pharmacovigilance Risk Assessment Committee 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 European Medicines Agency or EOF make public information referred to in paragraphs 2 and 3, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

CHAPTER 3

Recording, reporting and assessment of pharmacovigilance data

Section 1

Recording and reporting of suspected adverse reactions

Article 142

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

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

By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive the Joint Ministerial Decision ΔΥΓ3/89292/2003 (Gov. Gazette B' 1973) for the approximation of the Directive 2001/20/EC for "clinical trials".

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

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

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non- serious suspected adverse reactions that occur in the European 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 European Medicines Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

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

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

Article 143

1. EOF shall record all suspected adverse reactions that occur in the Greek State and are brought to the attention from healthcare professionals and patients. EOF involve the patients and healthcare professionals, as appropriate, in the follow up of any reports they receive, in order to comply with article 134(c) and (e).

EOF shall ensure that reports of such adverse reactions may be submitted by means of national medicines web-portals or by any other means.

2. In case the marketing authorisation holder submits reports of events that have occurred in the Greek State, it is also responsible for the additional follow-up of the reports.
3. EOF and the competent authorities of other Member States shall collaborate with the European Medicines Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.
4. Within 15 days following the receipt of the reports for the serious suspected adverse reactions referred to in paragraph 1, EOF shall submit the reports electronically to the Eudravigilance database.

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

The marketing authorisation holders shall access those reports through the Eudravigilance database.

5. EOF shall ensure that reports of suspected adverse reactions arising from an error associated with the use of the medicinal product, that are brought to their attention are made available to the Eudravigilance database and to any authority, body, organization and/or institution responsible for the patient safety outside Greece. In addition, EOF is informed of any the suspected adverse reaction brought to the attention of any authority within Greece. These reports shall be appropriately identified in the standard forms referred to in article 25 of the Regulation (EC) 726/2004.

6. EOF shall not impose to the marketing authorisation holders any additional obligations on a separate basis, for the reporting of suspected adverse reactions, unless there are justifiable grounds resulting from pharmacovigilance activities.

Section 2
Periodic Safety Updated Reports (PSUR) (formerly Reports for the Periodic Monitoring of Safety (RPMS)

Article 144

1. Marketing authorisation holders shall submit to the European Medicines Agency periodic safety updated reports (PSUR) containing:

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

b) 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 the data from clinical trials in unauthories indications and populations.

The periodic safety updated reports shall be submitted electronically.

2. The European Medicines Agency shall make availabl the report stated in paragraph 1 to EOF, to the other competent national authorities, to the members of the Pharmacovigilance Risk Assessment Committee, to the Committee for

Medicinal Products for Human Use and to the Co-ordination Group, by the means of the repository referred to in article 25a of the Regulation (EC) 726/2004.

3. By way of derogation from paragraph 1 of this article, the marketing authorisation holders of generics or medicinal products of standard use or homeopathic medicinal products or traditional medicinal products of herbal origin, submit periodic safety updated reports (PSUR) for such medicinal products in the following cases:

a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Articles 34 or 35 or or

b) when requested by EOF or any other competent authority,on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted. The assessment reports of the requested periodic safety update reports shall be communicated to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in the articles 145, paragraph 4 and article 147 to apply.

Article 145

1. The frequency with which the periodic safety updated 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 authorization.

2. Holders of marketing authorisations which were granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 4, 5 or 6.

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

a) where a medicinal product has not yet been placed on the market, at least every 6 months following authorisation and until the placing on the market;

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

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

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the

context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.

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

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

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

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

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

a) the date of the first marketing authorisation in the European Union of a medicinal product containing that active substance or that combination active substances;

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

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

a) for reasons relating to public health, b) on order to avoid the duplication of assessment, c) in order to achieve international harmonisation. Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, shall either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made public by the Agency. The marketing authorisation holders shall accordingly submit an application for a variation of the marketing authorisation. 7. The Agency shall make public a list of European Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal

Any changes to the dates of submission and frequency of the periodic safety updated reports specified in the marketing authorisation, as a result of the application of paragraphs 4, 5 and 6, shall take effect six months after the date of such application.

Article 146

EOF cooperates with the competent authorities of other Member States to assess the periodic safety updated reports, to determine whether there are new

risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

Article 147

A single assessment of periodic safety update reports shall be performed for medicinal products authorized in more than one Member State and, in the cases of paragraphs 4 to 6 of Article 145, for all medicinal products containing the same active substance or the same combination of active substances and for which a European Union reference date and frequency of periodic safety update reports has been established.

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

a) EOF or the competent authority of another Member State which is 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;

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

When selecting EOF or of the competent authority in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 45 paragraph (1).

EOF or the competent authority of another 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 European Medicines Agency and to the Member States concerned. The European Medicines Agency shall send the report to the marketing authorization holder.

Within 30 days of receipt of the assessment report, EOF and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State provided that such authority is not EOF.

Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The European Medicines Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 25a of Regulation (EC) No 726/2004 and forward both to the marketing authorisation holder.

Article 148

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

EOF adopts the necessary measures in order to maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 149

1. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 147 paragraph 1 which does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach agreement on the action to be taken by consensus, the chairman shall record the agreement and send it to the marketing authorisation holder and the Member States. EOF 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 EOF 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 50, 51 and 52.

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

3. In the case of a single assessment of periodic safety update reports that recommends any action concerning more than one marketing authorisation in accordance with Article 147 paragraph 1 which includes at least one marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the

marketing authorisations concerned, including a timetable for the implementation of the opinion.

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

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the European Commission shall adopt, in accordance with article 50, 51 and 52 of this Ministerial Decision, a decision addressed to EOF and to the competent Authorities of other Member States, concerning the to be taken in respect of marketing authorisations granted by EOF and the competent authorities of the other Member States and concerned by the procedure provided for in this section.

Section 3
Signal Detection
Article 150

1. Regarding medicinal products authorised in accordance with this Ministerial Decision, EOF in collaboration with other Member States and the European Medicines 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 34, 35 and 36.

b) assess updates to the risk management system

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

2. EOF takes into account the initial analysis and prioritisation of the signs of new or altered risks or for any changes in the risk-benefit balance, which are prepared by the Pharmacovigilance Risk Assessment Committee as well as the evaluation of the necessity to adopt follow up measures. The assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The European Agency, EOF and the other competent authorties 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.

The marketing authorisation holders are obliged to notify the European Medicines Agency and EOF, in the event of new risks or risks that have changed or when changes to the risk-benefit balance of a medicinal product have been altered.

Section 4
Urgent Union Procedure
Article 151

1. EOF shall initiate the procedure provided for in this section, by informing the other Member States, the competent authorities of the other Member States, the European Medicines Agency and the European 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 the possibility of suspending or revoking the marketing authorisation.
b) it considers the possibility of prohibiting the supply of a medicinal product.
c) it considers the possibility of 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 is considered that a new contraindication, a reduction in the recommended dose or a restrictions to the indications, is necessary.

If the above procedure is initiated by the competent Authority of another Member State or the European Commission, EOF respectively participates as well.

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

Where the medicinal product involved is authorised in more than one Member State, EOF, if it is the authority which initiated the procedure shall be informed by the European Medicines of the outcome of this verification, and the procedures laid down in Articles 152 and 153 shall apply. Otherwise, the safety concern shall be addressed by EOF. EOF, shall make information that the procedure has been initiated available to marketing authorisation holder

2. Without prejudice to the provisions of paragraph 1 of this Article, and Articles 152 and 153, EOF may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned in the Greek State until a definitive decision is adopted. It shall inform the European Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

3. At any stage of the procedure laid down in Articles 152 to 153, EOF, if it has granted marketing authorisation for the specific medicinal product, takes into account the request, if any, of the European Comission to take temporary measures immediately.

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

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

5. If EOF initiates the procedure referred to in paragraph 1, in parallel with the information referred to in paragraph 1, he shall make available to the European

Medicines Agency all relevant scientific information that it has at its disposal and any assessment that he may have.

Article 152

1. Following receipt of the information referred to in Article 151 paragraph 1, the European Medicines Agency shall publicly announce the initiation of the procedure by means of the European medicines web-portal. In parallel, EOF may publicly announce the initiation on the national medicines web-portals.

The announcement shall specify the matter submitted to the European Medicines Agency in accordance with Article 151, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter which has been submitted to the European Medicines Agency in accordance with Article 151. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and EOF I it is the Reference Member State for the medicinal products concerned.

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

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

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

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

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

a) no further evaluation or action is required on a EU level.

b) the marketing authorisation holder must conduct a further evaluation of the data together with the follow up of the results of that evaluation

c) the marketing authorisation holder should sponsor of a post-authorisation safety study together with the follow up evaluation of the results of that study

d) risk minimisation measures must be implemented by the marketing authorisation holder or EOF and the competent Authorities of other Member States.

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

f) the marketing authorisation should be varied.

For the purposes of point 1(d), the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

Where, in the cases referred to in point 1 (f), it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and where in the summary of the product characteristics, labelling or package leaflet such wording should be placed.

Article 153

1. Where the scope of the procedure, as determined in accordance with Article 151 paragraph 4, does not include any marketing authorisation granted in accordance with the centralised procedure provided for in Chapter 1 of Title II of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, EOF 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. EOF shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

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

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in articles 50, 51 and 52.

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

3. Where the scope of the procedure, as determined in accordance with Article 151 paragraph (4), includes at least one marketing authorisation granted in accordance with the centralized procedure provided for in Chapter 1 of Title II of

Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, and on the basis of a proposal by its chairman, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

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

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission pursuant to article 50, 51 and 52 of this Ministerial Decision, adopt a decision addressed to EOF and the competent authorities of other Member States concerning the measures to be taken in respect of marketing authorisations that are granted by EOF and the competent authorities of other Member States that are subject to the procedure provided for in this section.

Section 5
Publication of assessments

Article 154

The final assessment conclusions, recommendations, opinions and decisions referred to in Articles 144 to 153 shall be made public by the European medicines web-portal.

Section 4
Supervision of the post-authorisation safety studies

Article 155

1. This Chapter applies to non-interventional post-authorisation safety studies which are initiated in Greece, managed or financed by the marketing authorisation holder of a medicinal product in Greece voluntarily or pursuant to obligations imposed by EOF in accordance with Articles 34 or 36 or the competent authority for the medicinal products of another Member State or the Pharmacovigilance Risk Assessment
2. This Chapter is without prejudice to national and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.
3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.
4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The marketing authorisation holder submits to EOF. the protocol and the progress reports in accordance with the relevant guidelines of the European Medicines Agency (Good Pharmacovigilance Practices, GVP Module VIII). An approval by EOF is required only in case the study is conducted exclusively and solely in Greece and relates to a non-interventional study that has been imposed on the marketing authorisation holder as a post-authorisation commitment.
6. The marketing authorisation holder sends to EOF, in accordance with the guidelines of the European Medicines Agency (GVPmoduleVIII), the final report on the study 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 EOF in accordance with Article 38, provided the medicinal product has a marketing authorisation in the Greek market, as well as to the competent authorities of the other Member States where the medicinal product has been approved.
The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 144.
8. Articles 156 to 159 apply exclusively to the studies referred to in paragraph 1, that are conducted in accordance with a requirement imposed by virtue of articles 34 or 36.

Article 156

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 solely in Greece following a requirement of EOF in accordance to article 38. For such studies, the marketing authorisation holder shall submit a draft protocol to EOF for approval.
2. Within 60 days from the submission of the draft protocol, E.O.F. or the Pharmacovigilance Risk Assessment Committee, shall issue:
a) a letter of approval by E.O.F. or positive opinion by the Pharmacovigilance Risk Assessment Committee for the draft protocol.
b) a letter of objections which shall set out in detail the grounds for the objection in any of the following cases:
i) if it considers that the conduct of the study promotes the use of a medicinal product;
ii) if it considers that the design of the study does not fulfil the study objectives
c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of DYG3/89292/2002 (Off. Gazette B/1973) on the transposition of Directive 2001/120/EC on clinical studies.
3. The study may commence only when the written endorsement from EOF or a positive opinion the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.
Where a letter of endorsement as referred to in paragraph 2 item (a) has been issued, the marketing authorisation holder shall forward the protocol to EOF and

the competent authority of the other Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol provided that he has also received a relevant decision from the Scientific Board of each institution where the study will be conducted.

Article 157

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to EOF or to the Pharmacovigilance Risk Assessment Committee, as appropriate. EOF 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 as well as the Scientific Board of each institution where the study is conducted.

Article 158

1. Upon completion of the study, a final study report shall be submitted to EOF or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection. The only exception to this clause is the case were EOF or the Pharmacovigilance Risk Assessment Committee, as appropriate have granted a written waiver.
2. The marketing authorisation holder estimates whether the results of the study have an impact on the marketing authorisation and, if it is considered as necessary, he submits to EOF and to the competent authorities of the other Member States that have issued a marketing authorisation, an application for its amendment. This obligation may be unilaterally imposed by E.O.F., it the latter considers that marketing authorisations holder should have done so, according to the conclusions of the study.
3. Together with the final report on the study, the marketing authorisation holder electronically submits a summary of the results of the study to E.O.F. or to the Pharmacovigilance Risk Assessment Committee, as the case may be.

Article 159

1. Based on the results of the study and following consultation with 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.
1. When recommendations are made for the variation, suspension or revocation of the marketing authorisation for a medicinal product that has been approved by E.O.F. according to the present ministerial decision, E.O.F., represented within the Co-ordination Group, participates in the formulation of a position on the matter, taking into consideration the recommendation referred to in paragraph 1 and including a timetable for the implementation of the agreed position.

If E.O.F. and the other competent Authorities of the Member States represented at the Co-ordination Group, 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 to the member states. E.O.F. 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 E.O.F. 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.
If an agreement by consensus cannot be reached, the position of the majority of the Member States in the Co-ordination Group shall be forwarded to the European Commission, which shall apply the procedure laid down in articles 50, 51 and 52.

Where the agreement reached by E.O.F. with the competent authorities of the Member States represented at the Co-ordination Group or the position of the majority differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Co-ordination Group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences, together with the recommendation.