Ε ΘΝΙΚΟΣ
Ο ΡΓΑΝΙΣΜΟΣ
Φ ΑΡΜΑΚΩΝ

Frequently Asked Questions on Pharmacovigilance

OF MEDICINES FOR HUMAN USE AND MATERIAL VIGILANCE

(Frequently Asked Questions- FAQs)

TABLE OF CONTENTS

1 GENERAL QUESTIONS

Reminder: The national implementation of European legislation is referred to in Ministerial Decrees Δ.ΥΓ3α / ΓΠ. 32221/2013 - Government Gazette 1049/B/ 29.04.2013 and the ΔΥΓ3α/Γ.Π. οικ.90023/2013 - Government Gazette 2485/B/ 3.10.2013.

There is a national requirement for a local contact point for Pharmacovigilance for the Greek territory for all MAHs.

1.1 Is it required to submit the Pharmacovigilance System Master File (PSMF) to the National Organization for Medicines (EOF)?

There is no requirement for the Pharmacovigilance System Master File (PSMF) to be submitted to EOF. The Marketing Authorization Holder (MAH) is responsible for its preparation, maintenance and update.

In the context of marketing authorization applications, the MAH should enter the relevant information referred to in Article 8 (3) (ia) of Directive 2001/83/EC (or paragraph II.B.2.1 of GVP II Pharmacovigilance System Master file) and concern the summary of the Pharmacovigilance system, in section 1.8.1 (module 1.8.1) of the application dossier.

1.2 Do the Pharmacovigilance System Master File (PSMF) and the qualified person responsible for pharmacovigilance in the EU (QPPV) have to be located in the same Country and at the same site?

The Pharmacovigilance System Master File (PSMF) shall be located either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance (QPPV)

operates (or works), regardless of its format (in print or in electronic form). The PSMF may also be located in Norway, Iceland or Liechtenstein, in accordance with European Economic Area (EEA) agreements. In the situation where the main activities of the MAH take place outside the European Union (EU), or a main site of MAH operations cannot be determined, the PSMF location should be the site where the QPPV is operating. The above information is included in paragraph II.B.2.2 of the GVP II Pharmacovigilance System Master File.

1.3 When should EOF be notified about the qualified person responsible for pharmacovigilance and what information should be provided?

EOF shall initially be notified of the name and contact information (address, 24-hour telephone number, fax number and e-mail) of the European qualified person responsible for pharmacovigilance (EU-QPPV) and the local contact person for pharmacovigilance and his/her deputy by the MAH via e-mail to adr@eof.gr. This notification will also include relevant information for the update of the Article 57 database and the current MFL number (PSMF location).

Any change to the above-mentioned data concerning the European qualified person responsible for pharmacovigilance and/or the local contact person for pharmacovigilance and/or their deputies, should be notified to EOF as described above.

1.4 What criteria should be fulfilled in order for a person to be appointed by the MAH as local contact person for pharmacovigilance?

Applicable criteria for the appointment of a local contact person for pharmacovigilance by a MAH are set out in Article 136 of the common Ministerial Decree No. Δ.ΥΓ3 α/Γ.Π. 32221/29 - 04 - 2013.*

** Relevant citation*

4. Without prejudice to paragraph 3, the qualified person referred to in Article 136 (3) (a) shall designate a pharmacovigilance contact person in Greece who shall report to the qualified person responsible for pharmacovigilance in the EU and shall meet all the following Criteria:

(a) have excellent knowledge of Greek and English

(b) hold a diploma, certificate or other evidence of formal qualifications awarded after a course of university level study or other course recognized as equivalent in Greece, of a minimum duration of four years of theoretical and practical training in one of the following disciplines: Pharmaceutical science, Medicine, Dentistry, Biology, Biochemistry and Chemistry, Veterinary medicine, Nursing (university level education).

In case of entry-level scientists who have completed two or more university courses, each lasting less than four years, at least one of the courses should be relevant to pharmaceuticals. In this case, the diploma, certificate or other evidence of formal qualifications attesting the university course in at least one of the above-mentioned disciplines, is considered satisfactory in terms of the duration condition, provided that the diplomas, certificates or other evidence of formal qualifications which certify the two courses of studies, are recognized as equivalent in Greece.

Where certain diplomas, certificates or other evidence of formal qualifications do not meet the criteria set out above, the qualified person referred to in Article 136 (3) (a) shall certify to EOF in writing and on his own responsibility, that the person concerned has sufficient knowledge of pharmacovigilance.

(c) have at least two years of practical experience specifically in the field of pharmacovigilance.

(d) do not belong to or hierarchically report to promotion or sales departments

Those who, at the date of entry into force of this Ministerial Decree, already hold the position of pharmacovigilance contact person in Greece are exempted from the requirements of the above criteria (b) and (c).

1.5 Where can someone find information on training in pharmacovigilance?

For Pharmacovigilance-related training, one should visit the site of the European Medicines Agency (EMA)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp

Additional seminars are provided by DIA at the site:

http://rs.diaglobal.org/en-GB/Meetings-and-Training.aspx

1.6 How can someone, who is a Marketing Authorization Holder (MAH) and/or a Clinical Study Sponsor, be registered in the EudraVigilance database of EMA for the first time or change the QPPV?

For a Marketing Authorization Holder or a Clinical Study Sponsor to obtain information on the steps for registering in the database of the European Medicines Agency (EMA), the following link should be consulted:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000687.jsp&mid=WC0b01ac0580a69262

In addition, the above link contains information related to the procedure to be followed for the change of QPPV in EudraVigilance.

1.7 What should be done in case of a system failure of the electronic reporting of Adverse Reactions?

In case of a system failure one should refer to the site of EMA for information:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000686.jsp#What%20to%20do%20in%20case%20of%20system%20failure

1.8 What are the obligations of an organization regarding the Pharmacovigilance system and the specifications of a quality system?

The obligations of an organization regarding the Pharmacovigilance system and the specifications of a quality system are described in detail in GVP I Pharmacovigilance systems and their quality systems.

1.9 Will there be a nullification or cancellation of Synopsis, Version I, 21.05.2007?

Due to the change in the Pharmacovigilance legislation, it would be appropriate not to take into account the afore-mentioned Synopsis. One should refer to the effective legislation and the guidelines for Good Vigilance Practices (GVPs).

1.10 Who are the nominated members of Greece at the European Pharmacovigilance Risk Assessment Committee (PRAC) and where can one find information related to nominated members from other Member States?

Information on the PRAC nominated members from Greece and from other Member States can be found by following the link below

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/PRAC/people_listing_000112.jsp

2 ADVERSE EVENT (AE) / ADVERSE REACTION (AR) REPORTING

2.1 How is the reporting of an Adverse Reaction (expected or non-expected) performed?

The reporting of an Adverse Reaction to EOF is performed by consumers and health care professionals via the below-mentioned routes:

- Via the electronic application of the Yellow Card (e- Κίτρινη Κάρτα), to which an individual can have access through EOF webpage (www.eof.gr) or by the link www.kitrinikarta.gr.

- Via fax at +30-210-6549585

- Via free postal service provided that the individual acquires the printed version of the Yellow Card from EOF. The Yellow Card must be send to: (Τμήμα Ανεπιθύμητων Ενεργειών, Μεσογείων 284, Χολαργός, Τ.Κ. 15562, Αθήνα) Department of Adverse Events, Mesogion 284, Holargos, P.C. 15562, Athens

- Via telephone (available numbers: +30-213-2040380, +30-2132040337).

Alternatively, the reporting of the Adverse Reaction can be performed by the consumers and the health care professionals (HCPs) towards the Marketing Authorization Holder (MAH) of the suspected product(s) using the contact details present in the Summary of Product Characteristics (SPC) for the HCPs and in the Patient Information Leaflet (PIL) for the consumers.

2.2 When is a follow up for a case report required and who is responsible for the above-mentioned action?

According to GVP VI section VI.B.3, a follow-up is required in the following cases:

For Adverse Reaction reports where information is incomplete. This is particularly relevant for monitored events of pregnancy, cases notifying the death of a patient, or cases reporting new risks or changes in the known risks.

For cases considered non-valid for submission to EudraVigilance (when any of the four minimum criteria is missing - patient, reporter, adverse reaction, suspect drug).

For cases where patient's age or age group are missing, especially for pediatric and elderly populations.

For cases where the Adverse Reaction is linked to a biological medicinal product and in order to improve the traceability of the products of this category, appropriate measures should be taken to clearly identify the names of the products and their batch numbers. With respect to this, it is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted report.

In cases that the report is received from a consumer, efforts should be made to obtain the consent of the patient to provide the details of his / her treating physician for the purpose of medical confirmation of the case.

In cases where an Adverse Reaction has occurred in Greece and the case has been submitted by the MAH, EOF may request the MAH to carry out additional follow-up to collect additional information on the cases referred in GVP VI section VI.C.2.1.

Responsible for performing the follow-up are the MAHs for the cases received by them and EOF for the cases received by EOF. Notification for the need of a

possible follow up is performed via EudraVigilance.

2.3 Should the treating physician be informed in cases that the report is received by a consumer?

It is not mandatory for the treating physician to be informed, when the reporter is a consumer. According to GVP VI paragraph VI.B.3, if the Adverse Event (AE) report is received from a consumer suggesting that an AE may have occurred and if the information is incomplete, then attempts should be made in order to obtain patient's consent to contact with his/her treating physician in order to obtain further information. Once the case is medically confirmed (totally or partially), there should be a documentation of that medical confirmation in the AE report.

2.4 Who is responsible for transmitting the case to Eudravigilance, when a hospital or a Health Care Professional (HCP) or a consumer sends a report to EOF and the corresponding MAH?

If the reporter provides information that support the existence of a duplicate case, a EudraVigilance check is recommended for the case, and the other recipient of the same AR should be notified of the occurrence of the duplicate case.

2.5 Where does the definition of "off-label" refer to and where can someone seek for clarifications?

The definition of "off-label" use is described in paragraphs VI.A.1.2 and VI.C.2.2.12 of GVP VI. The same definition can be found in GVP Annex I. European Medicines Agency (EMA) should be the reference source for further clarifications regarding the term.

2.6 Which are the obligations regarding an Adverse Drug Reaction

report when a medicinal product has been used off-label?

Information regarding handling of cases in which a medicinal product has been used "off-label", can be found in VI.C.2.2.12 of GVP VI.

2.7 How should a MAH handle any safety-related information originated from the internet or any other digital medium?

For the handling of any internet or digital medium derived safety-related information received by a MAH, one should refer to paragraph VI.B.1.1.4 of GVP VI.

2.8 When should the reporting obligation of a product whose license has been revoked or withdrawn stop?

Within the framework of Good Pharmacovigilance Practice, the MAH is recommended to continue the pharmacovigilance activities for a reasonable period of time after the revocation or withdrawal of the product related to the nature of the medicinal product. "A collection of ADRs within the European Union in order to facilitate any review of late presented ADRs or retrospectively reported events, is recommended" (VI.C.2.2.8 of GVP VI).

2.9 Hypothetical scenario: The suspected medicinal product belongs to another MAH (i.e. it is a product with the same active substance but marketed under a different invented name). How should the MAH who initially receives the Adverse Reaction information and has already transmitted it to EudraVigilance act?

The answer is provided in GVP VI hypothetical scenario 12. The case should not be nullified. The MAH who receives the initial information and has already transmitted it to EudraVigilance should notify the other MAH about the case. The notification should also include the 'Worldwide Unique Case Identification

Number' (ICH-E2B (R2) A.1.10 / ICH-E2B (R3) C.1.8.1). In addition, the MAH who received the initial information should submit to EudraVigilance a follow-up report mentioning that the other MAH has already been notified.

The second MAH (of the suspected medicinal product) should create a new case in EudraVigilance and specify the reference case number and the name of the initial sending Marketing Authorization Holder (ICH-E2B (R2) section A.1.11 / ICH-E2B (R3) section C.1.9.1 'Other case identifiers in previous transmissions').

If the case has not been transmitted to EudraVigilance, then action should be performed by the MAH who received the initial information to notify the concerned MAH within a reasonable period of time.

3 RISK MANAGEMENT PLANS (RMPs)

3.1 How is the submission of the revised Risk Management Plans, which do not contain (Additional) Risk Minimization Measures, performed?

The submission of Risk Management Plans of centralized procedure is performed either via initial (marketing authorization) dossier submission or via variation at e-Submission Gateway or via Web Client in eCTD-format. You may find instructions for the submission of the above Risk Management Plans on EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000171.jsp&mid=WC0b01ac0580a53f5f

The submission of Risk Management Plans of Decentralized Procedure, Mutual Recognized Procedure and National Procedure is performed either via initial (marketing authorization) dossier submission or via variation as per EOF Circular "Electronic submission of applications of Medicinal Products for Human and Veterinary use exclusively through the Common European Submission Portal (CESP)", Protocol. No: 24179, 29-03-2017. You may find additional information at below the link:

https://www.eof.gr/web/guest/home?p_p_id=62_INSTANCE_2WKd&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&_62_INSTANCE_2WKd_struts_action=%2Fjournal_articles%2Fview&_62_INSTANCE_2WKd_groupId=12225&_62_INSTANCE_2WKd_articleId=1927743&_62_INSTANCE_2WKd_version=1.0

In all the above situations, an additional submission to EOF Adverse Reaction

Department is not required.

3.2 How is the submission of the Risk Management Plans which contain (Additional) Risk Minimization Measures performed?

For Risk Management Plans which contain (Additional) Risk Minimization Measures e.g. Educational Materials, the submission of the Material(s) is performed via the general register of EOF to the Adverse Reactions Department. The following are required to be submitted:

- In paper format:

- Cover letter signed by the MAH's local contact person for pharmacovigilance (for whom the Adverse Reaction Department of EOF should have received notification), in which it should be legible written:

1) the date of submission,

2) the version of the Risk Management Plan,

3) the product name and the active substance,

4) the type of regulatory procedure which has led to the submission and its number,

5) the reason of the submission (initial submission or revision) of the material under approval (eg new risk of hepatic lesion, new indication) and the current marketing status of the product in the Greek market (it is useful to be indicated if the product will be placed immediately in market and otherwise the expected launch date),

6) the texts (of Educational Material) submitted for approval,

7) the proposed distribution/communication plan

- In digital format (in CD):

1) the texts to be approved, e.g. the Educational Material in both Greek and English,

2) the current marketing authorization of the product with its current restrictions,

3) the current Risk Management Plan

The Blue Box must be submitted supplementary in the frame of submission of (Additional) Risk Minimization Measure for new products.

For the submission of (Additional) Risk Minimization Measure(s) for a product, which is subjected to additional monitoring, the black inverted triangle and the relevant wording should be included in the texts which are under approval.

4 PERIODIC SAFETY UPDATE REPORTS (PSURS)

4.1 How is a Periodic Safety Update Report (PSUR) performed?

For products authorized through central, mutual recognition and decentralized procedure as well as products authorized through national procedure, if the active substance is listed in the EURD list and requires a PSUR submission (PSUSA single assessment procedure), the submission of the PSUR is performed through the PSUR Repository of European Medicines Agency at the following link with relevant fee:

http://esubmission.ema.europa.eu/esubmission.html

For products where the active substance is not reported in the EURD list (non-PSUSA procedure) the submission, where appropriate, shall take place both at PSUR repository (without fee deposit) and the CESP on the basis of EOF circular letter "Electronic Submission Requests for Medicinal Products for Human and Veterinary Use exclusively through the Common European Submission Portal (CESP)" Protocol Number 24179, 29-03-2017. The submission to CESP will be performed along with the submission of the relevant fee with the aim to be assessed by EOF Adverse Events Department.

The requirements for the PSUR submission are also outlined in the link:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000041.jsp&mid=WC0b01ac0580023e7d

5 SIGNAL DETECTION

5.1 How is the notification of a detected signal alert which meets the definition of Standalone Signal performed to EOF and EMA by the MAH?

A notification of a signal alert which meets the definition of the Standalone Signal according to GVP IX Signal Management is performed within 30 days after the MAH has completed the assessment of the signal and concluded that further analysis is required by the Competent Authorities. For the notification the MAH should complete the Standalone signal notification form and send it to the European Agency via email at: MAH-EV-signals@ema.europa.eu and to EOF at pv-signal@eof.gr . The notification to EOF will concern products that have been approved in Greece.

More information can be found on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp

in paragraph IX.C.4.3 of GVP IX Signal Management and in relevant EOF announcement.

5.2 How is the notification of a detected signal alert which meets the definition of an Emerging Safety Issue performed to EOF and EMA by the MAH?

A notification of a signal alert which meets the definition of an Emerging Safety Issue is performed by the MAH within 3 days from the date of establishing that a validated signal or a safety issue arising from any source meets this definition, to the European Medicines Agency at the email: p-pv-

emerging-safety-issue@ema.europa.eu and to EOF at the email: pv-esi@eof.gr . The notification to EOF will concern products that have been approved in Greece.

More information can be found on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/q_and_a/q_and_a_detail_000079.jsp&mid=WC0b01ac05800294a8

in paragraph IX.C.2 of GVP IX Signal Management and in relevant EOF announcement.

6 NON INTERVENTIONAL POST-AUTHORIZATION SAFETY/EFFICACY STUDIES PASS / PAES

6.1 What is the approval process for Non-Interventional Post-Authorization safety/efficacy PASS / PAES studies?

The above process follows the Circular 82798/22-11-2012 which stipulates that the non-interventional post-authorization safety or efficacy PASS / PAES studies that are conducted exclusively in Greece, are to be submitted for approval to EOF. The submission should be performed via the general register of EOF to the Clinical Trial Section in the form of a CD-ROM accompanied by a cover letter.

The documents that should be included in the approval dossier are described in Circulars 55480/6-9-2006 and 82798/22-11-2012.

Furthermore, in accordance to Circular 82798/22-11-2012 for non-interventional studies that are conducted in more than one Member States and are assessed and a recommendation is issued by the European Pharmacovigilance Risk Assessment Committee (PRAC), they must be notified to the Clinical Trials Section of EOF in parallel with the registration in the EU PAS Register.

6.2 When should the final safety report for Non-Interventional Safety Studies (final study report) be submitted?

In accordance with paragraph VIII, B. 4.3.2. of GVP VIII Post-authorization safety studies:

'For non-interventional PASS conducted pursuant to an obligation imposed by an EU competent authority, the final study report shall follow the format described in this section (IR Annex III) and shall be submitted within 12

months of the end of data collection'.

6.3 In PASS studies, should the progress report and the final study report be submitted together with the PSUR or separately?

In accordance with paragraph VIII, B 4.3.1. GVP VIII Post- authorization safety studies: *'Upon request from a national competent authority, progress reports for PASS imposed as an obligation or conducted voluntarily shall be submitted to the competent authorities of the Member States in which the study is conducted. Requests for progress reports may be made before the study commences or any time during the study conduct. The timing of the submission of progress reports should be agreed with the relevant competent authorities and specified in the study protocol when they have been agreed before the study commences.'*

The submission of both the progress report and the final study report should be performed separately from the Periodic Safety Update Reports (PSUR) via the General Register of EOF in electronic format (CD) with accompanying cover letter addressed to the Clinical trials Section, notifying the Adverse Events Department of EOF.

7 LITERATURE MONITORING

7.1 How does a MAH handle reports identified in literature?

MAHs are required to monitor literature in line with paragraph VI.B.1.1.2 of GVP VI.

Since 01 September 2015, European Medicines Agency is responsible for the monitoring of international literature for a list of active substances. More details regarding the MLM service are available on the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000633.jsp

According to article 107 paragraph 3 of Directive 2001/83/EC, MAHs are not required to report to Eudravigilance suspected Adverse Reactions described in the international literature for products containing active substances included in the list of substances being monitored by EMA.

MAHs are required to monitor all the remaining literature and to submit suspected Adverse Reactions.

According to GVP VI, depending on the type of the electronic submission to Eudravigilance used by the MAH, for E2B (R2) format literature articles should be send via email to: EVLIT@ema.europa.eu, whereas for E2B (R3) format they will be retransmitted to Eudravigilance (GVP VI.App.2.10).

7.2 What are the requirements for literature monitoring by the MAH in Greece according to EOF?

Monitoring of local literature (Greek journals and conferences) should be performed by the MAH. Valid reports of suspected Adverse Reactions resulting from the literature monitoring, should be transmitted to Eudravigilance within 15 calendar days for serious adverse reactions and

within 90 calendar days for non-serious adverse reactions.

Upon EOF's request for specific reports, the MAH should send the literature article, to the following email address: evlit@eof.gr. The mailing should include a copy of the full article corresponding to the Adverse Reaction, in the published language. In case acquisition of the article is not possible due to copyright restrictions, the MAH should provide at least excerpt(s) of the article which verify the safety report. Every attempt for the acquisition and dispatching of the full article should be documented by the MAH. English translation shall be requested by EOF if deemed necessary. The file will be sent to the aforementioned email address in pdf format. The file name of the literature article and the respective email should match the Worldwide Unique Case Identification Number (and in case of follow up the Worldwide Unique Case Identification Number with the respective sequence number which corresponds to the relevant follow up), according to GVP VI (VI. App.2.10).

It is clarified that the above cases will be sent to EOF only if the country of incidence in Greece.

8 PRE-APPROVAL / EARLY ACCESS PROGRAMS (COMPASSIONATE USE PROGRAMS)

8.1 Where can I find information on pre-approval access programs for groups of patients (compassionate use programs) and on the management of Adverse Reactions?

Information on the reporting of Adverse Reactions to Eudravigilance in the context of pre-approval programs for groups of patients (compassionate use programs) is provided in paragraph VI.C.1.2.2 of GVP Module VI as well as in Ministerial Decision OGG 558/ 08-04-2011.

Furthermore, the person responsible for the Pre-approval Access Program (Compassionate Use Program) should report the occurrence of any serious Adverse Reaction immediately or within no more than 15 calendar days* to the Directorate that issued the approval decision for the implementation of the Compassionate Use Program, as well as to the Adverse Reactions Department.

*If the Adverse Reaction concerns an Emerging Safety Issue, notification should be done immediately or within a notification period of no more than 3 days (see "Signal Detection").

9 DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

9.1 How is the submission to EOF of Direct Healthcare Professional Communication (DHPC) performed and what should the submission include?

The Direct Healthcare Professional Communication (DHPC) is submitted to the Adverse Reaction Department via EOF's general register. A cover letter in hard copy format and the following documents in digital form (CD) in pdf format shall be submitted:

1) The Direct Healthcare Professional Communication letter (DHPC) in English and in Greek.
2) Communication plan approved by the European Medicines Agency (EMA) along with the procedure that led to the DHPC and the reference to the Committee which approved the dissemination.
3) Suggested list of recipients in Greece.

In order to facilitate the approval all submitted documents as well as the cover letter are to be notified by the MAH via email to: adr@eof.gr.

9.2 What is the procedure when more than one MAHs are involved for one active substance?

- When the dissemination of DHPC involves several MAHs, one assumes the role of the coordinator MAH (usually the Originator) who is responsible of contacting EOF.

- Subsequently, the coordinator contacts EOF via email to: adr@eof.gr sending the DHPC in English along with the approved by EMA communication plan asking EOF for the list of all MAHs involved in the

relevant DHPC.

- After receiving the list of MAHs and with their consent, the coordinator MAH proceeds with the submission as per 9.1.

- EOF gives the final approval for the dissemination and the dispatch of the DHPC is coordinated by the coordinator MAH.

9.3 Is the proof of submission of the letters to Hellenic Post sufficient proof of dispatch?

The dispatch shall be performed via registered mail. The evidence that the recipient received the letter is considered sufficient proof of receipt of the Letter. On a second step, the return of Letters will be recorded and managed.

9.4 Where could information on the regulatory requirements concerning Direct Healthcare Professional Communication (DHPC) be found?

Information on Direct Healthcare professional Communication (DHPC) can be found in GVP XVI whereas templates of Letters on EMA website (Final GVP Annex II – Templates)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

10 MEDICAL DEVICES VIGILANCE

10.1 How is the submission of a White Card performed to EOF and to the Product Manufacturer?

The White Card, that is available at EOF's website (see below), can be printed and after its completion, it can be sent by Health Care Professionals, patients or other medical device users.

https://www.eof.gr/web/guest/whitegeneral

The White Card is sent:

i. To Product Manufacturer (or local representative) and,

ii. To EOF

By:

- Post mail to EOF Adverse Event Department, Mesogion 284, Holargos, P.C. 15562, Athens (tel.: +30 213 2040528 or +30 213 2040542),
- Fax to +30 210 6549585,
- Electronic mail to vigilancematerial@eof.gr

10.2 Which is the current legislation on Medical Devices Vigilance?

For the current legislation on Medical Devices Vigilance, guidance can be found in regulations (EU) 2017/745 and (EU) 2017/746 at the following links:

http://eur-lex.europa.eu/legal-content/yEN/TXT/?qid=1516652174694&uri=CELEX:32017R0745

http://eur-lex.europa.eu/legal-

content/EL/TXT/?uri=CELEX:32017R0746&qid=1516651845451

In addition, at the website of the European Union in regards to the current MEDDEV guidelines (2.12 Market surveillance)

https://ec.europa.eu/growth/sectors/medical-devices/guidance_en#meddevs

10.3 How a Manufacturer or Local Representative should act upon, when receiving a White Card?

Primarily, the Local Representative ensures that the reported material is send to the Manufacturer.

The Manufacturer of the material should carry out a quality check of the reported material.

The Manufacturer of the material should inform EOF for any action taken related to the incident.

Additionally, the Manufacturer informs the reporter of the results of the quality check that has been carried out.

EOF can intervene to any stage of the quality check, if deemed appropriate.

10.4 Where could the following documents be found: Manufacturer's Incident Report (MIR) Form, Field Safety Corrective Action (FSCA) Form, Field Safety Notice (FSN), Trend Report (TR), Periodic Safety Report (PSR), Device Specific Vigilance Guidance (DSVG)?

In the European Union, for uniformity purposes in regards to reporting and corrective actions for medical devices, the standard forms, as defined in the MEDDEV guidelines, are being used. Links to the aforementioned standard forms:

https://ec.europa.eu/growth/sectors/medical-devices/guidance_en#meddevs

http://ec.europa.eu/DocsRoom/documents/15506/attachments/1/translations

11 CLINICAL TRIALS PHARMACOVIGILANCE

11.1 Which is the procedure for the submission of Suspected Unexpected Serious Adverse Reactions (SUSARs) by the sponsor to EOF?

Clinical trial sponsor should follow the indirect route of SUSARs submission. According to the "Explanatory Circular of EOF no. 64745/ 7.7.2014 regarding the management and reporting of safety issues in the context of clinical trials conduct", *"Any Suspected Unexpected Serious Adverse Reaction (SUSAR) detected in the Greek territory is submitted in electronic reporting form (E2B) directly to the EudraVigilance (EVCTM) email address within 7/15 calendar days after the sponsor becomes aware of the event"*

11.2 Are Suspected Unexpected Serious Adverse Reactions (SUSARs) notified to the Investigators and when?

For the management and reporting of safety issues for the Greek territory, at least the "Explanatory Circular of EOF no. 64745/ 7.7.2014 regarding the management and reporting of safety issues in the context of clinical trials conduct" should be followed, according to which *"Any Suspected Unexpected Serious Adverse Reaction (SUSAR) derived from the site of a specific Investigator is sent to that investigator by the sponsor under reporting form (CIOMS form) within 7/15 calendar days after the sponsor becomes aware of the event"*

In addition, the Circular states that *"The Periodic Catalogue of Suspected Unexpected Serious Adverse Reactions (SUSAR -line listing) from the worldwide experience of the investigational medicinal product (e.g. from other clinical trials of the same sponsor), is sent by the sponsor to the investigator*

for his/her information according to section 7.10 of 'CT-3".

11.3 How is an (annual) Development Safety Update Report (DSUR) of an investigational medicinal product submitted to EOF?

The (annual) Development Safety Update Report (DSUR) of an investigational medicinal product is submitted in electronic format (CD) accompanied by a cover letter to the attention of the Clinical Trial's Department of EOF via EOF's general register.

11.4 Until when is the annual Development Safety Update Report (DSUR) of an investigational medicinal product to be submitted to EOF if the clinical study has been completed in Greece but not in other countries?

According to subparagraph 126 of article 8 of Directive (2011/C 172/01) "CT-3", *"The Updated Safety Report of an investigational medicinal product (DSUR) should be submitted to the National Competent Authority of the Member State and the National Ethics Committee if the treatment of patients is still ongoing in that Member State concerned".*

11.5 Should the Investigative New Drug Safety Reports (INDR) be submitted to the National Ethics Committee (NEC)?

The National Ethics Committee (NEC) will not accept submission of Investigative New Drug Safety Reports (INDR).