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## **PHARMACOVIGILANCE**

***SUMMARY OF THE OBLIGATIONS FOR MARKETING AUTHORISATION  
HOLDERS OF MEDICINAL PRODUCTS  
&  
FOR THE CLINICAL STUDIES' SPONSORS.***

# **CONTENT**

## **INTRODUCTION**

### **CHAPTER 1**

*QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE WITHIN THE EUROPEAN AREA*

### **CHAPTER 2**

*REQUIREMENTS FOR PHARMACOVIGILANCE SYSTEMS, MONITORING OF COMPLIANCE AND PHARMACOVIGILANCE INSPECTIONS*

### **CHAPTER 3**

*RISK MANAGEMENT SYSTEM*

### **CHAPTER 4**

*MANAGEMENT OF ADVERSE REACTIONS*

I. MANAGEMENT OF SPONTANEOUS ADVERSE REACTIONS

II. MANAGEMENT OF ADVERSE REACTIONS ARISING FROM INTERVENTIONAL CLINICAL TRIALS CONDUCTED IN GREECE WITH THE SUSPECT MEDICINAL PRODUCT

III. MANAGEMENT OF ADVERSE REACTIONS ARISING FROM NON-INTERVENTIONAL STUDIES (OR OTHER ORGANIZED DATA COLLECTION SYSTEMS)

### **CHAPTER 5**

*PERIODIC SAFETY UPDATE REPORT (PSUR)*

### **CHAPTER 6**

*DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION OF NEW SAFETY DATA USING “DEAR HEALTHCARE PROFESSIONAL” LETTERS (Direct Healthcare Professional Communication, DHPC)*

### **ANNEX I**

*GUIDELINES ON THE TRANSITION TO THE ELECTRONIC SUBMISSION OF ADVERSE REACTIONS*

### **ANNEX II**

*CIOMS FORM TEMPLATE*

### **ANNEX III**

*TEMPLATE OF THE CIOMS FORM COVER LETTER FOR REPORTING SPONTANEOUS ADVERSE REACTIONS*

### **ANNEX IV**

*TEMPLATE OF THE CIOMS FORM COVER LETTER FOR REPORTING ADVERSE REACTIONS FROM INTERVENTIONAL CLINICAL TRIALS*

### **ANNEX V**

*TEMPLATE OF THE CIOMS FORM COVER LETTER FOR REPORTING ADVERSE REACTIONS FROM NON-INTERVENTIONAL CLINICAL STUDIES*

### **ANNEX VI**

*DETAILS & ENVELOPE TEMPLATE OF THE “DEAR HEALTHCARE PROFESSIONAL” LETTER*

## **INTRODUCTION**

This is a summary of the requirements of EOF regarding the submission of the adverse reactions by the companies ie. of the Marketing Authorisation Holders of Medicinal Products (MAHs), the

Sponsors of Clinical Studies, the Contracted Research Organisms (CROs), conducting pharmacovigilance procedures.

This summary refers to the obligations of the companies towards EOF and possibly the competent authorities of the European Economic Area (e.g. EMEA) and not to the obligations of the companies towards independent committees such as the Ethical Committees of Institutions, the National Ethical Committee etc.

## **1. LEGAL FRAMEWORK**

1. EudraLex, Volume 9A
2. Law Nr. 2472/1997, Official Gazette Issue Nr. 50A, “Protection of the person from the treatment of personal data” and its amendments (Law nr. 3471/2006, Official Gazette Issue Nr. 133A)
3. Regulation (EC) Nr. 726/2004
4. Community Directive 2001/83/EC, as amended (2004/27/EC) and the harmonized with it Greek Legislation [ ΔΥΓ3(α)/83657, Official Gazette Issue Nr. 59B]
5. Community Directive 2001/20/EC and the harmonized with it Greek Legislation [ ΔΥΓ3/89292, Official Gazette Issue Nr. 1973B]
6. Regulations (EC) 1901/2006 & 1902/2006 (Medicinal products for pediatric use)
7. EudraLex Vol 10: ENTR/CT3 Revision 2 (Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, April 2006)
8. EudraLex Vol 10: ENTR/CT3 Revision 1 (Detailed guidance on the European Database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance- Clinical Trial Module), April 2004]

**This summary is not intended to replace the abovementioned legislations /guidelines, but only to clarify them.**

After the publication of this summary, all precedent clarifying circulars of EOF regarding pharmacovigilance and specifically

1. Circular of EOF nr. 19853/17.5.1996
2. Pharmacovigilance circular of EOF nr. 30798/21.9.1999
3. Circular of EOF nr.8929/2.2.2001
4. Clarifying circular of EOF nr.53566/3.12.2001

are not in force anymore.

## **2. PHARMACOVIGILANCE SYSTEM**

The Marketing Authorisation Holder must ensure that it has an appropriate system of pharmacovigilance in place in order to collect safety data for the products of his responsibility and to submit the relevant data to EOF, the other competent authorities of the EEA and the EMEA, following proper assessment.

The Marketing Authorisation Holder may assign some or all the functions of the Pharmacovigilance System to a third person, a Contract Research Organization (CRO), who may undertake the conduct of Pharmacovigilance or another Pharmaceutical Company (e.g. in the case of products under co-promotion). In this case, there should be a clear and detailed description of the procedures assigned to third parties under a contractual agreement. The Marketing Authorisation Holder is then responsible to inform EOF regarding such contractual agreements.

In any case the Marketing Authorisation Holder is mainly responsible for the proper function of the pharmacovigilance system through the Qualified Person responsible for Pharmacovigilance residing within the European Economic Area (EEA QPPV, see Chapter 1 & 2).

Particularly, in the frame of the pharmacovigilance system of the Marketing Authorisation Holder detailed records for all the suspected adverse events (serious or not) must be kept, that are notified to the MAH from any country worldwide (Greece, countries of the EEA and third countries outside the EEA). Additionally the MAH, should be able, anytime, to provide information to EOF, the EMEA or other competent authority, upon request.

The MAH should be able to process the pharmacovigilance data that are kept into the records of his pharmacovigilance system. Additionally the Marketing Authorisation Holder should assure the confidentiality for the personal data, that may be included into his records and to prove that he has the possibility to protect them from any natural destruction or illegal activities/ interventions of third parties.

It is clarified that there is not an upper time limit for the pharmacovigilance data to be kept. The safety data are kept indefinitely.

The Marketing Authorisation Holder is not allowed to communicate any safety data<sup>1</sup> to anyone in the Greek territory, without the previous notification and positive opinion from the Pharmacovigilance department of EOF.

It should be noted that the Marketing Authorisation Holder is obliged to submit the Detailed Description of the Pharmacovigilance System to EOF, in compliance with Chapter 2.

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<sup>1</sup> With the exception of those included in the Summary of Product Characteristics and the Package Leaflet in force and those provided by the relevant legislation concerning the promotion of the medicinal products (e.g. published studies)

## **CHAPTER 1**

### **QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE WITHIN THE EUROPEAN AREA**

#### **1. GENERAL PRINCIPLES**

The Marketing Authorisation Holder for a medicinal product in the European Economic Area should permanently and continuously have at his disposal a qualified person assigned as Qualified Person Responsible for Pharmacovigilance in the European Economic Area, EEA QPPV). The qualifications and the responsibilities of this person are defined in the Community Guideline 2001/83/EC and are described in the EudraLex, Volume 9A and the relevant clarifying guidelines.

The EEA QPPV is particularly responsible for the safety of all medicinal products for which the Marketing Authorisation Holder is holding the Marketing Authorisation in the European Economic Area and the contact person for any safety issue that would arise.

In order to facilitate the communication the Marketing Authorisation Holder may also appoint a local person responsible for the communication of pharmacovigilance issues, who would operate as a representative of the EEA QPPV in Greece and who should fulfill the following criteria:

- 1.1. He/She is a permanent employee of the Marketing Authorisation Holder in Greece
  - A permanent employee of a third company acting by proxy of the Marketing Authorisation Holder (e.g. a company providing Pharmacovigilance services, a CRO, having a contractual agreement) may be assigned as the local person responsible for the communication of pharmacovigilance issues, provided that he/she fulfills the criteria 1.2, 1.3.
- 1.2 He/She is a scientist in the sector of Health (a Physician, a Pharmacist, a Veterinarian, a Dentist, a Nurse of University Education) or
  - Scientist in the area of Bio-sciences (Biologist, Biochemist, Geneticist etc) provided that his/her CV proves that he/she disposes expertise in the pharmacovigilance sector.
- 1.3. The local person responsible for the communication of pharmacovigilance issues should not report hierarchically to the Sales and Marketing Departments of the company.

The responsibilities of the EEA QPPV and of the local person responsible for the communication of pharmacovigilance issues should be described in the detailed description of the Pharmacovigilance System of the Marketing Authorisation Holder (see Chapter 2), the organogram of the Marketing Authorisation Holder and in any agreement for the conduct of work contracted with third parties (contractual agreements) and would be available for inspection at any time.

#### **2. COMMUNICATION CONTACT DETAILS REGARDING PHARMACOVIGILANCE ISSUES**

The Marketing Authorisation Holder must submit to EOF<sup>2</sup>:

##### **2.1 Contact details of the EEA QPPV:**

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<sup>2</sup>This procedure doesn't depend upon the submission of the Detailed Description of the Pharmacovigilance System

- Full Name
- Qualification
- Short C.V.
- Telephone number for communication (company's and 24-hour availability)
- Fax number
- E-mail

2.2 Contact details of the local person responsible for the communication of pharmacovigilance issues.

- Full name
- Qualification
- Short C.V.
- Telephone number for communication (company's and 24-hour availability)
- Fax number
- E-mail

The abovementioned details are submitted to the general register of EOF to the attention of the Pharmacovigilance Department and are also sent electronically (by e-mail) to the address [adr@eof.gr](mailto:adr@eof.gr). Any modification of the communication details should be directly notified to EOF by the Marketing Authorisation Holder and the detailed description of the pharmacovigilance system should be properly updated.

## CHAPTER 2

### REQUIREMENTS FOR PHARMACOVIGILANCE SYSTEMS, MONITORING OF COMPLIANCE AND PHARMACOVIGILANCE INSPECTIONS

The requirements regarding the pharmacovigilance system of the Marketing Authorisation Holder are set out in the Vol 9A (Requirements for the Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections).

#### 1. DETAILED DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEM

A detailed description of the Pharmacovigilance system is composed on the basis of the instructions of the Vol. 9A (Chapter 1.2) and with the responsibility of the Qualified Person Responsible for Pharmacovigilance.

The detailed description of the pharmacovigilance system is composed in English and refers to all the products for which the Marketing Authorisation Holder is responsible. If there are specific pharmacovigilance procedures for a certain product –in addition to the general ones described in the detailed description of the pharmacovigilance system- they should be annexed to the system.

For the products that have already a marketing authorisation the submission of a detailed description of the pharmacovigilance system retrospectively is not required. However, after the publication of this guidance, a detailed description of the pharmacovigilance system should be submitted by the Marketing Authorisation Holder together with the upcoming application for a variation of the product.

The detailed description of the pharmacovigilance system is part of the Marketing Authorisation / Variation Application dossier of the product (Module 1/ section 1.8.1). The detailed description of the pharmacovigilance system is submitted to the Pharmacovigilance department of EOF. It should be submitted in parallel with the Marketing Authorisation / Variation Application of the product, while in the Marketing Authorisation / Variation Application of the product a copy of the document substantiating the submission of the last updated detailed description of the pharmacovigilance system should be included. In cases where this document hasn't been submitted, and in case that the submitted last updated description of the pharmacovigilance system has been assessed to be inadequate, the application for the authorisation or the variation is not accepted.

The local Marketing Authorisation Holder (a representative, or the local company providing pharmacovigilance services) representing products of different pharmaceutical companies that have in place different Pharmacovigilance systems, is required to submit a Detailed Description separately for each one Pharmacovigilance Systems, stating clearly the products to which each system refers<sup>3</sup>.

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<sup>3</sup>It is clarified that each detailed description of the pharmacovigilance system is required to include the data regarding the activities of the local representative / company providing pharmacovigilance services. These activities may be submitted as an annex to the detailed description of the main pharmacovigilance system (eg. The parent company).

The detailed description of the pharmacovigilance system is submitted via CD-Rom, in English to the EOF general register .

## **2. MONITORING OF COMPLIANCE AND PHARMACOVIGILANCE INSPECTIONS**

EOF should monitor the adequacy of the pharmacovigilance system of the Marketing Authorisation Holder.

The monitoring of the adequacy of the pharmacovigilance systems and the potential inspections of the Marketing Authorisation Holder should be performed in compliance with the guidelines set out in Vol. 9A (Chapter 1.2).

## CHAPTER 3

### RISK MANAGEMENT SYSTEM

A Risk Management System is a set of pharmacovigilance activities designed to identify, characterise, prevent or minimise the risks in relation to the use of medicinal products and to assess the effectiveness of those interventions.

The requirements for the existence of a Risk Management System, in Greece and generally in the EEA, is fulfilled with the submission of a Risk Management Plan.

Detailed instructions regarding the elaboration of a Risk Management Plan (needs for the elaboration, the mode of the presentation, the mode of the application, the assessment of the effectiveness) are set out in the relevant chapter of EudraLex Vol 9A (Chapter 1.3).

It should be noted that the Risk Management Plan might be necessary to be submitted in both the pre- authorisation and the post-authorisation phase.

Regardless of the registration procedure of the Pharmaceutical Product, the EEA QPPV of the Marketing Authorisation Holder is responsible for the final elaboration, the presentation, the overall application and assessment of the Risk Management Plan in Europe.

#### **1. MEDICINAL PRODUCTS AUTHORISED THROUGH THE CENTRALISED PROCEDURE:**

- Pre-authorisation and post- authorisation phase:  
The instructions set out in Vol 9A (Chapter 1.3.4) should be followed regarding the elaboration of a Risk Management Plan.

The Risk Management Plan which has been approved by the EMEA is notified to EOF by the Marketing Authorisation Holder. The notification includes the original (approved by the EMEA) and the educational material adjusted<sup>4</sup> to the Greek language. The notification should be accompanied by a letter by which the local person responsible for pharmacovigilance issues confirms the accurate implementation of the Risk Management Plan in Greece. The submitted Risk Management Plan is considered to be approved provided that the Pharmacovigilance department of EOF doesn't express any objection.

Any deviation from the centrally approved Risk Management Plan should be showed, the local Marketing Authorisation Holder is required to report the reasons of the deviation. In such case the Marketing Authorisation Holder doesn't proceed to apply the Plan until the local Risk Management Plan has been approved by EOF.

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<sup>4</sup> The adjustment of the educational material (eg. For the healthcare professionals, the patients, etc) into the Greek language, is made with the collaboration of the local person responsible for the communication of pharmacovigilance issues of the Marketing Authorisation Holder of the product in Greece.

## **2. MEDICINAL PRODUCTS AUTHORISED THROUGH THE MUTUAL RECOGNITION/ DECENTRALISED PROCEDURE**

The instructions of the Vol. 9A (Chapter 1.3.4) are applied.

- Pre-authorisation phase:

The Risk Management Plan (original<sup>5</sup> and adjusted in the Greek language<sup>6</sup>) is submitted to the Pharmacovigilance Department of EOF and the document substantiating this submission is included into the Marketing Authorisation Application dossier submitted to the the Administrative Services Department for the Monitoring of the Medicinal Products of EOF.

The submitted Risk Management Plan is considered to be approved, provided that the Pharmacovigilance department of EOF doesn't express any objection until the date of approval of the medicinal product.

- Post-authorisation phase:

The Risk Management Plan (original<sup>5</sup> and adjusted in the Greek language<sup>6</sup>) is submitted to the Pharmacovigilance Department of EOF and its implementation should be approved by EOF.

## **3. MEDICINAL PRODUCTS AUTHORISED THROUGH NATIONAL PROCEDURE:**

The instructions described for the medicinal products authorised through the mutual recognition/ decentralized procedure should be followed. The Risk Management Plan submitted first in any country of the EEA is considered to be the "original" one.

Regardless of the registration procedure followed, the Risk Management Plan is submitted to the Pharmacovigilance Department of EOF, in parallel as hard copy and via CD-ROM, to the general register of EOF.

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<sup>5</sup> The Risk Management Plan submitted to the Reference Member State (in English).

<sup>6</sup> The adjustment of the educational material (eg. For the healthcare professionals, the patients, etc) into the Greek language, the submission of the Risk Management Plan and its implementation in Greece is made with the collaboration of the local person responsible for the communication of pharmacovigilance issues of the Marketing Authorisation Holder of the product in Greece.

## CHAPTER 4

### MANAGEMENT OF ADVERSE REACTIONS

#### GENERAL PRINCIPLES FOR THE ELECTRONIC SUBMISSION OF INDIVIDUAL CASE REPORTS

After the publication of this guidance, any communication of individual case reports should be made electronically. The case narrative for any electronically submitted individual event should be made in English.

In principle, any event identified in the Greek territory and fulfilling the requirements for expedited reporting to EOF should be sent electronically, using EudraVigilance, to the address of EOF (GEOF).<sup>7</sup> EOF is then responsible to inform the central data base of EudraVigilance in relation to the case received.

Any event identified in non EEA countries fulfilling the requirements for expedited reporting, should not be sent to GEOF. The events occurred in non EEA countries should be sent, with the responsibility of EEA QPPV, directly to the central data base of EudraVigilance at EMEA (EVPM or EVCTM).

- In order to avoid duplicate reporting to the central data base of the EudraVigilance, any event that a Marketing Authorisation Holder (MAH) reports to EOF (GEOF) should not be sent by the MAH to the central data base of EudraVigilance. Similarly, any event sent directly by the MAH to the central data base of the EudraVigilance should not be sent to EOF (GEOF) by the MAH.

Any event occurring in another EEA country, should be reported in compliance with the local legislation and the circulars in force into the country, where the event has occurred and under the responsibility of the EEA QPPV.

The electronic submission through EudraVigilance may be performed either centrally, or locally. In any case the EEA QPPV defines the person(s), who will be responsible for the electronic submission of the individual case reports.

It is necessary for the MAH to provide as many information as possible in relation to the adverse reactions, in the timelines defined as follows.

It is expected that **the initial report** will be followed by **complementary follow-up reports**, in order that a more complete description of the event could be formed.

The timelines for the submission of adverse reactions to EOF, the EMEA and the other authorities into EU, are in force **for the initial report and for any complementary follow-up report**.

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<sup>7</sup> After the publication of this guidance and until a new notice is published and only for the events occurring in Greece (and therefore are sent to GEOF): the same event should be submitted via a CIOMS form to the general register of EOF (to the attention only of the Pharmacovigilance Department).

It should be noted that all the reports received by EOF directly from other sources except the from the Marketing Authorisation Holder (eg. through the Yellow Card), will be forwarded electronically to the Marketing Authorisation Holder and the EMEA, concomitantly.

The requirements regarding the management of the adverse reactions sent to EOF are set out in the following sections<sup>8</sup>.

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<sup>8</sup> For the cases of medicinal products approved or under approval through the mutual recognition /decentralised procedure: The EU QPPV of the MAH is required to ensure the reporting of all the individual events set out in Chapter 4 (section I,II,III) to the reference member state (RMS, rapporteur) taking into account the requirements of the legislation of the reference member state.

## 1. MANAGEMENT OF SPONTANEOUS ADVERSE REACTIONS

### 1. SPONTANEOUS REPORTS FROM HEALTHCARE PROFESSIONALS OCCURRING INTO THE GREEK TERRITORY

For all medicinal products independently of the registration procedure the Marketing Authorisation Holder should report all the **Suspected Serious Adverse Reactions** brought to their attention by a healthcare professional and occurring in Greece within **15 calendar days** from the initial receipt of the information (**expedited procedure**).

Any suspected transmission via a medicinal product of an infectious agent occurring in Greece is considered a serious adverse reaction and is reported accordingly.

The management of the adverse reactions occurring in Greece will be performed via EudraVigilance, as it is set out afterwards:

The notification to EOF is conducted by reporting directly to the electronic address of EOF (production ID) in EudraVigilance, which is: GREOF

The Marketing Authorisation Holder files the electronic acknowledgment of receipt of the event to the address GREOF.

- Non serious adverse reactions occurring in Greece are reported through the expedited procedure only upon request of EOF, otherwise they are included into the upcoming PSUR.
- All the reports forwarded to the Marketing Authorisation Holder by EOF, should be examined by the Marketing Authorisation Holder and be included to the upcoming PSUR. If the Marketing Authorisation Holder has made any variation to the content of the event (eg. an addition of comments) then he is required to send the event to EOF within the same time lines.

### 2. SPONTANEOUS REPORTS FROM HEALTHCARE PROFESSIONALS OCCURRING IN NON-EEA COUNTRIES.

The Marketing Authorisation Holder, independently of the registration procedure of the medicinal product, is requested to record and to report to EMEA all the **Suspected Serious Unexpected<sup>9,10</sup> Adverse Reactions** and any **suspected transmission of infectious agent via a medicinal product** brought to his knowledge **from non-EEA countries, within 15 calendar days** from the initial receipt of the information (expedited procedure).

The management of the Adverse Reactions occurring in non-EEA countries would be performed using the EudraVigilance, as it is set out afterwards:

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<sup>9</sup> Unexpected in relation to the (last approved) Summary of Product Characteristic in force in Greece.

<sup>10</sup> It is suggested, in compliance to Vol. 9A, the expedited reporting, even for all the expected serious adverse reactions from non-EEA countries, provided that the submission is made directly to the electronic address of the central data base of EudraVigilance (EVPIM).

2.1 The EMEA is notified by sending the report directly to **the electronic address of the central data base of the EudraVigilance EVPM (EVHUMAN)** and not to the electronic address of EOF (in relation to the events outside of EEA, the direct notification to the EMEA is concomitantly notification to EOF).

2.2. The responsible person for the transmission of the electronic report is filing the acknowledgment of receipt by the EVHUMAN.

- The abovementioned are in force also for the reports received by the Marketing Authorisation Holder via the Competent Authorities of the non-EEA countries.
- The serious expected and non serious adverse reactions from non-EEA countries are reported through the expedited procedure only on request of EOF or of the EMEA, otherwise they are included to the upcoming PSUR.

### **3. REPORTS OF WHICH THE MARKETING AUTHORISATION HOLDER IS RATIONALLY EXPECTED TO BE AWARE**

Independent to the registration procedure of the medicinal product, the Marketing Authorisation Holder is obliged to record in its pharmacovigilance system and to report to EOF electronically any other serious adverse reaction, of which he rationally is expected to be aware.

Some characteristic cases of reports that the Marketing Authorisation Holder is rationally expected to be aware are (see EudraLex Vol. 9A):

- Reports from the literature, published announcements from congresses<sup>11</sup>. The relevant article /publication should also be sent to EOF, using the electronic mail to the address [adr@eof.gr](mailto:adr@eof.gr). This article should be in pdf format with the title defined in Vol 9A (Chapter III.7).
- Events reported in the website of the direct responsibility of the Marketing Authorisation Holder and events that are notified through the web.
- Reports from patients or other consumers, that have been confirmed by a healthcare professional.
  - The date of the receipt of the event is considered to be the date of the initial notice to the Marketing Authorisation Holder from the consumer.
  - The Marketing Authorisation Holder should make any effort to confirm the event (fax, electronic mail, telephone communication). The reports from consumers that bear attached the relevant documents (the opinion of a physician, the laboratory examinations, the death certificate etc) are considered medically confirmed reports. See EudraLex Vol.9A.
  - If the event has not been medically confirmed, it is not sent to EOF using the expedited procedure. In such a case it is included into the upcoming PSUR.
  - If the event is medically confirmed and meets the criteria for the expedited report to EOF it will be submitted within 15 calendar days after the date of the receipt of the confirmation.
- The reports from the compassionate/named patient use, since the therapy is not applied in the frame of an interventional clinical trial. The definition for the compassionate therapy is given into the regulation 726/2004 EC and in the EudraLex Vol. 9A.

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<sup>11</sup> If it is not possible to identify the trade name of the suspect medicinal product mentioned in the publication: in order to avoid duplicate submissions of the same event from different MAHs, only the cases for the products marketed in Greece will be reported. A contractual agreement is allowed between the MAHs concerned in order that the submission of the publications from the literature in relation to the products with the same active ingredient is not duplicate. This agreement should be mentioned into the detailed description of the pharmacovigilance system of the MAH.

The method for the management of the adverse reactions for which the Marketing Authorisation is expected to be aware is described above for the Spontaneous Adverse Reactions from Healthcare Professionals. For the events coming from the Greek territory the guidance of the Paragraph 1 is followed, but for the events coming from non- EEA countries the guidance of the Paragraph 2 applies.

In the reports which the Marketing Authorisation Holder is expected to be aware of the reports from non-interventional studies or from other organised data collection systems, of the competence of the Marketing Authorisation Holder are also included. The management of these events is described in the section III.

#### **4. REQUIREMENTS FOR REPORTING IN SPECIAL SITUATIONS**

The requirements for reporting that have been described above apply also to the special situations, as they are laid out in EudraLex Vol.9A (chapter 1.5). These special situations include:

- Reporting in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation.
- Reporting following suspension or withdrawal of the marketing authorisation for safety or commercial reasons, upon request of EOF or the EMEA.
- Reporting of outcomes of use of a medicinal product during pregnancy.
- Reporting of adverse reactions after the use of a medicinal product during breastfeeding.
- Reporting of data on use of medicinal products in children.
- Reporting of lack of efficacy.
- Reporting in relation to overdose, abuse or misuse
- Reporting of medication errors
- Reporting in the event of a public health emergency.

The criteria for reporting in these special situations are in force as they are described in Vol. 9A.

#### ***CLARIFICATION:***

*It is noted that in this phase any spontaneous report, , submitted electronically to the electronic address of EOF (GEOF)<sup>12</sup>, should be submitted concomitantly in hard copy via CIOMS form (see Annex II), accompanied by the document of the Annex III).*

*The hard copy should be submitted via the general register of EOF, to the attention of the Pharmacovigilance Department.*

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<sup>12</sup> i.e. the events occurring only inside the Greek territory

## II. MANAGEMENT OF ADVERSE REACTIONS ARISING FROM INTERVENTIONAL CLINICAL TRIALS CONDUCTED IN GREECE WITH THE SUSPECT MEDICINAL PRODUCT

The investigator is obliged to report to the Sponsor any Serious Adverse Event arising during the conduct of the clinical trial, **as soon as possible**<sup>13</sup>. Only upon request of EOF, the Investigator provides information to EOF directly.

The Sponsor is responsible for the continuous monitoring of the safety of the investigational product (including any comparator product of the clinical trial)<sup>14,15</sup>. The Sponsor should have at his disposal systems and Standard Operating Procedures (SOPs), through which he ensures the reliable and qualitative collection of data, the maintenance, the validation, the assessment, the recording and the reporting of the events.

### REPORTS OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

The Sponsor of an interventional clinical trial that is conducted in at least one , investigational site in the Greek territory (from the initiation of the first investigational site – even if the study was at the screening phase and yet any patient had not been enrolled ) and through out the conduct of the study [as defined in the approved protocol of the study in relation to the requirements of the safety monitoring or at least until the close out visit of the last investigational site of the trial in Greece], has the obligation to report electronically (using the EudraVigilance) the Suspected Unexpected Serious Adverse Reactions (SUSAR), notified to him.

#### 1. EXPEDITED REPORTING OF SUSAR

The management of the Suspected Unexpected Serious Adverse Reactions (SUSAR), related to the conduct of interventional clinical trials is described in the Tables 1 and 2 dependent to whether the events occur in the frame of the interventional clinical trial or are coming from other sources, except of interventional clinical trials.

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<sup>13</sup>It is expected that the Investigator informs the Sponsor within 24 hours from the time he becomes aware of the serious adverse event.

<sup>14</sup> a) When the Sponsor is also the Marketing Authorisation Holder (or applicant) of the Investigational Medicinal Product, he should be aware of all the safety data of the product worldwide, independent of their source of reporting [reporting described in the Sections I and III (Chapter 4) and reporting from interventional clinical trials].

b) When the Sponsor is not the Marketing Authorisation Holder (or applicant) for the Investigational Medicinal Product, he should be aware of all the safety data of the product, arising from any study (interventional clinical trial, non-interventional study etc) in which he also is the Sponsor, worldwide.

<sup>15</sup> Regarding the adverse reactions for which a co-administrated investigational medicinal product is considered suspect: if the Sponsor is also MAH of the suspect medicinal product, he is obliged to report the event to EOF, within the timelines in force. If the Sponsor is not MAH of the suspect medicinal product, it is considered to be **worthwhile** to inform the MAH of the suspect medicinal product. After the sponsor informs the MAH, the MAH should submit the event to EOF within the timelines **in force**.

It is clarified that the SUSAR occurring in other EEA countries should be forwarded to the relevant country in compliance with the legislation in force (under the responsibility of the EEA QPPV) and therefore have not been included in the following tables.

Table 1. Management SUSAR occurring during interventional clinical trials							
Frame where the event occurred	State of approval in EEA	Country of origin of SUSAR	Destination (transmission to)	Time lines for the submission	Form	Person submitting	Relevant legislation/ references
A. When SUSAR is arising from interventional clinical trial and there is at least one investigational site in Greece and the Sponsor or the person acting on behalf of the Sponsor conducts the trial:							
Interven. Clinical trial	Pre- authorisation <sup>17</sup>	Greece	GREOF <sup>18</sup>	7/15 days <sup>19</sup>	E2B <sup>20</sup>	Sponsor (inside EEA)	2001/20/EC
Interven. Clinical trial	Post- authorisation <sup>21</sup>	Greece	GREOF	7/15 days	E2B	Sponsor (inside EEA)	2001/20/EC
Interven. Clinical trial	Pre- authorisation	Outside EEA <sup>22</sup>	EVCTM <sup>23</sup>	7/15 days	E2B	Sponsor (inside EEA)	2001/20/EC
Interven. Clinical trial	Post- authorisation	Outside EEA	EVCTM	7/15 days	E2B	Sponsor (inside EEA)	2001/20/EC
B. When SUSAR is arising from interventional clinical trial without any investigational site in Greece, but the investigational medicinal product is investigated in another interventional clinical trial to at least one investigational site in Greece and the Sponsor or the person acting on behalf of the Sponsor conducts the trial in Greece:							
Interven. Clinical trial	Pre- authorisation	Outside EEA	EVCTM	7/15 days	E2B	Sponsor (inside EEA)	2001/20/EC
Interven. Clinical trial	Post- authorisation	Outside EEA	EVCTM	7/15 days	E2B	Sponsor (inside EEA)	2001/20/EC, EudraLex Vol 9A
C. When SUSAR is arising from interventional clinical trial without any investigational site in Greece and the Investigational Medicinal Product is not investigated in another interventional clinical trial in Greece:							
Interven. Clinical trial	Pre- authorisation	Outside EEA	None	None	None	None	The submission is not required
Interven. Clinical trial	Post- authorisation	Outside EEA	EVCTM	15 days	E2B	MAH <sup>24</sup> (inside EEA)	2001/83/EC, Vol 9A (see section I) <sup>25</sup>

<sup>16</sup> the person who submits: the person who is responsible to ensure the submission to the central base of EudraVigilance and to the members of EEA.

<sup>17</sup> Pre-authorization: when any marketing authorisation for the medicinal product in any EEA country **does not** exist.

<sup>18</sup> GREOF: the electronic address of EOF in EudraVigilance.

<sup>19</sup> 7/15 days: in case of death or life threatening SUSAR the initial submission is made until the 7<sup>th</sup> calendar day since the event was brought to the knowledge of the Sponsor, followed by a follow up report within the next 8 calendar days. For all the remaining SUSARs the initial submission should only be performed until the 15<sup>th</sup> calendar day.

<sup>20</sup> ICH E2B: see Data elements for transmission of individual case safety reports, Amended Guideline

<sup>21</sup> Post-authorization: when there is a marketing authorisation in at least one EEA country

<sup>22</sup> Outside EEA: SUSAR occurred in a country outside the European Economic Area

<sup>23</sup> EVCTM: Where is mentioned EVCTM, the sponsor doesn't transmit SUSAR to the electronic address of EOF (GREOF). But he has the obligation to ensure that SUSAR is sent to the central data base of EudraVigilance (Clinical Trial Module).

<sup>24</sup> MAH: the person responsible for the communication of pharmacovigilance issues of the Marketing Authorisation Holder in Greece or the person responsible for the Pharmacovigilance in EEA (EEA QPPV)

<sup>25</sup> The reporting of these SUSARs is made on the basis of section I (Paragraph 2) of the Chapter 4 of this guidance.

Table 2. Management of case reports that meet the criteria for SUSAR and that occur out of the frames of any interventional clinical trial <sup>26</sup> .							
Frame where the event occurred	State of approval in EEA	Country of origin of SUSAR	Destination (transmission to)	Time lines for the submission	Form	Person submitting	Relevant legislation/ references
A. When SUSAR occur out of the frames of any interventional clinical trial, but it concerns the medicinal product used as the Investigational Medicinal Product in one at least investigational site in Greece during the conduct of a interventional clinical trial and the Sponsor or the person acting on behalf of the Sponsor is conducting the trial.							
Out from any Interventional Clinical Trial	Pre-authorisation <sup>29</sup>	Greece	GREOF <sup>30</sup>	7/15 days <sup>31</sup>	E2B <sup>32</sup>	Sponsor (inside EEA)	2001/20/EC, only if the sponsor is aware of the event
Out from any Interventional Clinical Trial	Post-authorisation <sup>33</sup>	Greece	GREOF	15 days	E2B	MAH <sup>34</sup> (Inside EEA)	2001/83/EC, 726/2004, Vol 9A (see section I) <sup>35</sup>
Out from any Interventional Clinical Trial	Pre-authorisation	Outside EEA <sup>36</sup>	EVPM <sup>37</sup>	7/15	E2B	Sponsor (inside EEA)	2001/20/EC, only if the sponsor is aware of the event.
Out from any Interventional Clinical Trial	Post-authorisation	Outside EEA	EVPM	15 days	E2B	MAH (inside EEA)	2001/83/EC, 726/2004, Vol.9A (see section I) <sup>38</sup>

<sup>26</sup> Out from any interventional clinical trial: refers to the adverse reactions described in sections I and II

<sup>27</sup> The person who submits: the person who is responsible to ensure the submission of the reports to EudraVigilance and to the members of EEA

<sup>28</sup> It is clarified that this table outlines the additional obligations of the Sponsor or the MAH for the electronic submission of the adverse reactions when interventional clinical trials with the suspect medicinal product are conducted. If interventional clinical trials with the investigated medicinal product are not conducted, should apply the obligations in line with the sections I and III.

<sup>29</sup> Pre-authorisation: when any marketing authorisation in any EEA country doesn't exist.

<sup>30</sup> GREOF: GREOF: the electronic address of EOF in EudraVigilance.

<sup>31</sup> 7/15 days: in case of death or life threatening SUSAR the initial submission is made until the 7<sup>th</sup> calendar day since the event was brought to the knowledge of the Sponsor, followed from a follow up report within the next 8 calendar days. For all the remaining SUSARs the initial submission should only be performed until the 15<sup>th</sup> calendar day.

<sup>32</sup> ICH E2B: see Data elements for transmission of individual case safety reports, Amended Guideline

<sup>33</sup> Post-authorisation: when there is a marketing authorisation in at least one EEA country

<sup>34</sup> MAH: **the person responsible for** the communication of **pharmacovigilance issues** of the Marketing Authorisation Holder in Greece or the person responsible for the Pharmacovigilance in EEA (EEA QPPV)

<sup>35</sup> The reporting of these SUSARs is made on the basis of section I (Paragraph 1) of the Chapter 4 of this guidance

<sup>36</sup> Outside EEA: SUSAR occurred in a country outside the European Economic Area

<sup>37</sup> EVPM: Where is mentioned EVCTM, the sponsor doesn't transmit SUSAR to the electronic address of EOF (GREOF). But he has the obligation to ensure that SUSAR is put in central data base of EudraVigilance (Post-marketing Module).

<sup>38</sup> The reporting of these SUSARs is made on the basis of section I (Paragraph 2) of the Chapter 4 of this guidance

In any case of electronic submission of SUSAR, the Sponsor is filing the electronic acknowledgement received from the relevant electronic address to which he sent the SUSAR.

**CLARIFICATION:**

*It is noted that in this phase any SUSAR, , submitted electronically to the electronic address of EOF (GEOF)<sup>39</sup>, should be submitted concomitantly in hard copy, also, via CIOMS form (see Annex II), accompanied by the document of the Annex IV).*

*The hard copy should be submitted via the general register of EOF, to the attention of the Pharmacovigilance Department.*

**2. PERIODIC REPORTS OF SERIOUS ADVERSE REACTIONS**

The following reports should be submitted directly after the initiation of the first investigational site – even if the study is in the screening phase and no patients have been enrolled yet- and through out the conduct of the trial [as it is defined in the approved protocol of the trial, in relation to the follow up of the safety of the patients or at least until the close out visit of the last investigational site of the trial in Greece].

**2.1 Annual Safety Report of Serious Adverse Reactions**

The Sponsor has the obligation to submit to the Pharmacovigilance Department of EOF through out the clinical trial, the line listing of all the Serious Adverse Reactions (including SUSARs) occurring worldwide, in relation to the investigational medicinal product administrated in the frame of an interventional clinical trial in Greece.

This line listing should also include a summary of the safety of the medicinal product, demonstrating the data of the related period.

The periodicity of the submission is annual and the date of the first approval of the first interventional clinical trial with the specified medicinal product, worldwide, is considered as the initial (birth) date.

The timelines for the submission of the report is **60 days** from the data lock point of the report.

This line listing is submitted in the electronic form (CD-ROM) **only**, via the general register of EOF.

**2.2 6-monthly Report of Suspected Unexpected Serious Adverse Reactions**

The Sponsor has the obligation to submit to the Pharmacovigilance Department of EOF a line listing of all the Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring worldwide, in relation to the investigational medicinal product administrated in the frame of an interventional clinical trial in Greece.

This line listing should also include a summary of the safety of the medicinal product, demonstrating the data of the related period.

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<sup>39</sup>Regarding the events occurring only in the Greek territory.

The periodicity of the submission is 6-monthly and the date of the first approval of the first interventional clinical trial with the specified medicinal product, worldwide, is considered as the initial (birth) date.

The timelines for the submission of the report is **60 days** from the data lock point of the report.

This line listing is submitted in the electronic form (CD-ROM) **only**, via the general register of EOF.

### **3. SPECIAL SITUATIONS OF REPORTING TO EOF IN RELATION WITH SAFETY ISSUES**

The Pharmacovigilance Department of EOF should be notified in an expedited manner (within 15 calendar days) regarding any change of the safety data found out during the conduct of an interventional clinical trial, in case that this change, after the assessment by the Sponsor, might increase the risk for the patients enrolled in the study or might influence the normal conduct of the study.

The notification to EOF is made in hard copy form, via the general register of EOF.

### III. MANAGEMENT OF ADVERSE REACTIONS ARISING FROM NON- INTERVENTIONAL STUDIES (OR OTHER ORGANIZED DATA COLLECTION SYSTEMS)

This section describes the obligations of the Sponsors of non- interventional studies, meaning any studies of the competency of EOF, which are not included into the scope of the Directive 2001/20/EC, like:

- Non-interventional Post-Authorisation Safety Studies (PASS)
- Other non-interventional studies which are not defined as post-authorisation safety studies, eg. pharmacoepidemiological studies, pharmaco-economic studies, drug utilization studies, investigator sponsored non- interventional studies

The Investigator should report, **as soon as possible**,<sup>41</sup> to the Sponsor any Serious Adverse Event brought to his knowledge during the conduct of the study.

The Sponsor is responsible for the follow up of the safety of all the medicinal products (including the comparator medicinal products) used in the abovementioned studies.<sup>42</sup>

#### 1. EXPEDITED REPORTING OF SERIOUS ADVERSE REACTIONS DURING THE CONDUCT OF NON- INTERVENTIONAL STUDIES IN GREECE

The Sponsor is required to report any Serious Adverse Reaction notified to him, in compliance with the procedure regarding the spontaneous reports, already described in the section I for the suspected serious adverse reactions.

#### **CLARIFICATION:**

*It is noted that in this phase any Serious Adverse Reaction coming from non-interventional study (or other organized data collection system), submitted electronically to the electronic address of EOF (GEOF)<sup>43</sup>, should be submitted concomitantly in hard copy via CIOMS form (see Annex II), accompanied by the document of the Annex V).*

*The hard copy should be submitted via the general register of EOF, to the attention of the Pharmacovigilance Department.*

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<sup>40</sup>Vol.9A, Chapter I.7. It is noted that the obligations mentioned in the section II apply to the interventional post-authorisation safety studies .

<sup>41</sup> The Investigator is expected to inform the Sponsor within 24 hours since he is aware of a serious adverse event.

<sup>42</sup> Regarding the adverse reactions for which a co-administered non-investigational medicinal product is considered to be suspect: Should the Sponsor be the MAH of the suspect medicinal product, he is required to report the event to EOF within the timelines in force. In case where the Sponsor is not the MAH of the suspect medicinal product it is advisable that he informs the MAH of the suspect medicinal product. Since the Sponsor has informed the MAH, the MAH should submit the event to EOF within the timelines in force.

<sup>43</sup> Meaning the events occurring only in the Greek territory

## 2. PROGRESS REPORT & FINAL SAFETY REPORT OF THE STUDY

### 2.1 NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDIES

The obligations for the submission of progress report and final safety report of the study apply in strict compliance with the Vol 9A (Chapter I.7) for the non-interventional studies approved as “Post-Authorisation Safety Studies’ (PASS).

The content and the periodicity of the submission of the progress reports and of the final safety report of the studies are defined in Vol. 9A (Chapter I.7.4.3).

The above reports are submitted **only** in the electronic form (CD-ROM) to the general register of EOF.

### 2.2. OTHER NON-INTERVENTIONAL POST-AUTHORISATION STUDIES

The Sponsor is required, regarding non interventional studies, non characterized “post-authorisation safety studies”, after the end of the study<sup>44</sup>, to submit the overall safety report for the study medicinal products. This overall report should include tables with the frequencies of serious and non-serious adverse reactions for each product, that occurred worldwide, during the conduct of the specified study.

The Sponsor is advised in order to compose the final safety report of the study to use as guide Vol.9A (Table I.7.C).

The timelines for the submission of the report is 60 days after the date of the study completion.

The Final Safety Report of the Study is submitted **only** in the electronic form (CD-ROM) to the general register of EOF.

## 3. REPORTING IN SPECIAL SITUATIONS IN RELATION WITH SAFETY ISSUES

The Pharmacovigilance Department of EOF should be notified in an expedited manner (within 15 calendar days) regarding any change of the safety data found out during the conduct of the non-interventional clinical study, in case that this change, after the assessment by the Sponsor, might increase the risk for the patients enrolled in the study or might influence the normal conduct of the study.

The notification to EOF is made in hard copy form, via the general register of EOF.

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<sup>44</sup> In case that the protocol of the non-interventional study doesn't state otherwise.

## CHAPTER 5

### PERIODIC SAFETY UPDATE REPORT (PSUR)

#### 1. GENERAL PRINCIPLES

The Periodic Safety Update Report (PSUR) is the mean through which EOF and the other competent authorities are notified regarding all safety data, for which the Company is aware from the worldwide experience, during a defined period of time after the authorisation of a medicinal product.

The Marketing Authorisation Holder is expected to include in the PSUR the precise summary of the data like the documented assessment of the risk/ benefit ratio of the product, in the light of new or changing information. This evaluation should lead to conclusions in relation to the potential need for further investigation or the potential change of the marketing authorisation and the prescribing information of the medicinal product.

The submission of the Periodic Safety Update Report of the product is required for any medicinal product with marketing authorisation in Greece<sup>45</sup>, independent to the procedure of approval and independent to whether the Marketing Authorisation Holder (applicant) has placed the product in the Greek market or in any market of any EEA country. Independent to the procedure of the approval of the product, the EEA QPPV is responsible to compose the PSUR of the medicinal product.

The first PSUR should be based on the European Birth Date of the product (see Vol 9A, Chapter 1.6).

In particular the Authorities of the member- states have taken the initiation to harmonise the European Birth Dates and the Data Lock Points (DLPs) for the products that have the same active substance and have been authorised via the national or the decentralized procedure. So, the competent authorities in EEA countries will achieve to coordinate the evaluation of the safety of the medicinal products with the same active substance, for the patients benefit.

The table with the harmonised European Birth Dates, the respective Data Lock Points and the information regarding the submission of the respective PSUR, are shown to the web site of Heads of Medicines Agencies<sup>46,47</sup>.

The Marketing Authorisation Holders of generic medicinal products are advised to follow the format agreed for the original medicinal product, ie. they submit to EOF the PSURs for the generic medicinal product on the basis of the harmonized European Birth Date and the Data Lock Point for the original medicinal product.

Detailed instructions regarding the format, the content and the periodicity of the PSURs are given to Vol.9A (chapter I.6).

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<sup>45</sup> The same requirements apply to the generic medicinal products, without any exception.

<sup>46</sup> For the time being, the relevant table with the harmonised European Birth Dates and the Data Lock Points refers to any medicinal product with an active substance for which a marketing authorisation has been issued in a country of the EU after the January 1<sup>st</sup> 1976. The submission of PSURs to EOF for medicinal products with an active substance, for which has been issued a marketing authorization before the January 1<sup>st</sup> 1976, is not required until the relevant table is set up.

<sup>47</sup> <http://hma.eu>

The PSUR should be written in English.

## **2. PERIODICITY & TIMETABLE FOR THE SUBMISSION OF PSURs**

Since this guidance comes in force, the PSUR to the Pharmacovigilance department of EOF for each product with marketing authorisation in Greece, will be submitted as follows:

2.1 Before the medicinal product is placed in the market of any country in European Union:

- On request by EOF.
- After the issuance of the marketing authorisation and until the product is placed in the market of any EEA country, the Marketing Authorisation Holder should compose and submit to EOF 6-monthly PSURs for the medicinal product.

2.2 Since the medicinal product has been placed for the first time in the market of any EEA country:

- The company should continue submitting the 6-monthly PSURs, until the completion of 2 years of experience after the marketing of the medicinal product for the first time in the market of any EEA country.
- After that the PSURs should be submitted annually for the next 2 years.
- Then the PSUR will be submitted every three years.
- Moreover, the PSUR should be submitted anytime, on request by EOF.

It is noted that the retrospective submission of the PSUR of products with a marketing authorisation in Greece at the time of publication of this guidance and which have already been placed in the market in any EEA country, is not required. In such situations the marketing authorisation holder should submit the last PSUR on the basis of the harmonised periodicity (on the basis of the agreed EBD and the DLP).

It is clarified that the renewal of the marketing authorisation is an independent procedure and therefore it doesn't influence the periodicity of the submission of the PSUR.

The marketing authorisation holder has the obligation to submit the PSUR to EOF within 60 days from the Data Lock Point in relation to the PSUR. In particular, in exceptional situations (eg. great data volume, specific safety issues that should be investigated on request by the Competent Authorities) is possible to permit a prolongation of 30 days for the submission of PSUR, although it will not influence the periodicity in force of the following PSURs.

In the case of submission of a yearly or every three years PSUR, the PSUR could be submitted as an overall report or, alternatively, as the summary of 2 or more half yearly PSURs. In the latter case it is compulsory that the relevant 6-monthly PSURs be accompanied with a report summarising the safety data (bridging summary report) of the overall period.

In the case where there is a gap of time between the data lock point of one PSUR and the subsequent time point on which EOF is requesting an exceptional submission of safety data (eg. in the case of renewal of the marketing authorisation or in order to evaluate the risk/ benefit ratio etc), the marketing authorisation holder should prepare an additional report (PSUR addendum report) to be included in the submission.

The PSUR is submitted in electronic form (CD-ROM) via the general register of EOF, to the attention of the Pharmacovigilance department.

### **3.DOCUMENTS ACCOMPANING THE PSURs**

Regarding the medicinal products authorized through the centralised procedure the submission of PSUR directly to EOF by the EEA QPPV of the marketing authorisation holder is acceptable.

Regarding the medicinal products authorized through the National, the Mutual or the Decentralised Procedure the local person responsible for the communication of pharmacovigilance of the marketing authorisation holder is responsible for the submission of PSUR to the Pharmacovigilance department of EOF.

Independent to the registration procedure (central, mutual/decentralised, national) each PSUR should be accompanied by:

3.1 A cover letter in which the following information is included:

- i Name of the product
- ii Name of the active substance
- iii The European Birth Date
- iv The registration procedure (central, mutual, decentralized, national)
- v The International Birth Date, if it differs from the European one
- vi The time period covered by the submitted PSUR
  - In the case that the medicinal product hasn't been placed in the market in any market in EU, a statement is required regarding the intention of the marketing authorisation holder to place in the market of the product in a time period covered by the subsequent PSUR and the identification of the member state (or the member states ) where the product is scheduled to be marketed.
- vii The time period covered by the subsequent PSUR.
- viii Communication information of the EEA QPPV (full name, phone number, fax number, e-mail).

Moreover, regarding the medicinal products authorised through the National, the Mutual or the Decentralised Procedure, each PSUR should be accompanied by:

- 3.2. Communication information of the person responsible for the communication of pharmacovigilance issues (full name, phone number, fax, e-mail)
- 3.3. A copy of the marketing authorisation in force in Greece
- 3.4. A copy of the Summary of the Product Characteristics in force in Greece
- 3.5. A copy of the Package Leaflet of the product in force in Greece.

### **4 SUBMISSION OF PSUR SPECIFICALLY FOR THE RENEWAL OF THE MARKETING AUTHORISATION**

Beyond the obligation to submit PSUR described above (Chapter 5, paragraph 2), the marketing authorisation holder is requested to submit PSUR, in particular, for the renewal of the marketing authorisation of the medicinal product. This specific PSUR should be submitted every six months before the expiration of the authorisation in force. The last date for the preparation of the PSUR should be less than 60 days before the submission of the PSUR. Given that the renewal of the marketing authorisation should be made every five years, the period covered will have a duration of 4 years and 4 months. Therefore the marketing authorisation holder should apply:

- The PSURs covering this time period from the date of the current marketing authorisation and, if required, the additional report (PSUR addendum report) covering the safety data until the expiration date, mentioned above.
- A bridging summary report for the safety, bridging all PSURs and the additional report (PSUR addendum report) required to cover the given time period.

The submission of PSURs for the renewal of the marketing authorisation are addressed to the Pharmacovigilance department of EOF, in the form of CD-ROM. The submission should be made to the general register of EOF.

The acknowledgment document for the PSUR submission is included in the dossier that the Marketing Authorisation Holder submits to the Administrative Services Department for the Monitoring of the Medicinal Products of EOF.

## **CHAPTER 6**

### **DIRECT HEALTHCARE PROFESSIONALS COMMUNICATION OF NEW SAFETY DATA USING “DEAR HEALTHCARE PROFESSIONAL” LETTERS**

#### **1. GENERAL ISSUES**

If new safety data arise then EOF, the EMEA or the Competent Authority of the Reference Member State may request the Marketing Authorisation Holder of the medicinal product to proceed to the publication and dispatch of the specific letter “Dear Healthcare Professional” (known as the letter “Dear Doctor-Letter”).

In cooperation with the EMEA or the Competent Authority of the Reference Member State, EOF would determine the time frame that the marketing authorisation holder would have at his disposal in order to complete the dispatch of the letter to the Greek territory, depending on the case.

The EEA QPPV of the marketing authorisation holder is responsible for the content of the letter, while the local person responsible for the communication of pharmacovigilance issues is responsible for the translation and the adjustment to the Greek language (if the original text is to another language).

The marketing authorisation holder should inform the Pharmacovigilance department of EOF prior to the communication of any information relevant to pharmacovigilance issues to the healthcare professionals and then look to the opinion regarding the content of the letter.

Detailed guidance regarding the conditions and the procedures for the dispatch of the DHPC are outlined in Vol 9A (Chapter IV.2).

#### **2. PROCEDURES OF PUBLICATION AND DISPATCH OF THE LETTER**

The provisions laid out in Vol. 9A (Chapter IV.2) are applied.

2.1 In the case of products authorised exclusively<sup>48</sup> through the national procedure, the original text is drafted in the Greek language and is transmitted directly to EOF (via e-mail (to the address [adr@eof.gr](mailto:adr@eof.gr)) accompanied together with its translation in English and the proposed specialities for the recipients of the letter. EOF comments regarding the final content and the recipients of the letter.

2.2 In the cases of products authorised through the centralised or the mutual recognition /decentralised procedure, products under arbitration, but also products authorized through the national procedure where another European Authority is at the head of the procedure for the publication, the text is drafted in English (working language) and is dispatched to the competent European Authority (contact point) in order to get an opinion /approval.

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<sup>48</sup> When the product has been authorised in Greece via the national procedure, has not been authorised in other EEA countries through the mutual recognition/ decentralised procedure or when another EEA country is not at the head of the procedure for the publication of the letter.

After having agreed the text with the competent European Authority (in English), the agreed text should be adjusted to the Greek language under the responsibility of the local person responsible for the communication of pharmacovigilance issues. The agreed text (in English) together with the translation in the Greek language and the proposed recipients of the letter is dispatched to EOF in order to get a local opinion. The dispatch is forwarded to the Pharmacovigilance department of EOF (electronically to the address [adr@eof.gr](mailto:adr@eof.gr) or alternatively via the general register of EOF). The marketing authorisation holder should expect the positive opinion/ approval for the Greek version of the letter from the Pharmacovigilance department of EOF. EOF should also define the final recipients of the letter to the Greek territory. Afterwards:

- The approved by EOF text and the recipients are binding, in relation to the medicinal products authorised through the National or the Mutual agreement/ the Decentralised procedure.
- The marketing authorisation holder is forwarding the approved by EOF text and proposed recipients to the EMEA /rapporteur, in relation to the medicinal products authorised through the central registration procedure and the products under arbitration.

After the final approval of the Greek text, the marketing authorisation holder undertakes to compose and dispatch the letter to the determined by EOF recipients, using the Dossier outlined to the Annex VI.

After the completion of the dispatch, the marketing authorisation holder is submitting to the general register of EOF, to the attention of the Pharmacovigilance department the following documents:

- A copy of the acknowledgment document from the post/ courier in which are mentioned:
  - The description: “ Letters regarding the adverse reactions of the product <name of the product>”
  - The total number of the letters dispatched.
- A list of the recipients, by speciality (in CD-ROM)
- A confirmation letter for the normal dispatch of the letter to the recipients. The marketing authorisation holder would also describe the taken measures, in order to achieve the information of the recipients, if there would be any problem during the dispatch.

## ANNEX I:

### GUIDELINES FOR THE TRANSITION TO THE ELECTRONIC SUBMISSION OF ADVERSE REACTIONS

The general principles for the electronic transmission of the adverse reactions are described extensively in Vol 9A (Part III), taking into account the clarifications by EOF mentioned in Chapter 4 of the present guidance.

#### 1. ACTIVATION OF THE CONNECTION & OPERATION OF THE ELECTRONIC SUBMISSION OF THE INDIVIDUAL CASE SAFETY REPORTS

In the frame of the transition to the electronic submission of the Adverse Reactions, the Pharmacovigilance department of EOF informs the Marketing Authorisation Holders, the Sponsors<sup>49</sup> of the clinical studies and those acting on behalf of them (eg. Contracted Research Organisms), herein after called “Companies”:

The Companies are required to obtain directly the connection with EudraVigilance (EudraVigilance Company ID) after their registration to EMEA and to proceed to a communication test with the central gateway of EudraVigilance EVTEST. Guidance on the way to register and to obtain a connection is in the website of EMEA: <http://eudravigilance.emea.europa.eu/human>.

The EEA QPPV of the company should submit the letter to EOF (electronically, as an attached pdf document, to the Address [adr@eof.gr](mailto:adr@eof.gr)) where he should affirm the registration to EMEA and confirm the successful completion of the communication test with the central portal of EudraVigilance. Moreover, it is needed to communicate:

- The electronic connection address with Eudravigilance (EudraVigilance Company ID) for the testing environment (testing environment Company ID) and for the production environment (production environment Company ID). **The latter should be used as the address to which EOF should send the events received through the yellow card from the Healthcare Professionals.**
- All the contact details of EEA QVVP of the Company [ full name, mail address, electronic address (e-mail), phone number, fax\number] and the contact details of the person competent for the operation of the EudraVigilance in central level.
- All the contact details of the local person responsible for the communication of pharmacovigilance issues [full name, mail address, electronic address (e-mail), phone number, fax number] and the contact details of the competent person for the operation of the EudraVigilance locally.

1.3 After the completion of the step 1.2, the Company is required to perform a communication testing with EOF. Companies are required to contact the Pharmacovigilance department of EOF in order to define the testing date.

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<sup>49</sup> To be clarified to the Sponsors of commercial studies, interventional or non-interventional (non-commercial sponsors eg. studies where the sponsor is the investigator or a certain cooperating physician group) and for the time until the registration and the connection of the Sponsor to the EudraVigilance: all serious adverse reactions are reported directly by the Sponsor (within 24 hours) to the Marketing Authorisation Holder of the relevant suspect medicinal product. The Marketing Authorisation Holder is continuously responsible for the electronic transmission of the events in compliance with the Chapter 4.

- 1.4. After the successful completion of the step 1.3, the company is required to proceed directly to the implementation of the electronic submission of the adverse reactions.
- 1.5. It should be noted that in the initial phase of implementation of the electronic submission for each event transmitted to the website of EOF (GEOF)<sup>50</sup> should be submitted via CIOMS form (see Annex II) accompanied by the appropriate cover document (see Annexes III, IV,V). The concomitant submission to the Pharmacovigilance department<sup>51</sup> of EOF should be made through the general register of EOF. It is noted that the date of the successful electronic submission of the report to EOF will be considered the official transmission date.
- 1.6. The company is required to record, as documents for the successful transmission of the reports to EOF, the following documents:
- The acknowledgement message received from the electronic address of EOF (GEOF) or the respective address of the EMEA where the event has been sent (EVPM, EVCTM).
  - Since the communication of other competent authorities of EU is required (eg. reports regarding products authorized through the mutual recognition/decentralised or central procedure), the Company should record also the acknowledgement document for the receipt to the site of the Competent Authority.

## **2. UPDATING OF THE MEDICINAL PRODUCT DICTIONARY (EudraVigilance Medicinal Product Dictionary, EVMPD).**

Apart of the electronic submission of the individual events to the EudraVigilance, each Company is required to introduce and to perform regular updates of the central data base of EudraVigilance (EVMPD) regarding the approved data (Summary of Product Characteristics in force in Greece) of the product of its responsibility.

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<sup>50</sup> ie. the events occurring in the Greek territory.

<sup>51</sup> After the implementation of the electronic reporting of the adverse reactions, the transmission of any event to the Clinical Trials department of EOF would not be required.

## **ANNEX II**

### **CIOMS FORM TEMPLATE**

It is intended only for the period of concomitant submission of E2B and CIOMS form or in the case of technical problem<sup>52</sup> to the electronic transmission.

The CIOMS form should be filled in English and the adverse reactions be coded using the latest version of MedDRA.

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<sup>52</sup> After the technical problem has been repaired, the marketing Authorisation Holder is required to send the event in the E2B form.

SUSPECT ADVERSE REACTION REPORT												

### I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
7+13 DESCRIBE REACTIONS (including relevant tests /lab data)									<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION OR <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING <input type="checkbox"/> CONGENITAL ANOMALY <input type="checkbox"/> MEDICALLY SIGNIFICANT <input type="checkbox"/> OTHER	

### II. SUSPECTED DRUG INFORMATION

14. SUSPECT DRU(S) (include generic name)		20. BID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE (S)	16. ROUTE(S) OF ADMINISTRATION	
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)		19. THERAPY DURATION

### III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRU(S) AND\ DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (eg. diagnoses, allergies, pregnancy with last menstrual period etc)

### IV. MANUFACTURER INFORMATION

24a NAME AND ADDRESS OF MANUFACTURER		COMMENTS
ORIGINAL REPORT NO.	24b MFR CONTROL NO.	
24c DATE RECEIVED	24d REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> HP <input type="checkbox"/> LITERATURE <input type="checkbox"/> OTHER	
DATE OF THIS REPORT	25a REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOW UP	

## **ANNEX III**

### **TEMPLATE OF THE CIOMS FORM COVER LETTER FOR REPORTING SPONTANEOUS ADVERSE REACTIONS**

It is intended only for the period of concomitant submission of E2B and CIOMS or in the case of a technical problem<sup>53</sup> to the electronic transmission.

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<sup>53</sup> After the technical problem has been repaired, the marketing Authorisation Holder is required to send the event in the E2B form.

**TO EOF PHARMACOVIGILANCE DEPARTMENT***Athens, DD/MM/YYYY***SUBJECT:** Report of **Spontaneous** Serious Adverse Event occurred in Greece

EudraVigilance Worldwide Case ID:

PRODUCT NAME:

ACTIVE SUBSTANCE:

Does the suspect drug has marketing authorisation in EEA;  Yes, in Greece  
 Yes, in another EEA country  
 No, it does not have marketing authorisation in EEA

**ADVERSE REACTIONS** (*use reporter's terminology*)**REPORTER'S INFORMATION**

NAME:

SPECIALITY:

HOSPITAL:

ADDRESS:

PHONE NUMBER:

**REPORT TYPE**INITIAL FOLLOW UP Number of Follow Up: *1<sup>st</sup>, 2<sup>nd</sup>*Date of Initial Report: *DD/MM/YYYY***INTERVENTIONAL CLINICAL TRIALS CURRENTLY CONDUCTED IN GREECE WITH THE SUSPECT DRUG**

Application to EOF Reference Number

EudraCT Number

EOF Approval Number

Is this report a SUSAR for the above Clinical Trials?  Yes  
 No

**INFORMATION OF LOCAL PERSON RESPONSIBLE FOR THE COMMUNICATION OF PV ISSUES**

NAME:

PHONE NUMBER:

FAX:

e-mail:

SIGNATURE:

**Attachments:** CIOMS form with MFR No: *(Fill in the MFR No)*

## **ANNEX IV**

### **TEMPLATE OF THE THE CIOMS FORM COVER LETTER FOR REPORTING ADVERSE REACTIONS FROM INTERVENTIONAL CLINICAL TRIALS**

Intended only for the period of the concomitant submission of E2B and CIOMS or in case of technical problem<sup>54</sup> to the electronic submission.

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<sup>54</sup> After the technical problem has been repaired, the marketing Authorisation Holder is required to send the event in the E2B form.

**TO EOF PHARMACOVIGILANCE DEPARTMENT**

*Athens, DD/MM/YYYY*

<b>SUBJECT:</b> Submission of <b>SUSAR</b> arising from Interventional Clinical Trial in Greece
EudraVigilance Worldwide Case ID:
PRODUCT NAME:
ACTIVE SUBSTANCE:
APPLICATION TO EOF REFERENCE NUMBER:
EudraCT NUMBER:
EOF APPROVAL NUMBER:

<i>ADVERSE REACTIONS (use reporter's terminology)</i>

<b>REPORTER'S INFORMATION</b>
NAME:
SPECIALITY:
HOSPITAL:
ADDRESS:
PHONE NUMBER:

<b>SUSAR TYPE</b>	
INITIAL <input type="checkbox"/>	
FOLLOW UP <input type="checkbox"/>	Number of Follow Up: <i>1<sup>st</sup>, 2<sup>nd</sup></i> Date of Initial Report: <i>DD/MM/YYYY</i>

OTHER INTERVENTIONAL CLINICAL TRIALS CURRENTLY CONDUCTED IN GREECE WITH THE SUSPECT DRUG		
Application to EOF Reference Number	EudraCT Number	EOF Approval Number

<b>INFORMATION OF LOCAL PERSON RESPONSIBLE FOR THE COMMUNICATION OF PV ISSUES</b>
NAME:
PHONE NUMBER:
FAX:
e-mail:
SIGNATURE:

**Attachments:** CIOMS form with MFR No: *(Fill in the MFR No)*

## **ANNEX V**

### **TEMPLATE OF THE CIOMS FORM COVER LETTER FOR REPORTING ADVERSE REACTIONS FROM NON-INTENTIONAL STUDIES**

Intended only for the period of concomitant submission of E2B and CIOMS, or in case of technical problem<sup>55</sup> to the electronic transmission.

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<sup>55</sup> After the technical problem has been repaired, the marketing Authorisation Holder is required to send the event in the E2B form.

**TO EOF PHARMACOVIGILANCE DEPARTMENT***Athens, DD/MM/YYYY***SUBJECT:** *Report of Serious Adverse Event occurred in Greece, in non interventional clinical study or other data collection system*

EudraVigilance Worldwide Case ID:

PRODUCT NAME:

ACTIVE SUBSTANCE:

APPLICATION TO EOF REFERENCE

NUMBER:

EOF APPROVAL NUMBER:

**ADVERSE REACTIONS** *(use reporter's terminology)***REPORTER'S INFORMATION**

NAME:

SPECIALITY:

HOSPITAL:

ADDRESS:

PHONE NUMBER:

**REPORT TYPE**INITIAL FOLLOW UP Number of Follow Up: *1<sup>st</sup>, 2<sup>nd</sup>*Date of Initial Report: *DD/MM/YYYY***INTERVENTIONAL CLINICAL TRIALS CURRENTLY IN GREECE WITH THE SUSPECT DRUG:**Application to EOF Reference  
Number

EudraCT Number

EOF APPROVAL  
NUMBERPresent report is a SUSAR for the above  
Interventional Clinical Trials?  Yes  
 No**INFORMATION OF LOCAL PERSON RESPONSIBLE FOR THE COMMUNICATION OF PV ISSUES**

NAME:

PHONE NUMBER:

FAX:

e-mail:

SIGNATURE:

**Attachments:** CIOMS form with MFR No: *(Fill in the MFR No)*

## **ANNEX VI**

### **DETAILS AND ENVELOPE TEMPLATE OF THE “DEAR HEALTHCARE PROFESSIONAL” LETTER**

#### **A. Details of the envelope of the letter “Dear Healthcare Professional”:**

Yellow envelope (colour code: CMY 001)

Dimensions of the envelope 16X23 cm

- Above left: Details of the Marketing Authorisation Holder (sender)
- Center :Details of the Recipient of the Letter
- Down : in the center with letters Arial (bold), 20-point type, in a frame with dimensions 2X19cm, with 1 ½ pt depth of line

#### **B. Model of the Envelope of the Letter “Dear Healthcare Professional”:**

(see next page)

Position for writing the details of the  
Marketing Authorisation Holder

Position for writing the details of the  
recipient of the letter

**ATTENTION!**  
**IT CONCERNS ADVERSE REACTIONS OF MEDICINAL PRODUCTS**