Guidance Notes for Pharmaceutical Companies on

Pharmacovigilance Obligations &

Adverse Drug Reaction (ADR) Reporting Requirements

for Medicinal Products for Human Use

November 2010

Issue 4

AWTORITÀ DWAR IL-MEDIĊINI

Guidance Notes for Pharmaceutical Companies on

Pharmacovigilance Obligations & Adverse Drug Reaction (ADR) Reporting Requirements for Medicinal Products for Human Use

1. Introduction

In line with the Medicines Act 2003, pharmaceutical companies have specific obligations with regards to pharmacovigilance. The information contained in this document is directed to pharmaceutical companies that hold marketing authorisations and to applicants for marketing authorisations for medicinal products on the Maltese market. It gives background information on the pharmacovigilance obligations of potential applicants and marketing authorisation holders (MAHs). The legal framework for these obligations is described in the following legislation:

1. Medicines Act 2003
2. Pharmacovigilance Regulations 2006 (L.N. 61 of 2006)
3. Codified Directive 2001/83/EC
4. Directive 2001/20/EC
5. Clinical Trials Regulations 2004 (L.N. 490 of 2004)

Throughout this document, frequent reference is made to the Notice to Marketing Authorisation Holders (NtMAHs) included in Volume 9A of the Rules Governing Medicinal Products in the European Union (Pharmacovigilance for Medicinal Products for Human Use)**,** which provides further detail on the collection, verification and presentation of ADR reports, Periodic Safety Update Reports (PSURs), Post-Authorisation Safety Studies (PASS) and ongoing benefit/risk evaluation. It is essential that these European guidelines are referred to and thoroughly consulted. Additional information can also be found in Volume 2A of the Rules Governing Medicinal Products in the European Union (Procedures for Marketing Authorisation). Volumes 2A and 9A of the Rules Governing Medicinal Products in the European Union can be downloaded from this website:

http://ec.europa.eu/health/documents/eudralex/vol-10/

2. Roles and Responsibilities of Pharmaceutical Companies

In accordance with Article 5 of Pharmacovigilance Regulations 2006, the MAH should have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance. The person responsible for pharmacovigilance will have the following responsibilities:

- To establish and maintain a pharmacovigilance system to ensure that any information about suspected adverse drug reactions reported to the personnel of the company and to medical representatives, is collected and collated in order to be made available to the Medicines Authority;
- To prepare necessary reports in accordance with the NtMAH;
- To reply fully and promptly to any request made by the Medicines Authority, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;
- To provide any other information to the Medicines Authority in relation to the evaluation of the risk-benefit balance of a medicinal product, including appropriate information on PASS.

According to Article 6 of Pharmacovigilance Regulations 2006, the MAH shall be legally obliged to carry out the following activities:

- To maintain detailed records of all suspected adverse drug reactions occurring either in Member States or in a third country;
- To immediately record and report to the Medicines Authority all suspected serious ADRs (both expected and unexpected) occurring in Malta not later than 15 calendar days from receiving the information;
- To immediately record and report to the Medicines Authority all suspected serious and unexpected ADRs occurring in the territory of a third country (i.e. outside the EU/EEA) not later than 15 calendar days from receiving the information;

- To report serious ADRs occurring outside Malta but within other EU/EEA Member States to the competent authority of the Member State in whose territory the adverse reaction occurred within 15 calendar days following receipt;
- To ensure that the Reference Member State (RMS) has access to any suspected serious ADRs which have occurred within the EU/EEA in the case of medicinal products authorised via mutual recognition or decentralised procedures;
- To submit a record of all ADRs including a scientific evaluation of the benefits and risks afforded by the medicinal product in the form of PSURs in accordance with the agreed timetable, as described in the NtMAH. (For further information on PSURs refer to section 5 of these guidance notes.)

In accordance with Volume 9A of the Rules Governing Medicinal Products in the European Union, MAHs shall use internationally agreed medical terminology e.g. MedDRA for the reporting of ADRs. Further information on MedDRA can be obtained from the following website: www.meddramsso.com

3. ADR Reports

The following requirements apply to **all** medicinal products for human use available in Malta, including products that have a marketing authorisation, products that do not have a marketing authorisation but have a licence to be placed on the market (qualified license) and unlicensed medicinal products.

For further information on medicinal products that do not have a marketing authorisation but have a licence to be placed on the market (qualified license), refer to Article 4 of Medicines (Marketing Authorisation) Regulations, 2007 (Legal Notice 324 of 2007), which can be downloaded from the following website: http://www.doi.gov.mt/EN/legalnotices/2007

Unlicensed medicinal products for human use include products which:

(i) are obtained from a hospital or a commercial supplier with a "specials" manufacturing licence;
(ii) have a licence in another country but are being imported and used on a "named patient basis".

DH Circular 137/2004 concerning the "Guidelines Governing the Use of Medicinal Products for Human Use without a Marketing Authorisation" should be consulted for further information on unlicensed medicinal products. The circular can be accessed at the following website: http://www.sahha.gov.mt/pages.aspx

In keeping with the Pharmacovigilance Regulations, 2006, the MAH should submit the following ADR reports to the Medicines Authority:

(i) all suspected serious ADRs (expected and unexpected) occurring in Malta;
(ii) all suspected serious and unexpected ADRs occurring in the territory of a third country (i.e. outside the EU/EEA, e.g. Switzerland, USA, Canada, Malaysia).

All the above reports should be sent on an expedited basis i.e. within 15 calendar days of first notification of any personnel within the company.

Serious ADRs occurring outside Malta but within other EU/EEA Member States do **not** require reporting to the Medicines Authority. They should, nevertheless, be reported within 15 calendar days following receipt to the competent authority of the Member State in whose territory the adverse reaction occurred. They should also be available for review upon request by the Medicines Authority.

The flowchart in Appendix 1 summarises the requirements for serious ADR reporting.

ADR reports from pharmaceutical companies may be submitted to the Medicines Authority either in paper format or in electronic format via EudraVigilance.

(i) Paper format

ADR reports being submitted in paper format can be presented on the company's own reporting form or, preferably, on a CIOMS form (Appendix 2) which can be downloaded from the following website: http://www.cioms.ch/cioms.pdf

CIOMS reports should be submitted only when Eudravigilance is down, in line with the steps to follow when there is a system failure when carrying out e-transmission of ICSRs to the EMEA (ie Eudravigilance is down). http://eudravigilance.emea.europa.eu/human/SystemFailureSteps.asp

When submitting ADR reports in paper format, these should be accompanied by a cover letter clearly identifying them as cases occurring in Malta or in a third country (non-EU/EEA). All correspondence should include the brand name(s) and marketing authorization number(s) of the suspect product(s) and the type of report (i.e. initial or follow-up). The company should additionally inform the Medicines Authority if it is aware that Maltese reports have been separately reported to the Medicines Authority by a healthcare professional. This information would help facilitate identification of duplicate cases.

Reports should be addressed to:

Pharmacovigilance Section,
Post-Licensing Directorate,
Medicines Authority,
203 level 3 Rue D'Argens,
Gzira. GZR 1368.
Malta.
Tel: (+356) 23439000
Fax: (+356) 23439161
Email address: postlicensing.mru@gov.mt

(ii) Electronic format

ADRs may be submitted electronically via EudraVigilance as Individual Case Safety Reports (ICSRs) in E2B(M) format. Information regarding electronic report submission via this European data-processing network and ICSR database system can be obtained from the following website:
http://eudravigilance.emea.europa.eu/human/

The applicable standards are available here:
http://eudravigilance.emea.europa.eu/human/docs/e2b.pdf
and
http://eudravigilance.emea.europa.eu/human/docs/ICH%20M2M.pdf

ICSRs concerning suspected serious adverse reactions originating in Malta should be transmitted electronically to the Medicines Authority with the message receiver identifier ADM. Parallel reporting of ICSRs in paper format would not be required. ICSRs concerning suspected serious and unexpected adverse reactions occurring in the territory of a third country (non-EU/EEA) should be submitted to EudraVigilance only with the message receiver identifier EVHUMAN. It is worth noting that ICSR submission to EVHUMAN encompasses reporting to the Agency and to all the Member State authorities (including the Medicines Authority) in line with the requirements of Directive 2001/83/EC and Pharmacovigilance Regulations 2006.

The Medicines Authority also accepts reports sent via EudraLink. EudraLink is a highly secure email system designed by the EMA for the transmission of confidential scientific data. Pharmaceutical companies can apply for a EudraLink account by contacting the EudraLink helpdesk at the EMA on telephone number Tel: +44 (0)20 7418 8400 or on the following email address: eudralink@ema.eu.int

The responsibility of ADR reports submitted via email and not using EudraLink rests with the pharmaceutical company.

4. Criteria for a Valid ADR Report

The following minimum criteria are required for an ADR report to be considered valid:

1. An identifiable reporter (profession, name, contact details)
2. Patient identifier i.e. initials or age or date of birth or sex
3. Name of the suspected medicinal product(s)
4. Details of the suspected reaction(s)

It should be stressed that these are the **minimum** criteria for a valid ADR report and that ADR reports should provide as much information as possible in order to facilitate evaluation by the Medicines Authority. The Medicines Authority may request further information regarding individual ADR reports, as appropriate.

5. Periodic Safety Update Reports (PSURs)

In keeping with their legal requirements, MAHs should submit PSURs in accordance with an agreed timetable defined at the time of granting of a **full** Marketing Authorisation for a medicinal product.

Until a full Marketing Authorisation is granted, companies are **no**t required to submit PSURs on a regular basis to the Medicines Authority. However, if the Medicines Authority requests a company to submit an interim PSUR, such a PSUR should be submitted to the Medicines Authority immediately upon request.

The format and content for a PSUR is outlined in the NtMAH, together with details of reporting requirements and circumstances where the PSUR cycle may be considered for amendment. The requirements for submission of PSURs are also specified in national legislation. Article 6(3) of Pharmacovigilance Regulations, 2006 (L.N. 61 of 2006), stipulates the following cycle for submission of PSURs:

- Immediately upon request
- 6-monthly after authorisation and until the placing on the market
- 6-monthly during the first 2 years after initial placing on the market
- Annually for the subsequent 2 years
- Thereafter at 3-yearly intervals

For those products that were initially granted a provisional Marketing Authorisation (PMA) prior to a full Marketing Authorisation, PSURs should be submitted by the MAH to the Medicines Authority in accordance with the MAH's established cycle of PSUR submission for the authorised medicinal products. Therefore, it will not be necessary to start a new six-monthly reporting cycle for products following the granting of a full Marketing Authorisation by the Medicines Authority.

For those products that were **not** initially granted a PMA, it will be necessary to start a new six-monthly reporting cycle for products following the granting of a full Marketing Authorisation by the Medicines Authority.

The following are the Medicines Authority's submission requirements for PSURs:

1. For products authorised via the national procedure, 1 electronic copy on CD-ROM accompanied by a relevant cover letter should be submitted;
2. For products authorised via the centralised, mutual recognition and decentralised procedures, 1 electronic copy on CD-ROM accompanied by a relevant cover letter should be submitted if Malta is a Concerned Member State (CMS);
3. For products authorised via the centralised, mutual recognition and decentralised procedures, 1 paper copy and 1 electronic copy on CD-ROM should be submitted if Malta is Rapporteur, Co-Rapporteur or Reference Member State (RMS).

The Medicines Authority's requirements for PSUR submission, and the relevant postage contact details are further outlined in Appendix 3.

6. Variations

Prior to marketing, the numbers of patients exposed to a medicinal product are extremely limited and the full safety profile of a product only becomes known when it is used in large numbers of patients over long periods of time. As a result of new information, changes to the product information will be required. Such changes may

be initiated by the MAH or requested by the Medicines Authority and require the MAH to submit a variation application to the Medicines Authority to amend the marketing authorisation documents. For further guidance on the regulations governing variations and their respective submission requirements consult the following website: http://www.medicinesauthority.gov.mt/psvariations.htm

7. Clinical Trials and ADR Reporting

The legal obligations of the sponsors of clinical trials are specified in Directive 2001/20/EC and the Clinical Trials Regulations 2004 (Legal Notice 490 of 2004). Further guidance on the requirements of sponsors and investigators is outlined in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" issued by the European Commission. This guidance can be obtained from the following website: http://ec.europa.eu/health/documents/eudralex/vol-10/

The Medicines Authority only requires expedited reporting of reactions arising from clinical trials conducted in Malta and from multi-centre clinical trials which also include Maltese centres. The requirements for clinical trial sponsors are as follows:

- To keep detailed records of all adverse events, and submit them upon request to the Medicines Authority and to the other competent regulatory authorities in whose territory the clinical trial is being conducted.
- To report all fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) as soon as possible to the Medicines Authority, to the other competent regulatory authorities in whose territory the clinical trial is being conducted, and to the Health Ethics Committee in Malta. Such fatal or life-threatening SUSARs should be reported not later than 7 calendar days after knowledge by the sponsor of such a case. Relevant follow-up information should be subsequently communicated within an additional 8 calendar days.
- To report all other SUSARs to the Medicines Authority, to the other competent

regulatory authorities in whose territory the clinical trial is being conducted, and to the Health Ethics Committee in Malta, not later than 15 calendar days of first knowledge by the sponsor.

- To provide the Medicines Authority, the other competent regulatory authorities in whose territory the clinical trial is being conducted, and the Health Ethics Committee, with an annual listing of all suspected serious adverse reactions and a corresponding report on the safety of the subjects participating in the clinical trial.

The Medicines Authority does **not** require:

- reporting of ADRs arising from clinical trials conducted outside Malta and which do not involve Maltese centres.
- reporting of SUSARs arising from foreign clinical trials which involve products authorised in Malta.
- Expedited reporting for reactions which are serious but expected
- Non serious adverse reactions, whether expected or not
- Reports considered unrelated to the investigational medicinal product.

<u>SUSARs associated with active comparator or placebo.</u>

The sponsor must report to the Medicines Authority and the Ethics Committee all SUSARs associated with a comparator product even if this product is authorised.
Events associated with placebo that satisfy the criteria for a serious adverse drug reaction must be reported in an expedited manner. Where SUSARs are associated with placebo (e.g. reaction due to an exipient), the sponsor must report such cases.

SUSAR reports may be submitted to the Medicines Authority either in paper format or in electronic format via EudraVigilance.

(i) Paper format

SUSAR reports being submitted in paper format can be presented on the

company's own reporting form or, preferably, on a CIOMS form which can be downloaded from the following website: http://www.cioms.ch/cioms.pdf

SUSAR reports together with a cover letter which clearly identifies them as clinical trial cases, should be addressed to the Pharmacovigilance Section within the Post-Licensing Directorate using the contact details as given under Section 3 of these Guidance Notes.

(ii) Electronic format

SUSARs may be submitted electronically via EudraVigilance in E2B(M) format. Information regarding the testing of such electronic submission can be obtained from the website: http://eudravigilance.emea.europa.eu/human

SUSARs arising from clinical trials conducted in Malta and from multi-centre clinical trials which include Maltese centres, should be submitted electronically by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM) using message receiver identifier EVCTMPROD. It is worth noting that SUSAR submission to EVCTM encompasses reporting to the Agency and to all the concerned Member State authorities (including the Medicines Authority) as per the requirements of Directive 2001/20/EC.

8. Annual Safety Reports (ASRs)

In addition to the expedited reporting, Contract Research Organisations (CROs) should submit, once a year throughout the clinical trial a safety report to the Medicines Authority and to the Health Ethics Committee, taking into account all new available safety information received during the reporting period describing concisely all new safety information relevant for the clinical trial(s) and to assess the safety conditions of subjects included in the concerned trial(s).

The annual safety report submitted to the Medicines Authority and to the Health Ethics Committee must be the same.

Content of the Annual Safety Report of a Clinical Trial

The annual safety report of a clinical trial should have three parts:
Part 1: Analysis of the subjects' safety in the concerned clinical trial.
Part 2: A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the concerned trial, including also serious adverse reactions from third
countries.
Part 3: An aggregate summary tabulation of suspected serious adverse reactions that occurred in the concerned trial.

For a detailed description of the ASR consult the 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use' in Eudralex Vol 10.

Reporting time frame for annual safety report

The reporting time frame for annual reports starts with the date of the first authorisation of the clinical trial by the Medicines Authority. The anniversary of this date is designated as the cut off for data to be included in the annual safety report. The sponsor should submit annual reports within 60 days of the data lock point.
However, if the trial in Malta is part of several clinical trials with the same tested investigational medicinal product in any Member State, the sponsor should prepare only one safety report covering the information necessary for all those trials. If the sponsor is the marketing authorisation holder (MAH) of the tested investigational medicinal product, the reporting period should be aligned with the international birth date. However, the Annual Safety Report and the Periodic Safety Update Report (PSUR) must be stand-alone documents.

If a marketing authorisation is granted for the investigational medicinal product for the first time in any Member State while it is being tested in a clinical trial, the reporting time frame for the investigational medicinal product would change from the first date of authorisation of a clinical trial in a Member State to the international birth date. If a marketing authorisation was granted for the investigational medicinal

product before the 1st of May 2004, the international birth date should be applied.

In case of a first-in-man trial and subsequent short term metabolism or pharmacokinetic studies the safety report should be notified within 90 days of the end of trial together with the notification of the end of the trial according to Article 10(c) of Directive 2001/20/EC. This report should contain at least an analysis of the subjects' safety and line listings, and if appropriate aggregate summary tabulations.

8. Further information

Further information can be obtained from the document titled "Frequently Asked Questions (FAQs) by Pharmaceutical Companies regarding Pharmacovigilance Obligations & Adverse Drug Reaction (ADR) Reporting Requirements" also available on the Pharmacovigilance Section of the Medicines Authority website at: http://www.medicinesauthority.gov.mt/phvigilance.htm

In case of additional queries, the staff of the Pharmacovigilance Section may be contacted at:

Pharmacovigilance Section,
Post-Licensing Directorate,
Medicines Authority,
203, level 3 Rue D'Argens,
Gzira. GZR 1368.
Malta.
Tel: (+356) 23439000
Fax: (+356) 23439161
Email address: postlicensing.mru@gov.mt

9 Revision History

Issue	Effective date	Reason for revision
GP.3.01	October 2004	First issue of the Guidance for Pharmaceutical Companies on Pharmacovigilance Obligations and Adverse Drug Reaction (ADR) Reporting Requirments for Medicinal Products for Human Use
GP.3.02	July 2008	Addition of the Clinical Trials directive of 2004 as the legal framework behind references to clinical trials. Updated date of pharmaceutical regulations to the last version publication date. Changed date of Legal Notice 324 of 2004 to the latest one of 2007 Re-worded section 3 paragraph 4 which refers to a DH circular for further information Added paragraph on electronic transmission of ICSRs in E2B in section 3. Removed section 5 (on Malta in preparation for EudraVigilance) since proceeded to production Edited section 7 (on Variations) Updated section 8 (on SUSARs)
GP.3.03	Febuary 2010	Revised text – no change neccessary Changed address of Medicines Authority Changed reference to EMEA with EMA, updated links to EMA website and changed EMA telephone numbers.
GP.3.04	October 2010	Added revision history Updated weblinks Updated section on SUSARs Added section on ASRs in CT

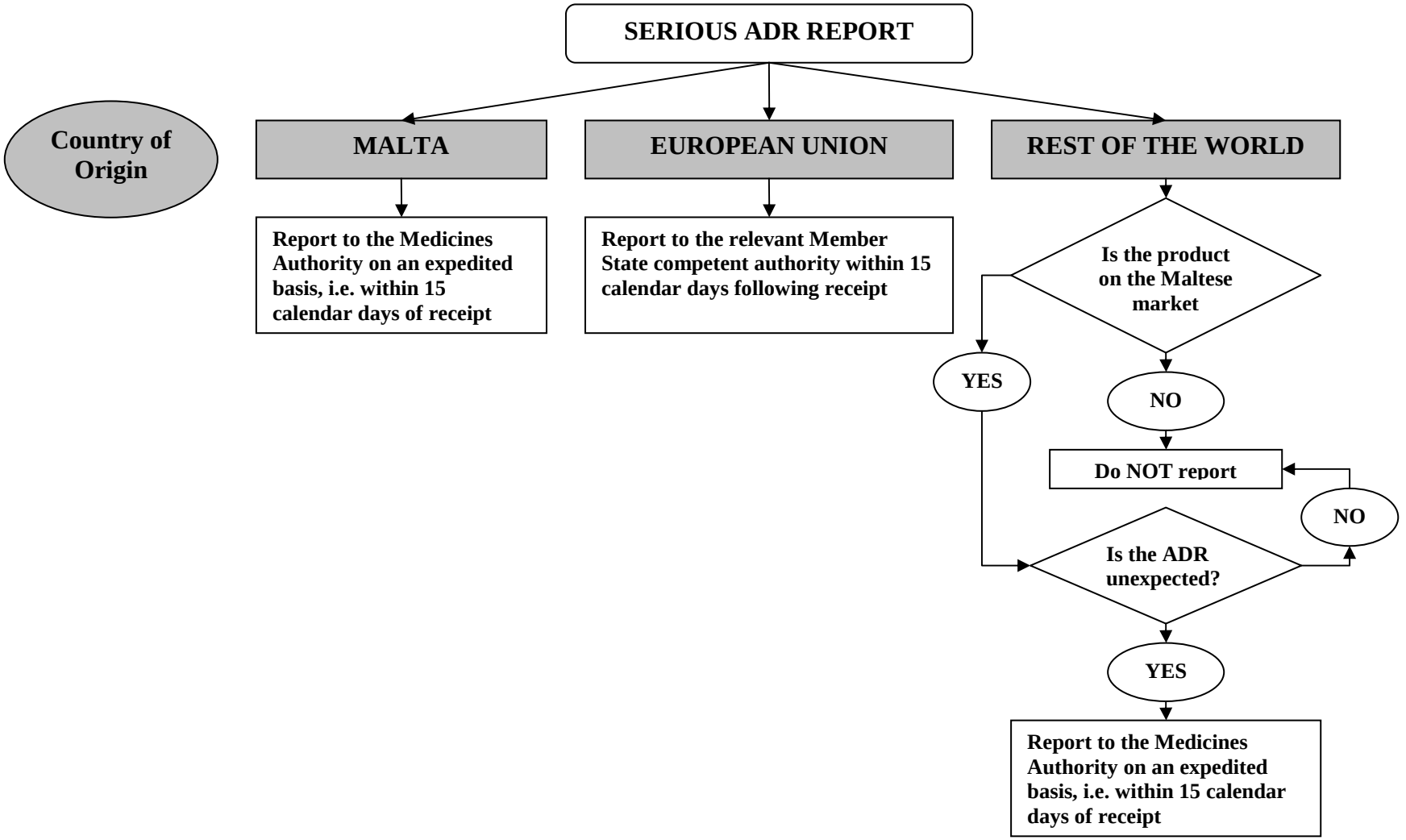
10. List of Appendices

Appendix 1 Flowchart for serious ADR report submission to the Medicines Authority

Appendix 2 CIOMS form

Appendix 3 Requirements for PSUR submission

Appendix 1 Flowchart for serious ADR report submission to the Medicines Authority



AWTORITÀ DWAR IL-MEDIĊINI

Appendix 2 CIOMS Form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Appendix 3 Requirements for PSUR submission

PSURs should be submitted to the Medicines Authority in the format and reporting frequencies as outlined below:

Report format and copies required	Addressee(s)
Products authorised via the National Procedure: **1 electronic copy on CD-ROM** Products authorized via the Mutual Recognition Procedure OR Decentralised Procedure: If Malta is RMS: **1 paper copy + 1 electronic copy on CD-ROM** If Malta is CMS: 1 electronic copy only on CD-ROM Products authorised via the Centralised Procedure: If Malta is Rapporteur/Co-Rapporteur: **1 paper copy + 1 electronic copy on CD-ROM** If Malta is **not** Rapporteur/Co-Rapporteur: 1 electronic copy only on CD-ROM	For ALL products: Six monthly and annual PSURs: Pharmacovigilance Section, Post-Licensing Directorate, Medicines Authority, 203, level 3 Rue D'Argens, Gzira. GZR 1368. Malta. Tel: (+356) 23439000 Fax: (+356) 23439161 Email address: postlicensing.mru@gov.mt Subsequent 3-yearly PSURs: Pharmacovigilance Section, Post-Licensing Directorate, Medicines Authority, 203, level 3 Rue D'Argens, Gzira. GZR 1368. Malta. Tel: (+356) 23439000 Fax: (+356) 23439161 Email address: postlicensing.mru@gov.mt Interim PSURs: To the person from the Post-Licensing Directorate making the request.