Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations for Medicinal Products for Human Use

Document Reference
GL-PL 03.05

March 2015

Medicines Authority
Post Licensing Directorate
Malta

Contents

Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations, and Reporting Requirements for Medicinal Products for Human Use

1. INTRODUCTION

Pharmaceutical companies have specific obligations with regards to pharmacovigilance. The information contained in this document is directed to pharmaceutical companies

- which hold marketing authorisations for medicinal products for human use, parallel import licenses and licences in accordance with article 126a of Directive 2001/83/EC as amended.
- that are applicants for marketing authorisations for medicinal products for the Maltese market.
- that have medicines which are available in Malta through a named patient basis or compassionate use programmes.
- that are license holders of products authorised in accordance with sponsors/investigators of Clinical Trials held in Malta.

The legal framework for these obligations is described in the following legislation:

1. Medicines Act 2003
2. Pharmacovigilance Regulations 2012 (S.L.458.35 amended by L.N 352 of 2013)
2. Codified Directive 2001/83/EC as amended by Directive 2010/84/EU and Directive 2012/26/EU
3. Commission Implementing regulation 520/2012
4. Clinical Trials New Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use,
5. Clinical Trials Regulations 2004 (S.L.458.43 amended by L.N 248 of 2007)
6. Parallel Import of Medicinal Products Regulations (S.L.458.40 amended by L.N

291 of 2014)

7. CT-3 Guidance notes

Furthermore, the Medicines Authority has fully adopted all measures laid out in the European Medicines Agency's Good Pharmacovigilance Practice guidance modules (GVP) for products authorised centrally and those authorised at national level. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Unlicensed medicinal products for human use do not fall under the scope of these pharmacovigilance guidance notes. Any provisions stipulated in DH Circular 137/2004 concerning the "Guidelines Governing the Use of Medicinal Products for Human Use without a Marketing Authorisation" should be consulted. The circular can be accessed at the following website: http://www.sahha.gov.mt/pages.aspx

2. ROLES AND RESPONSIBILITIES OF PHARMACEUTICAL COMPANIES

After granting of the marketing authorisation, the Marketing Authorisation Holder (MAH) of a medicinal product is responsible for the quality, efficacy and safety of its products. The MAH must operate appropriate pharmacovigilance and risk management systems in order to take responsibility for identifying risks with their products and ensure that pharmacovigilance data are continuously monitored, options for risk minimisation and prevention are considered and that appropriate measures are taken as necessary.
In accordance with Article 6 of Pharmacovigilance Regulations 2012, the Marketing Authorisation Holder (MAH) has the following general responsibilities:

- To establish and maintain a pharmacovigilance system in order to collect information on the risks of medicinal products in particular to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from outside the terms of the marketing authorisation (such as abuse and medication errors) and to adverse reactions associated with occupational exposure.

- This information should be collected and collated, including follow up information in order to be made available within Eudravigilance and to the Medicines Authority upon request;
- The MAH must evaluate scientifically all information from the collection of adverse drug reactions, consider options for risk minimisation and take appropriate measures as necessary.
- To perform a regular self-audit of the pharmacovigilance system and to place a note concerning the main findings of the audit on the pharmacovigilance system master file and to ensure that an appropriate corrective action plan for the findings is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.
- As part of the Pharmacovigilance system, the MAH should have permanently and continuously at his disposal an appropriately qualified person responsible for Pharmacovigilance.
- As part of the Pharmacovigilance system the MAH must maintain a Pharmacovigilance system master file that is available on request.
- 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 Post Authorisation Safety Studies (PASS) and Post Authorisation Evaluation Studies (PAES).

3. THE QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV) AND LOCAL PHARMACOVIGILANCE CONTACT PERSON

In accordance with articles 6(4) of Pharmacovigilance Regulations 2012, a Marketing Authorisation Holder must have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance (the QPPV) must reside and operate in the European Union and is responsible for operating the

pharmacovigilance system. The MAH or the local representative of that MAH must submit the name, contact details and Curriculum Vitae of the qualified person to the Medicines Authority and to the European Medicines Agency.
This may be done in soft copy to postlicensing.medicinesauthority@gov.mt or else as a hardcopy letter to;
The Medicines Authority/Postlicensing Directorate: 203, level 3 Rue D'Argens Gzira GZR 1368

The Medicines Authority may request the nomination of a contact person for Pharmacovigilance issues at national level, reporting to the qualified person responsible for pharmacovigilance activities. If such a contact person is requested, this person may or may not be medically qualified. Unless specifically requested, it is the prerogative of each company to decide on the nomination of a person for pharmacovigilance. Should such a person be nominated, a free text email notification should be sent to postlicensing.medicinesauthority@gov.mt

4. COMMUNICATIONS

In line with article 14(1) of Pharmacovigilance Regulations 2012, the MAH must inform the Medicines Authority, the European Medicines Agency and the European Commision if it intends to make a public announcement relating to information on pharmacovigilance. The MAH must inform the authorities at the same time, or before the public announcement is made. The MAH must ensure that information to the public is presented objectively and is not misleading.

Any communications related to pharmacovigilance should be sent by email to postlicensing.medicinesauthority@gov.mt

Operating a medical information service aiming to support medicinal product prescription and use practices which are in line with those of the SmPC for healthcare professionals and PL for patients is the responsibility of pharmaceutical companies.

5. RISK MANAGEMENT

5.1 Risk Management System

A **Risk Management System** means a set of Pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions. A **Risk Management Plan (RMP)** is a detailed description of the risk management system for a medicinal product(s).

For marketing authorisations granted after 21 July 2012, Marketing Authorisation Holders (MAHs) are required to operate a risk management system for each medicinal product.

Holders of marketing authorisations granted before this date are not required to operate a risk management system for each medicinal product unless the Medicines Authority or MAH are concerned about risks affecting the benefit-risk balance of an authorised medicinal product. In such a situation, the Medicines Authority may request (with justification) a detailed description of a risk management system including a Risk Management Plan (RMP) that the MAH intends to introduce for the medicinal product concerned as well as a time-frame for submission of the description of the intended risk management system .

This obligation will be confirmed or withdrawn by the Medicines Authority based on the response and justifications given in response by the MAH. This response must be received by the Medicines Authority within 30 days of receipt of the written notification of the obligation to submit a Risk Management Plan (RMP).

Should a risk management system for a medicinal product be set up, the MAH is legally obliged to:

- Monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing

authorisation;

- Update the risk management system and monitor pharmacovigilance data to check for new risks, or to establish whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

5.2 Conditions of the marketing authorisation

At the time of finalising an opinion for a procedure both pre and post authorisation, the European Medicines Agency's committee(s) or the Licensing Authority of Malta may agree that the applicant or MAH should perform additional activities as necessary from a public-health perspective to educate healthcare professionals on specific issues or to generate additional data to enhance the safety and, in certain cases, the efficacy of authorised medicinal products.

The specific obligations tied to marketing authorisations are legally binding and enforceable and it is the duty of MAHs, representatives of the MAH and of local importers to implement those conditions of the marketing authorization which apply to Malta.

In order to find what specific obligations are assigned to a marketing authorisation MAHs should screen the community register at regular intervals at the following site http://ec.europa.eu/health/documents/community-register/index_en.htm .

The Community Register lists all medicinal products for human and veterinary use as well as orphan medicinal products that have received a marketing authorisation through the centralised procedure as well as information on medicinal products for which a Commission decision was necessary. These medicinal products, listed by the name of their active substance are listed under the heading EU Referrals. Screening of the community register should include a process of checking the annexes of Commission Decisions for any pharmacovigilance related obligations.

If screening is being done by local wholesale dealers or marketing authorisation holder affiliates, then the relevant responsibilities for these obligations should be clarified with the MAHs.

5.3 Risk Minimisation Measures Approval Process

Risk Minimisation Measures (RMMs) are a set of activities which will be done to reduce the risk of an event occurring, or to reduce the harm from the event associated with a particular safety concern. The risks identified with a product are specified in the Risk Management Plan.

There are two types of Risk Minimisation Measures:

(1) Routine risk minimisation measures
(2) Additional risk minimisation measures

Routine risk minimisation is applicable to all medicinal products, and involves the use of the following tools, which are described in detail in Module V of GVP Module XVI on Risk Minimization Measures:

- the summary of product characteristics (SmPC)
- the package leaflet
- the labelling
- the pack size and design
- the legal (prescription) status of the product

Additional risk minimisation measures are activities put in place to reduce the probability of an event occurring through for example;

- Educational materials for doctors, pharmacists or patients
- Limiting the size of a package or having a Pregnancy Prevention Programme (PPP)

http://www.cbg-meb.nl/CBG/en/human-medicines/pharmacovigilance/pregnancy-prevention-programme/default.htm

All additional Risk Minimisation Measures (RMM) (whether voluntarily introduced by a marketing authorisation holder or set as a condition of a marketing authorisation) must be approved by the Medicines Authority prior to their distribution.

When submitting Risk Minimisation and Educational Materials to the Medicines Authority the following documents should be included in the submission when applicable;

- Word version of education materials (clean and tracked changed versions for updated materials)

- Distribution list (a list of healthcare professionals)
- Proposed timelines for distribution
- Annex IIB and/or Annex IV (conditions of marketing authorisation)

For all Risk Minimisation Materials the company must ensure that a call-for-reporting section which encourages the reporting of adverse events is included within each educational material or other form of additional risk minimisation measure. The following text is recommended:

> Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent by post or email to;
>
> **P**: ADR reporting/ 203, level 3 Rue D'Argens Gzira GZR 1368
>
> **E**: postlicensing.medicinesauthority@gov.mt

The company details for ADR reporting should also be included in the call-for-reporting section.

The Medicines Authority may also request that patient educational materials and alert cards, are translated into Maltese on a case-by-case basis depending on the nature and content of the educational material in question.

For products with a marketing authorization in Malta which have been placed on the Maltese market then risk minimization measures as well as their updates should be distributed to healthcare professionals with a distribution method that is appropriate and agreed to by the Medicines Authority.

If a product is authorised in Malta but has never been placed on the market as is the case with several centrally authorised products then the risk minimization measures should be submitted for review to the Medicines Authority before introduction of the product to the Maltese market.

Following approval of the materials by the Medicines Authority, the final versions of the materials are hosted on the Medicines Authority website at the following location www.medicinesauthority.gov.mt/safetyinfo. This search function can be used to look for

copies of Direct Healthcare Professional Communications as well as Risk Minimisation Measures using the name of product, ATC Code, active ingredient or authorisation number. One can also list all DHPCs or RMMs by typing DHPC or RMM in the search box. The latest version of a file can be identified by the date which is the suffix number in the file name.

The MAH should confirm when distribution of the RMMs to the agreed list of stakeholders has been finalised. This is done by sending an email to postlicensing.medicinesauthority@gov.mt. Any relevant documentation which can be considered as confirmation that the materials have been distributed to healthcare professionals must be retained by the company and made available for any Medicines Authority Pharmacovigilance Inspections.

5.4 Additional Monitoring

In the new pharmacovigilance legislation, a new concept of additional monitoring was developed, which aims to further characterise the safety profile of newly authorised medicinal products or those requiring further safety data. The purpose of additional monitoring is to promote the reporting of suspected adverse reactions. Medicinal products under additional monitoring are identified by an inverted black triangle.

Medicinal products under additional monitoring should have the inclusion of a standard text in the product information expressly asking healthcare professionals and patients to report suspected adverse reactions in accordance with their national spontaneous reporting system (see section 5.5).

The following medicinal products are subject to additional monitoring:

- medicinal products authorised in the EU that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU
- any biological medicinal product authorised after 1 January 2011
- products for which a PASS was requested at the time of marketing authorization
- products authorised with specific obligations on the recording or suspected

adverse drug reactions exceeding those referred to in Chapter 3 of Directive 2001/83/EC

- products which were granted a conditional marketing authorization
- products authorised under exceptional circumstances

Other products may also be included on the list of medicinal products subject to additional monitoring. This may be done at the request of the European Commission or a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC). The situations that could form the basis for a request for inclusion in the list are defined in GVP Module X on Additional Monitoring.
Additional monitoring status may also be assigned to a medicinal product at any time during the product lifecycle if a new safety concern is identified.

The European list of products under additional monitoring is available on the European Medicines Agency (EMA) website and is reviewed every month by the PRAC. Medicinal products may be included or removed from this list either in the context of a regulatory procedure (e.g. marketing authorisation application, extension of indication, renewal) or outside of a regulatory procedure. MAHs should therefore maintain their awareness of the products included in the list.

The additional monitoring list is available at the following page; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852

5.5 National implementation of the additional monitoring pharmacovigilance text and the black triangle symbol

The Medicines Authority recommends the following approach to the addition of local adverse drug reaction reporting details within product information in order to prevent any impact on the availability of medicinal products in a small market. The following guiding principles apply;

- The addition of the Medicines Authority contact details for ADR reporting is encouraged within the product information;
- For packages which are not produced specifically for Malta, ie. joint packs, or

packs sourced from markets which have product information in the English language, then the pharmacovigilance product information text specific to Malta is currently not mandatory but inclusion is encouraged where this is feasible.

- For product packaging which is made specifically for Malta, such as packs sourced from non-english speaking countries, the Medicines Authority ADR reporting details should be incorporated. In such cases, the guide for the text provided by QRD template version 9 is preferred.

The QRD template and Annex V are available on the EMA website at the following address
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800022c59&jsenabled=true

Specifically; the following information within Annex V applies to Malta
ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

OR

ADR Reporting
www.medicinesauthority.gov.mt/adrportal

Both ADR reporting details (long and short versions) are acceptable within the product information.

Products which are under additional monitoring should have their product information updated with the black triangle symbol.
A type IA variation can be submitted with any other variation submission.

For promotional material/detail aids/Risk Minimization Measures on medicinal products which are under additional monitoring the black triangle should be included.

6. DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION (DHPC)

Direct Healthcare Professional Communications (also known as "Dear Dr Letters") are an important communication tools that aim to improve the safe and effective use of marketed medicines. A DHPC should not include any material that might constitute advertising or be considered promotional or commercial. A DHPC can be related to one medicinal product or it can be an active substance/class DHPC in which case many medicinal products will be within the scope of the letter. For the latter type of DHPC, that is, those based on active substance and which therefore involve more than one company, then companies may request the joint DHPC coordination service of the Medicines Authority (see section 6.4).

The content, format, timeline for distribution, intended recipients and method of distribution of any DHPC should be agreed with the Medicines Authority.

The key principles for DHPCs include:

- Should be sent when healthcare professionals are to be notified of significant, new, or emerging information
- Situations where a DHPC should be considered as part of the risk-management process include: suspension, withdrawal; revocation of a marketing authorisation with recall of the medicine from the market for safety reasons; important changes to the Summary of Product Characteristics (eg new warnings or contraindications, reduced recommended dose, or restricted indications or availability); or a change in the balance of benefits and risks for a medicine.

6.1 DHPC approval process

The Marketing Authorisation Holder should submit a draft copy of the DHPC and the

communication plan by email to the Medicines Authority on postlicensing.medicinesauthority@gov.mt. The submission should include a timetable, a list of recipients and the dissemination method.

DHPCs on new information are required and must be disseminated for all products with a marketing authorisation or license in Malta. However some exemptions may apply depending on the specific context/scenario for the DHPC (see section 6.3).

6.2 Key principles for preparation of a Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication should be written in English, no Maltese version of the letter is necessary.

- As an example, an acceptable template of a DHPC would be arranged with the following sections, other formats may also be acceptable: Summary—brief description of safety information and recommendations; this section should be in a larger font compared with the rest of the text
- Further information—detail of safety information (with frequency of event or adverse reaction), risk in the context of benefit, reference to annexed revised product information, follow-up action
- Recommendations—advice and instructions for risk minimisation
- A section with a Call for Reporting of suspected Adverse Drug Reactions and medication errors including the details of the Medicines Authority and of the company.

  Suggested wording is as follows: Adverse Drug Reaction and medication errors should be reported. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and sent to **ADR reporting/ Post-Licensing Directorate**/Medicines Authority, 203, Level 3, Rue D'Argens, Gzira GZR 1368, Malta, or sent by email to: Postlicensing.medicinesauthority@gov.mt
- Annexes—revised product information, reference list, and other information.

The following should also be considered:

- Safety information should be clear and concise

- The reason for dissemination should be explained (eg availability of new data)
- Recommendations to healthcare professionals should be given on how to minimise risk, if known
- The safety concern should be placed in the context of the overall benefit of treatment
- Safety information must be objective and not misleading
- If time allows, the text should be reviewed by representatives of the target audience
- The Direct Healthcare Professional Communication should include the content of any information communicated directly to the general public
- Estimated timescales for follow-up action should be stated if required.
- Contact details for further information should be provided, including the website address, telephone number, and postal address of the marketing authorisation holder
- Relevant references should be cited as an annex.

› Template for Direct Healthcare Professional Communications (27Kb)

Following approval of the DHPC by the Medicines Authority, the final version of the DHPC is hosted on the Medicines Authority website at the following location www.medicinesauthority.gov.mt/dhpc. The MAH should confirm distribution of the DHPC by sending an email to postlicensing.medicinesauthority@gov.mt. Any relevant documentation which can be considered as confirmation that the DHPC has been distributed to healthcare professionals must be retained by the company and made available for any Medicines Authority Pharmacovigilance Inspections.

6.3 Obligations for DHPC dissemination

To facilitate the understanding of obligations for MAHs with respect to DHPC circulation in relation to products authorised in Malta the Medicines Authority has compiled the following tables of scenarios. These tables have been construed to factor in the following parameters to determine who is obliged to disseminate a DHPC;

- the type of authorization and marketing status of medicinal products
- whether a DHPC is relating to a single medicinal product or whether it is an active

substance based DHPC.

When a DHPC is on a single particular medicinal product then the product specific scenario applies (see Table 1).
Ex. A DHPC on cases of Necrotising Fasciitis Reported only with TradeName X would fall under the product specific scenario.

When a DHPC is on an active substance and involves more than 1 medicinal product then the product specific scenario applies (see Table 2).
Ex. A DHPC on updated indications of <paracetamol> and posology to minimise risk of <hepatic> adverse effects is an active substance based DHPC. Since there are many paracetamol contianing products the release of a single joint letter would be favored.

Definitions

Marketed: a medicinal product which has been placed for sale or use within a pharmacy or pharmacy store. In cases where a product was marketed in the past but is not currently being sold/marketed the requirement for a DHPC should be raised by the company and will be assessed by the Medicines Authority on a case-by-case basis.

Not marketed: a product which has never been imported and placed for sale, or else is housed solely within an importers medical store.

Product specific DHPC: DHPC which involves one branded medicinal product only

Active substance DHPC: DHPC which involves more than one brand of medicinal product

Paper: means a paper copy (hard copy) through normal mail is required. Alternatively a suitably validated medium of dissemination that will reach the same amount of recipients may be accepted.

Website: means that the DHPC is required for upload on the Medicines Authority website (www.medicinesauthority.gov.mt/dhpc)

MA: denotes a marketing authorisation. Can be either a national marketing authorisation (evident from the MA prefix of the marketing authorisation number ex. MA001/xxxxx) or else a marketing authorisation granted via the centralised procedure (evident from the EU prefix of the marketing authorisation number ex EU/x/xx/xxx/xxx)

PI: an authorisation for importation of products in line with SL 458.40 on Parallel Importation of medicinal products regulation. PI product authorizations may be distinguished from the PI/xxx/xxx prefix in the authorization number.

126a: a license for placing medicinal products on the market in accordance with the provisions laid out in article 126a of directive 2001/83/EC. The prefix denoting this type of authorization is AA/xxx/xxx

TABLE 1: Requirement for DHPC circulation in a product specific scenario

Product Specific Scenarios			
	marketed	**marketed**	**marketed**
	MA	PI	126a
paper	yes	no	yes
website	yes	no	yes
	marketed	**not marketed**	**not marketed**
	MA	PI	126a
paper	yes	no	no
website	yes	no	no
	marketed	**marketed**	**not marketed**
	MA	PI	126a
paper	yes	no	no
website	yes	no	no
	not marketed	**marketed**	**marketed**
	MA	PI	126a
paper	yes	yes	yes
website	yes	yes	yes
	not marketed	**not marketed**	**marketed**
	MA	PI	126a
paper	yes	no	yes
website	yes	no	yes
	not marketed	**marketed**	**not marketed**
	MA	PI	126a
paper	yes	yes	no
website	yes	yes	no
	not marketed	**not marketed**	**not marketed**

	MA	PI	126a
paper	no	no	no
website	no	no	no

TABLE 2: Requirement for DHPC circulation in an active substance based scenario

Active substance mandated scenario			
	marketed	**marketed**	**marketed**
	MA	PI	126
paper	yes	no	yes
website	yes	no	yes
	marketed	**not marketed**	**not marketed**
	MA	PI	126
paper	yes	no	yes
website	yes	no	yes
	marketed	**marketed**	**not marketed**
	MA	PI	126
paper	yes	no	yes
website	yes	no	yes
	not marketed	**marketed**	**marketed**
	MA	PI	126
paper	yes	yes	yes
website	yes	yes	yes
	not marketed	**not marketed**	**marketed**
	MA	PI	126
paper	yes	no	yes
website	yes	no	yes
	not marketed	**marketed**	**not marketed**
	MA	PI	126
paper	yes	yes	yes
website	yes	yes	yes
	not marketed	**not marketed**	**not marketed**
	MA	PI	126
paper	no	no	no
website	no	no	no

6.4 Joint DHPC service

When more than 1 MAH is obliged to circulate the same DHPC or more than 1 product is the subject of a DHPC, then MAHs/license holders/affiliates may request the service of the Medicines Authority to circulate the letter on their behalf. MAHs/license holders and

affiliates are not obliged to participate in the joint DHPC however they must still send the letter to the stakeholders unilaterally.

The process is as follows;

1. A trigger is received by any company requesting the Medicines Authority to co-ordinate a joint DHPC.
2. The final EMA Committee approved DHPC is obtained by Medicines Authority staff.
3. Costs for the letter are calculated depending on who the stakeholders of the letter should be.
4. A list of MAHs involved is obtained from the Malta Medicines database at http://medicinesauthority.gov.mt/medicinesdatabase
5. MAHs/affiliates/licence holders are contacted with an Expression of Interest to participate and with a projection of the costs. A deadline for response is given.
6. After the number of participants expressing interest to participate is obtained, MAHs who expressed interest will be informed of the final expected price. At this stage, MAHs who have expressed interest to participate may still opt out of the joint DHPC and proceed with their own distribution. Any changes to the expected costs will always be communicated to the interested participants.
7. The Medicines Authority then obtains all the data/registers/addresses/details necessary to compile a comprehensive list of stakeholders to be contacted.
8. Letters are then updated with participating companies details, printed, folded, stapled and grouped according to country
9. Letters are posted and proof of payment is maintained (receipt),
10. Once posted, MAHs are informed that the DHPC has been disseminated and are sent a Eudralink package of the individually addressed DHPC letters
11. The final DHPC is saved on website as pdf.
12. An invoice is raised to participants.

7. ADVERSE DRUG REACTIONS (ADRS)

7.1 Adverse Drug Reaction reports

According to Articles 15 to 20 of Pharmacovigilance Regulations 2012, the MAH is legally obliged to carry out the following activities. For ADR reporting requirements for companies which are not marketing authorisation holders, section 15 may apply.

- To maintain detailed records of all suspected Adverse Drug Reactions (ADRs) occurring either in Member States or in a third country, whether reported spontaneously by patients or healthcare professionals, or occurring within the context of a post-authorisation study.
- To immediately record and report electronically to the Eudravigilance database to receiver identifier EVHUMAN 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 electronically to the Eudravigilance database to receiver identifier EVHUMAN all suspected serious (expected 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 submit electronically to Eudravigilance database to receiver identifier EVHUMAN information on all non-serious suspected adverse reactions that occur in the EU within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.
- MAHs should establish procedures to obtain accurate and verifiable data for the scientific evaluation of ADR reports
- The MAH must collaborate with the European Medicines Agency (EMA) and other member states in the detection of duplicate adverse reaction reports;
- If the suspected adverse reactions occur within the context of a clinical trial, they must be reported and recorded in line with Clinical trials regulation 536/2014.

Reporting requirements applicable to marketing authorisation holders in the interim period can be found in the following URL;

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127657.pdf

ADR reports from pharmaceutical companies may only be submitted to the

Eudravigilance database in electronic E2B (M) format to EVHUMAN as message sender identifier.

The MAH are legally obliged to consider all reports received electronically or by any other means from both patients and healthcare professionals. MAHs should use MedDRA terminology for the reporting of ADRs. Further information on MedDRA can be obtained from the following website: www.meddramsso.com

To ensure the transmission of high quality data to Eudravigilance, MAHs should make every effort to obtain as much information as possible about a case.

7.2 Electronic format of ADRs

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, directly to the Eudravigilance database with the message receiver identifier EVHUMAN. Parallel reporting of ICSRs in paper format is not required. ICSRs concerning suspected serious and unexpected adverse reactions occurring in the territory of a third country (non-EU/EEA) should also be submitted to EudraVigilance 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 2012.

7.3 Reporting of Medication Errors

Medication errors may lead to adverse drug reactions and so a medication error reporting system has been developed to capture medication error related information. MAHs are required to report within 15 calendar days all serious ADRs associated with medication errors and within 90 days all non-serious ADRs associated with medication errors directly to Eudravigilance EVHUMAN. Medication errors which do not lead to an adverse drug reaction can also be reported using the Medicines Authority ADR-Medication Error form or any other MAH form for medication errors. The Medicines Authority form for the reporting of Adverse Drug Reaction (ADRs) has been updated to capture information on medication errors. The form and full instructions are available at www.medicinesauthority.gov.mt/adrportal

7.4 Literature Monitoring for ADR reports

Marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals regarding medicinal products which have a marketing authorisation in Malta. Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts of scientific articles should be reviewed and assessed by the company to identify and record ICSRs and transmit them to the Eudravigilance database.

Examples of local journals (this list is not exhaustive) that MAHs could monitor include:

- The Malta Medical journal
  http://www.um.edu.mt/umms/mmj/
- The Journal of the Malta College of Pharmacy Practice
  http://www.mcppnet.org/publications.htm
- Images in Paediatric Cardiology
  http://www.impaedcard.com/coredocs/instau.htm#top
- The Synapse
  http://www.thesynapse.net/
- Journal of the Malta College of Family Doctors

http://mcfd.org.mt/jmcfd

Any ADRs identified during literature monitoring should be transmitted to Eudraviglance as ICSRs directly to Eudravigilance (identifier EVHUMAN). The scientific literature article itself should be fully cited in the ICSR case narrative but need not be sent in parallel to the Medicines Authority unless specifically requested. If such a request is made, the submission should be made electronically in digital format.

7.5 Steps to follow in case of system failure

Fallback solutions in the case of failure of the MAHs Eudravigilance gateway, or for companies operating with EVWEB, or from EMAs side of operation are given in this document:

http://eudravigilance.ema.europa.eu/human/docs/Steps%20to%20follow%20in%20case%20of%20system%20failure.pdf

In such an event where the Medicines Authority requires an ICSR while the MAHs system is in failure, 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. When EudraLink cannot be obtained, the generic email address postlicensing.medicinesauthority@gov.mt may be used.

7.6 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.
For biological medicinal products, healthcare professionals and patients should report adverse reactions by brand name and batch number.
The Medicines Authority may request further information regarding individual ADR reports, as appropriate.

7.7 Criteria for a Valid Medication Error Report

For a Medication Error report to be valid, it must
(1) be related to a medicinal product and
(2) have a description of the event.

In order to foster a no-blame approach towards reporting of medication errors, the Medicines Authority has a policy to destroy reporter details after any follow-up requests for information have been obtained.

8. REGISTRATION WITH EUDRAVIGILANCE

MAHs need to register with EudraVigilance to facilitate the electronic reporting of suspected serious adverse reactions in the post-authorisation phase in accordance with Regulation (EC) No 726/2004 and Directive 2001/83/EC.

MAHs also need to register with EV to facilitate the electronic submission of information on medicines in accordance with Article 57(2), second subparagraph of Regulation (EC) No. 726/2004. This refers to XEVMPD electronic submission of information on medicines. The pharmaceutical company headquarter and its affiliate(s) must be registered with EudraVigilance.

Sponsors of clinical trials need to register with EudraVigilance to facilitate the electronic submission of information on Investigational Medicinal Products (IMPs) (Product

Messages) in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). This refers to CT-3 IMPs electronic submission of information. Sponsors of clinical trials also need to register with EudraVigilance to facilitate the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) in accordance with Clinical trials regulation 536/2014and the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). This refers to SUSAR reporting. Sponsors and, if applicable, its affiliates/subordinates (e.g. clinical research departments) must be registered with EudraVigilance.

The registration process depends on the different categories outlined above. Information on how to register can be found on this website http://eudravigilance.ema.europa.eu/human/HowToRegister.asp

9. CLINICAL TRIALS AND ADR REPORTING

The legal obligations of the sponsors of clinical trials are specified in Clinical trials regulation 536/2014 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 centers. 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) occurring in Malta 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 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 report should be in the Development Safety Update Report (DSUR) format (see section 10.2).

The Medicines Authority does **not** require:

- reporting of ADRs arising from clinical trials conducted outside Malta and which do not involve Maltese centers.
- 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.
- 6 monthly aggregated line listings.

9.1 SUSARs associated with active comparator or placebo.

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.

SUSARs may be submitted to the Medicines Authority electronically via EudraVigilance in E2B(M) format, directly to EudraVigilance clinical trials module (EVCTM). 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 Clinical trials regulation 536/2014.

9.2 Developmental Safety Update Reports (DSURs)

In addition to expedited reporting of SUSARs or ICSRs, for clinical trials approved after September 2011, Contract Research Organisations (CROs) should submit, once a year throughout the clinical trial a Development Safety Update Report (DSUR) 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 DSURs submitted to the Medicines Authority and to the Health Ethics Committee must be the same.

For a detailed description of the DSUR consult the 'ICH guideline E2F 'Note for guidance on development safety update reports'

The Health Ethics committee in Malta is a separate entity from the Medicines Authority. Information on requirements can be obtained from

Contact hec@gov.mt
Health Ethics Committee

Department of Health Information & Research
95, Guardamangia Hill,
Guardamangia PTA 1313
Malta

Phone: (+356) 25599000

https://ehealth.gov.mt/healthportal/others/regulatory_councils/health_ethics_committee/health_ethics_committee.aspx

9.3 Reporting time frame for DSUR

The reporting time frame for DSURs starts with the date of the first authorisation of the clinical trial by the Licensing Authority. The anniversary of this date is designated as the cut off for data to be included in the DSUR. The sponsor should submit DSURs within 60 days of the data lock point. Once the trial is over in Malta, DSURs are no longer required to be submitted to the Medicines Authority. As part of the DSUR submission package the sponsor should indicate that the final DSUR serves as the last annual report for the investigational medicinal product. The sponsor should also indicate whether or not there are clinical trials continuing elsewhere.

If the clinical trial is done on a medicinal product that is already being marketed, then the information within it may somewhat overlap with the medicinal products Periodic Safety Update Report PSUR. However, the DSUR 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.

10. PERIODIC SAFETY UPDATE REPORTS (PSURS)

The EMA has published the list of European Union reference dates and frequency of submission of periodic safety update reports (PSURs) known as the 'EURD list'.

Marketing authorisation holders are required to submit PSURs to the National Competent Authorities or the EMA according to the dates published in the EURD list.

The PSUR frequency and related data lock points for a given active substance or combination of active substances in the EURD should be followed and supersedes any conditions related to the frequency of submission of a PSUR included in the marketing authorisation. If a submission frequency is specified in the marketing authorisation, then a variation should be submitted to remove the frequency. The format and content of PSURs are described in GVP module VII on PSURs and need to be compatible with the objective of performing a benefit-risk evaluation in a cumulative way.

10.1 Submission

PSURs should be submitted as established in GVP Module VII as follows:

- within 70 calendar days of the data lock point for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and within 90 calendar days of the data lock point for PSURs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs requested by competent authorities will be normally specified in the request, otherwise the ad hoc PSURs should be submitted within 90 days of the data lock point.

Until the European Medicines Agency's PSUR repository is in place then submission of PSURs to the Medicines Authority is still required.

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

1. For products authorised via any procedure (national, MRP, DCP) c 1 electronic copy on CD-ROM accompanied by a relevant cover letter should be submitted;

For the interim period PSURs should be sent to

The Medicines Authority Post-Licensing Directorate

203,Level 3
Rue D'Argens
Gzira GZR 1368
MALTA

Submission of PSURs to the the Medicines Authority via CESP is not acceptable at this stage.

10.2 PSURs for products authorised under Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC

Products authorised under in Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC are exempted from routine submission of PSURs unless otherwise specified in the EURD list. Alternative mechanisms such as signal management and emerging safety issues channels should be used to communicate relevant new safety information to regulatory authorities (GVP Module VI and Module IX).
It is the responsibility of Marketing Authorisation Holders to ensure that their product information is kept up-to-date in line with Article 16(3) of Regulation (EC) No 726/2004/Article 23(3) of Directive 2001/83/EC by submitting the appropriate variations taking account of the current scientific knowledge, which includes the conclusions of the assessment and recommendations made by the EMA and National Competent Authority websites and, when available, the European medicines web-portal.

11. POST-AUTHORISATION SAFETY STUDIES (PASS) AND POST-AUTHORISATION EFFICACY STUDIES (PAES)

Pharmacovigilance Regulations 2012 apply to non-interventional post-authorisation safety and efficacy studies managed or financed by the MAH voluntarily or imposed by Articles 21a and 22a of Directive 2001/83/EC as amended, and which involve the collection of safety data from patients or health professionals.

When conducting these studies the MAHs should ensure that;

- The PASS does not promote the use of a medicinal product;
- Payment to healthcare professionals for their participation should be restricted to the compensation for time and expenses incurred;
- The final report of the study is to be submitted to the Medicines Authority if the study is conducted in Malta, within 12 months of the end of data collection unless a waiver is requested and accepted by the Medicines Authority;
- While the study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications on the benefit-risk balance of the medicinal product concerned
- If any new information which might influence the benefit risk balance of the medicinal product must be communicated not only to the Medicines Authority but also to the competent authorities of the member states where the product is authorised.

If a study is to be conducted only in Malta at the request of the Medicines Authority according to Article 22a of Directive 2001/83/EC, the MAH must submit a draft protocol to the Medicines Authority.

If a study is to be conducted in more than 1 member state, then the MAH must submit the protocol to the Pharmacovigilance Risk Assessment Committee (PRAC).

Within 60 days of submission of the draft protocol to either the Medicines Authority or the PRAC, the Medicines Authority or the PRAC shall issue the MAH with:
- a letter of endorsement or
- a letter of objection detailing the grounds for objection or
- a letter notifying the MAH that the study is a clinical trial falling under the scope of Clinical trials regulation 536/2014

Commencement of the study may only take place when the MAH receives the letter of endorsement from the PRAC or the Medicines Authority. When the letter of endorsement has been issued, the MAH should forward the protocol to the competent authorities of the other member states in which the study is to be conducted.

After commencement of the study, any substantial amendments to the protocol should be

submitted to the Medicines Authority or the PRAC before their implementation. These amendments will be assessed and the MAH will be informed of the outcome through a letter of endorsement or objection.

Depending on the outcomes of the study the MAH should submit any variations to the marketing authorisation to the Medicines Authority and other competent authorities (where there are marketing authorisations) in other member states.

12. VARIATIONS

Guidance on the regulations governing variations and their respective submission requirements consult the following website:
http://www.medicinesauthority.gov.mt/variations

13. PHARMACOVIGILANCE INSPECTIONS

13.1 The inspection process

For an outline of the inspection process please contact inspectorate.adm@gov.mt or on +35623439000 (and ask for inspectorate and enforcement Directorate).

13.2 Types of inspections

There are three types of inspections:
Routine national inspections: these are scheduled inspections that MT market authorisation holders (MAHs) undergo on a periodic basis. MAHs are notified of these inspections in advance. These inspections are generally systems based, meaning that inspectors examine the systems and procedures used by a MAH to comply with existing EU and national pharmacovigilance regulations and guidance.

'Ad hoc national inspections': these are ad-hoc inspections that are triggered as a result of, for example, safety issues, suspected violations of legislation relating to the monitoring of the safety of medicines, referrals by other Member States. In rare circumstances, MAHs may not be notified of these inspections in advance.

Committee on Human Medicinal Products (CHMP) requested inspections: the CHMP may request inspections of MAHs in association with specific centrally authorised products. These can either be routine or triggered. The general organisation and process for CHMP-requested pharmacovigilance inspections is described in GVP guidelines. The procedures for EU pharmacovigilance inspections requested by the CHMP can be found on the EMEA website (www.ema.europa.eu).

13.3 How will MAHs be contacted in preparation of an inspection?

Where a Marketing Authorisation Holder (MAH) is notified in advance of an inspection, they will be notified in writing, typically by email. If a MAH has concerns about the veracity of a notification, it is recommended that the MAH contacts the Medicines Authority either by email (insepectorate.adm@gov.mt) or via TC on +35623439000.

The MAH should initially acknowledge receipt of the notification and provide details of the relevant contact person for future correspondence about the inspection. The MAH will be provided with a deadline for submitting pre-inspection documentation, which is required to enable the inspection team to prepare for the inspection.

13.4 Grading of inspection findings

Deficiencies found during Inspections are graded in one of three ways:

Critical: a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major: a deficiency in pharmacovigilance systems, practices or processes that could

potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Other: a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

13.5 Inspection report

Once the inspection has been completed, an inspection report is prepared by the lead inspector. It should be noted that the factual matter contained in the inspection report relates only to those things that the inspection team sees and hears during the inspection process.

For additional information such as fees for pharmacovigilance inspections please contact inspectorate.adm@gov.mt

14. SAFETY RECALLS

From time to time, recall of stock of medicinal products for human use due to pharmacovigilance/safety issues or combined safety and quality issues may be required.

Almost without exception the recall of a medicinal product for human use on safety/pharmacovigilance issues follows the publication of a commission decision (in the Official Journal of the EU) or a decision taken by a marketing authorisation holder.

Safety/pharmacovigilance recalls are carried out in much the same manner as quality related recalls. The MAH should inform the Medicines Authority about its co-ordinated plan to carry out the recall; the submission package could contain as applicable:

1) The action plan for the recall including anticipated timelines
2) Direct Healthcare Professional Communication (DHPC) and Action Plan

3) Details about stopping the supply to Wholesale Dealer or pharmacies and the date of implementation
4) Letters to Pharmacies and WHDs.

The Medicines Authority will then review and approve the materials and upload any DHPC/Safety Circulars/Letters as applicable.

After the recall has been carried out a Reconciliation Report should be sent to the Medicines Authority.

15. NOTE ON PHARMACOVIGILANCE OBLIGATIONS OF PARALLEL IMPORTED PRODUCTS AND PRODUCTS AUTHORISED IN ACCORDANCE WITH ARTICLE 126A

15.1 126a authorisations

For this marketing authorisation, although a waiver is granted for an applicant not to submit a dossier in line with 2001/83/EC, the same directive stipulates that that no exemption/waiver of obligations are allowed for pharmacovigilance and advertising of these medicinal products.

The ownership of the 126a authorisations could fall into one of the following 2 groups:

1) The MAH of the product with its medicinal product registered in another EU member state in line with Directive 2001/83/EC

2) Another entity that is not the MAH (like a Wholesale Dealer) either established in another EU country or in the Member state itself.

Obligations that authorisation holders have to meet for PhV purposes include:-

a) Having a system to report Adverse Drug Reactions (ADRs)

ADR submissions have to be made to Eudravigilance in accordance with legislation and the provisions in this guide. This element can be achieved by groups 1 and 2. If the Eudravigilance software is not available to the licence holder then Group 2 should have Standard Operating Procedures (SOPs) whereby the ADR can be transmitted to the Marketing Authorisation Holder (MAH) abroad

b) Having a Pharmacovigilance System Master File (PSMF)

Both group 1 and 2 126a holders can have a Pharmacovigilance System Master File (PSMF).

c) Submission of PSURs

Wholesale dealers who have an authorisation need not submit Periodic Safety Update Reports (PSURs). Directive 2010/84/EU introduces the concept of single assessment PSURs. Therefore, through this system, the EU network would have the PSURs that all agencies can have access to through the central PSUR repository of the EMA. However, until the PSUR repository is in place, authorisation holders should submit PSURs to the Medicines Authority in accordance with the provisions in this guide (see Section 10).

d) Implementation of Risk Minimisation Measures (RMMs) (including Direct Healthcare Provider Communications- DHPCs)

Group 1 and 2 authorisation holders must have a quality system on how to identify that their products have got RMMs to be implemented. Thus a method of screening community decisions is required as well as SOPs in place for implementing RMMs and DHPCs.

e) Pharmacovigilance inspections

Pharmacovigilance inspections in MT are held for groups 1 and 2. PhV inspections (based on a risk based approach) can also focus on the implementation of RMMs. This is currently being carried out by MT GxP inspectors.

f) System for Safety Recalls

A system on safety recalls at the distributor needs to be in place for both 126a and PI

products.

15.2 Parallel Imported Products

The Parallel Import (PI) product is originally placed on the EU market by the Marketing Authorisation Holder. The pharmacovigilance obligation of the product is that of the Marketing Authorisation Holder. Therefore Parallel Importers are not fully responsible for the pharmacovigilance obligations of the medicinal product. However, they must have at least:

a) a system to identify and send ADRs to the MAH, who then has to comply with pharmacovigilance legislations and comply with Directive 2001/83/EC obligations

b) a system of safety recalls

c) a system to implement RMMs/DHPCs

Before placing a PI product on the Maltese market, the PI distributor should check and request from the MAH the provision of all RMM materials associated with that medicinal product to be imported. The PI importer alone or together with the MAH, then needs to comply with the distribution of the RMMs set in the conditions of its marketing authorisation. The Parallel Importer should remind MAH that the ultimate responsibility of the products safety lies with the MAH.

16. XEVMPD POPULATION

The Extended Eudravigilance Medicinal Product Dictionary (XEVMPD) was designed to support the collection, reporting, coding and evaluation of authorised and investigational medicinal product information in a standardised and structured way. In December 2010 new pharmacovigilance legislation amending existing legislation was adopted in the European Union (EU) resulting in the need to update the XEVMPD in accordance with the format for of the electronic submission of information on medicines published by the

Agency on 1 July 2011.

The XEVMPD is populated with medicinal product information related to the pre- and postauthorisation phase. The data are provided by Sponsors of Clinical Trials conducted in the European Economic Area (EEA) and Marketing Authorisation Holders (MAHs). Each MAH should enter in the XEVMPD medicinal product information, for which the MAH holds
a marketing authorisation. For pharmaceutical companies, which are organised in form of an EU headquarter and affiliates in different Member States, the MAH must be specified in accordance with the granted authorisation for each medicinal product.

The entry of medicinal product information in the XEVMPD takes place through EudraVigilance Product Report Messages (EVPRMs). The 'Sender' of an EVPRM is the formal owner of the data in the EVMPD and is therefore the only one authorised to update, vary or nullify such medicinal product information.

Sponsors must enter all IMPs, which they study in a clinical trial conducted in the EEA in the XEVMPD.

17 ATMPs Pharmacovigilance obligations

An Advanced Therapy Medicinal Products (ATMP) is a medicinal product which is either a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product or their combination. ATMPs and combined ATMPs have been defined in Part IV of Annex I to Directive 2001/83/EC and in Regulation (EC) 1394/2007. Regulation (EC) 1394/2007 also provides the ATMP regulatory framework. It is an amendment to Directive 2001/83/EC on human medicinal products for human use and establishes the requirements for the market authorisation, supervision and pharmacovigilance of ATMPs. It is mandatory that ATMPs are authorised through the centralised procedure.

17.1 Hospital Exemption

This relates to ATMPs which are exempted from the centralised marketing authorisation procedure. It was included in the regulation in recognition of the small scale and developmental nature of cell-related activities within hospitals. The exemption applies to ATMPs which are prepared on a non-routine basis, according to specific quality standards, and used within the same member state in a hospital in accordance with a medical prescription for an individual patient. In these cases under no circumstances should the hospital exemption be considered to be a facilitated pathway for bringing ATMPs to the clinic.

The Regulation stipulates that manufacture of ATMPs under the hospital exemption must be authorised by the Medicines Authority as the national competent authority. It is of note that traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to ATMPs for which a centralised market authorisation would be granted by the EMA.

Pre-authorisation requirements: Compliance with GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice) guidelines. Specific rules for labelling/packaging, quality and traceability of ATMP

Post-authorisation requirements: Follow-up of efficacy and adverse reactions, and risk management, Active surveillance, Specific clinical follow-ups for patients

The Medicines Authority can be contacted on postlicensing.medicinesauthority@gov.mt for advice on ATMP applications under the hospital exemption.

18. FEES FOR PHV OBLIGATIONS

Fees payable to the Medicines Authority are specified in Subsidiary legislation 458.46 Medicines Authority (Fees) Regulations.

http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=11284&l=1

19. FURTHER INFORMATION

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.medicinesauthority@gov.mt

20. 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	February 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	November 2010	Added revision history Updated weblinks Updated section on SUSARs Added section on ASRs in CT
GL-PL 03.05.	March 2015	Update of the guide to add information on new requirements brought about by the new pharmacovigilance directives and national legislation. Most sections were updated and several new sections were introduced.

LIST OF APPENDICES

Appendix 1 ADR-Medication error report form

ADVERSE DRUG REACTION REPORT FORM

ADVERSE DRUG REACTION AND MEDICATION ERROR REPORT FORM

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in

Please complete as much information as possible

Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☐	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS ____ ☐MALE ☐FEMALE AGE (at time of reaction) ____ WEIGHT (in kg, if known) ____ RACE ____ AREA ____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) (list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started dd	mm	yr	Date stopped dd	mm	yr
Medicine 1								
Medicine 2								
Medicine 3								

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side effect in as much detail as possible)

	Date started dd	mm	yr	Date stopped dd	mm	yr
ADR 1						
ADR 2						
ADR 3						

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	mm	yr	Date stopped dd	mm	yr

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☐	☐
If yes, which		
Is this the first time you reported this ADR	☐	☐

1.8 ADDITIONAL RELEVANT INFORMATION (if known)

(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe):	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?

☐ **Yes - please fill in section 2 and 3.** ☐ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

Form1P016/3version02

MEDICATION ERROR REPORT FORM

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
	If the same details were filled in section 1.2, you can leave this section blank		
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT

Date event occurred: ___/___/____ Date event was detected: ____/___/____

2.3 DESCRIBE THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE) RELATED TO THE MEDICINE

Free Text (eg Wrong route; wrong dose; wrong medicine; other):

For medication errors – tick the stage the error may have occurred

- Prescribing ☐
- Dispensing ☐
- Preparation ☐
- Storage ☐
- Distribution ☐
- Administration ☐

2.4 LOCATION WHERE THE EVENT OCCURED

(eg Nursing home, Home, Hospital, Pharmacy, Clinic, Other)

2.5 SUSPECTED CAUSE OF THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE

2.6 ANY FACTORS CONTRIBUTING TO THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE

(eg. Omission of meals, concomitant alcohol intake, over exposure to heat and sun, other)

2.7 WAS THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT PREVENTABLE? ☐ Yes ☐ No

2.8 WAS ANY REMEDIAL ACTION RELATED TO THE MEDICINE TAKEN?

☐ Yes (please describe): _____ ☐ No

2.9 RECOMMENDATIONS TO PREVENT REPEAT INCIDENT

2.10 DID THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RESULT IN AN ADVERSE DRUG REACTION?

☐ **Yes - please fill in section 1.** ☐ **No - please fill in your details below**

SECTION 3: REPORTER DETAILS

Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient
Name:
Address:
Telephone/Mobile:
E-mail address:

Signature _____ **Date** _____

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP910/3version02

INSTRUCTIONS FOR REPORTING ADVERSE DRUG REACTIONS AND MEDICATION ERRORS OR OTHER CAUSATIVE EVENT

Terms and Definitions

Definition for Patients/users of medicines (consumers)

Side effects (also referred to as adverse drug reactions or adverse events) are those troublesome effects, symptoms or feelings that show up when you are using a medicine. When medicines are used incorrectly they are more likely to cause a side-effect.

For this reporting system a medication error is an event, related to how medicines were used, which affected or could have potentially affected a patient's safety and caused or had the potential to cause that patient to experience a side-effect.

Definition for Healthcare Professionals

Adverse Drug Reaction (ADR): An ADR is a response to a medicinal product which is noxious and unintended. This includes side effects resulting from the authorised use of a medicinal product at normal doses, medication errors, off-label use and the misuse and abuse of medicinal products.

Medication error: For the scope of this reporting system, medication errors that require reporting to the Medicines Authority are those which are related to the use of medicinal products. The adopted definition of a medication error is: *Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health-care professional, patient or consumer.* (National Coordinating Council for Medication Error Reporting and Prevention)

Other Causative Events: include occupational exposure, abuse, overdose etc.

Section 1: Side Effect Reporting

1.1 Patient Details: Only initials must be used, never the whole name. The identity is kept in strict confidence by the Medicines Authority.

Age at time of event or date of birth: Provide information that is as accurate as possible. Enter the birth date, if known, or the age at the time the side-effect started. For age, indicate time unit used (e.g., years, months and days).

Gender: Enter whether male or female. If the side-effect or medication error concerns a congenital anomaly (birth defect) report the gender of the child.

Weight: Indicate whether the weight is in kilograms or any other unit. If the exact weight is unknown, try and make the best estimate.

1.2 Suspected Medicine(s)/Vaccine(s)/Blood product(s): For these reports, a suspect medicine is one that you think was associated with the side effect, interaction or medication error. Use the trade names as marketed. If this is unknown, use the active ingredient and the manufacturers name if known.

Dose: Report the strength and form of the medicine in the appropriate units. The frequency of administration and the route of administration should be included in this field e.g. 500mg tablets, twice daily, orally (by mouth). For medication errors involving a wrong dose, write the dose that was used in error.

Prescribed for: Provide the reason (indication) for which the medicine was prescribed as accurately as possible.

Therapy dates: Provide the date when the medicine was started (or best estimate) and the date the medicine was stopped (or best estimate). If no dates are known, an estimated duration is acceptable (e.g. 6 months) or, if less than 1 day then duration is appropriate e.g. 1 dose or infused over 1 hour.

1.3 Suspected Adverse Drug Reaction(s): Describe the side effect in as much detail as possible, including a description of what happened and a summary of all relevant medical information. Example 1 – A hemorrhage from the use of too much anticoagulant (such as heparin) is a side effect caused by treatment.
Example 2 – The common side effects of cancer treatment including fatigue, nausea, vomiting, decreased blood cell counts, hair loss, and mouth sores are instances of side effects that occur in addition to the desired anticancer effect.

Date of event: Provide the actual or best estimate of the date the side effect first started. If day is unknown, month and year are acceptable. If day and month are unknown, year is acceptable.

1.4 Other Medicines: Enter all other medicines (herbal, over the counter medicines) that were being used at the time of event but that there is no suspicion of involvement in the event. Be as complete as possible.

1.5 How serious do you consider each Adverse Drug Reaction?: The seriousness of each Adverse Drug Reaction should be marked in the appropriate box within the table. The following outcomes: fatal, life-threatening, hospitalisation, disability, birth defect and medically significant conditions are considered to be serious adverse drug reactions.
Fatal – only mark this box if it is suspected that death was an outcome of the reaction to the medication.
Life-threatening – only mark this box if it is suspected that the patient was at substantial risk of dying as a result of the ADR.
Hospitalisation - initial/prolonged – only mark this box if there is a suspicion that admission to hospital or prolongation of hospitalisation was a result of the ADR by the medicine.
Disability or Incapacity – only mark this box if the adverse reaction resulted in a disruption of a person's ability to conduct normal life functions.
Birth defect – mark this box if you suspect that exposure to a medicine before conception or during pregnancy may have resulted in an adverse outcome in the child.
Medically significant condition – mark this box when the ADR was a hazard to the patient and may require medical or surgical intervention to prevent further outcomes.
Non serious - mark this box if the consequences of the ADRs were non-serious (ie none of the above).

1.6 Outcome for each Adverse Drug Reaction: The outcome for each Adverse Drug Reaction reported, should be marked in the related ADR box within the table (eg Adverse Drug Reaction 1 was headache and the outcome was recovered; the Adverse Drug Reaction 2 was rash and the outcome was 3 symptoms continuing).

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For the Adverse Drug Reaction: Fill in whether the Suspect medicine(s) indicated in field 1.2 were stopped. *Was medicine restarted*: indicate whether the patient was rechallenged. *Was the manufacturer notified*: Please check the appropriate box depending on whether the Marketing Authorisation Holder, the company that holds a license for the medicine – this information can be found on the box and the patient information leaflet) has been notified. *Treatment required*: indicate whether the adverse drug reaction needed to be treated and if yes, please describe.
Is this an initial report: Please check the appropriate box depending on whether this is the first report of this Adverse Drug Reaction, or whether this report includes additional/follow up information to a previously submitted report.

1.8 Additional relevant information: Provide all appropriate information including medical history, negative test results, differential diagnosis, synopsis of any relevant pathology or further information on the course of events. *If pregnant*: in the case of a pregnancy please specify the number of weeks into the pregnancy at the time the ADR occurred.

1.9 Was this adverse drug reaction caused by a medication error or other causative event: Please tick applicable response and follow instructions within the form to report a complete incident report to the Medicines Authority.

Section 2: Medication error reporting

A medication error may cause harm (an actual Adverse Drug Reaction) or may have the potential to cause a Adverse Drug Reaction. The Medicines Authority would like to hear about any type of medication error related to medicines, since it can be a source of knowledge on how medicinal products' usage can be changed to minimise risk.

2.1 Medicines involved in medication error or other causative event (eg occupational exposure): Please provide the trade name as marketed. If this is unknown, use the active substance name with the manufacturers name if known. If the error involves look-alike or sound-alike medicine packaging, include detail on both products.

2.2 Date of event: Please indicate to the best of your ability, when the medication error occurred and the date when it was discovered.

2.3 Describe the medication error or other causative event related to the medicine: Described the medication error and the events that were related to it, in as much detail as possible, including a description of what happened, how the error was discovered, and who was involved (in a general way without identifying people).

2.4 Location where the event occurred: please describe the place where the event (medication error or other cause event) occurred like for example at home or at a pharmacy etc.

2.5 Suspected cause of medication error or other causative event related to the medicine: Describe the suspected cause(s) in as much detail as possible. Some examples of suspected causes are sound-alike and look-alike medication or packaging, or instructions on dispensing bottles or package etc.

2.6 Any factors contributing to the medication error or other causative event related to the medicine: Describe the suspected contributing factor(s) in as much detail as possible (eg. whether there was any omission of meals, concomitant alcohol intake, over exposure to heat and sun etc.)

2.7 Was the medication error or other causative event preventable?: Tick the yes or no box in order to give your view on whether the medication error could have been prevented.

2.8 Was any remedial action related to the medicine taken?: Tick the yes or no box according to whether any action was taken to prevent the same error from occurring again. If action was taken please describe what this action was.

2.9 Recommendations to prevent repeat incident: If no action was taken, you can give your opinion on what remedial action could have been taken. If action was already taken and you would like to add to this, please insert your opinion in this box.

2.10 Did the medication error or other causative event result in a Adverse Drug Reaction?: If the medication error resulted in a Adverse Drug Reaction, section 1 on Adverse Drug Reactions should be filled in. If the medication error did not lead to an Adverse Drug Reaction, please fill in section 3 on reporter details.

Section 3.0 Reporter details,

Please provide the name, electronic address and/or mailing address and telephone number. Indicate whether you are a healthcare professional, or consumer/patient by circling the appropriate listing. All reporter information will be destroyed once the ADR is reported to Eudravigilance (a central EU database used by EU regulators to identify risks associated with medicines).

Submit electronically to the Medicines Authority pacificenq.medicinesauthority@gov.mt

AWTORITÀ DWAR IL-MEDIĊINI