

**Frequently Asked Questions (FAQs) by Pharmaceutical Companies regarding
Pharmacovigilance Obligations & Adverse Drug Reaction (ADR)
Reporting Requirements**

Reporting of ADRs

Q1. What is an Adverse Drug Reaction (ADR)?

- A. An ADR is a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Q2. What is a serious ADR?

- A. A serious ADR is any untoward medical occurrence that:
- results in death
 - is life-threatening
 - requires inpatient hospitalisation or prolongation of existing hospitalisation
 - results in persistent or significant disability/incapacity
 - is a congenital anomaly/birth defect

Q3. What is an unexpected ADR?

- A. An unexpected ADR is one whose nature, severity or outcome is not consistent with domestic labelling or marketing authorization, or expected from the pharmacological/toxicological characteristics of the drug.

An increased frequency of expected ADRs should also be considered as unexpected for the purposes of expedited reporting.

Q4. Is ADR reporting mandatory for pharmaceutical companies?

A. Yes, in keeping with national and EU legislation i.e.:

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)

pharmaceutical companies are legally obliged to report suspected ADRs brought to their attention to the Medicines Authority, as outlined below in Q5.

Q5. What are the Medicines Authority's ADR reporting requirements?

A. Pharmaceutical companies should submit the following ADR reports for all medicinal products for human use available in Malta, to the Medicines Authority:

- all suspected serious ADRs (expected and unexpected) occurring in Malta;
- 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.

Q6. What are the Medicines Authority's ADR reporting formats and systems?

A. 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 which can be downloaded from the following website: <http://www.cioms.ch/cioms.pdf>

ADR reports submitted in paper format 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 the testing of such electronic report submission can be obtained from the following website:

<http://eudravigilance.emea.europa.eu/human/>

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 EMEA for the transmission of confidential scientific data. Pharmaceutical companies can apply for a EudraLink account by contacting the EudraLink helpdesk at the EMEA on telephone number +44 (0) 207 523 7523 or on the following email address: eudralink@ema.europa.eu

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

Q7. Should ADRs associated with use of unlicensed medicinal products i.e. products with a “specials” manufacturing license and those used on a “named patient basis” be reported?

A. Yes, ADR reports associated with the use of unlicensed medicinal products should also be reported on an expedited basis if they meet the criteria outlined in response to Q9.

Q8. Should ADRs associated with off-label use of medicinal products be reported?

A. Yes, ADR reports associated with off-label use of medicinal products should also be reported on an expedited basis if they meet the criteria outlined in response to Q9.

Q9. What are the minimum criteria for a valid ADR report?

A. 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.

Q10. Is there a requirement for pharmaceutical companies to report ADRs for products that are not currently available in Malta?

A. No, pharmaceutical companies are **not** required to report ADRs for products that are not currently available in Malta.

Q11. Will the Medicines Authority acknowledge receipt of all the ADR reports it receives?

A. The Medicines Authority will acknowledge receipt of reports of ADRs originating in Malta and will provide a local case reference number which should be quoted in all subsequent correspondence regarding the ADR reported.

The Medicines Authority will **not** acknowledge receipt of reports of ADRs occurring outside Malta.

Use of MedDRA

Q12. Is it necessary to use MedDRA when reporting ADRs?

A. 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

Submission of Periodic Safety Update Reports (PSURs)

Q13. What is a Periodic Safety Update Report (PSUR)?

- A. A PSUR is a periodical report containing the records referred to in Article 6 (3) of Pharmacovigilance Regulations, 2006 (L.N. 61 of 2006).

Q14. When is a PSUR required?

- A. Unless the marketing authorisation makes different provisions¹, PSURs are required at the following intervals:

- 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

¹ For detailed guidance on reporting requirements and circumstances where the PSUR cycle may be amended, please refer to Volume 9A of the Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance for Medicinal Products for Human Use), available at the following website:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm

Q15. Does the Medicines Authority require submission of PSURs for medicinal products before they are given a full Marketing Authorisation?

- A. No, the Medicines Authority does **not** require submission of PSURs for medicinal products before they are given a full Marketing Authorisation.

Q16. Will it be necessary for MAHs to start a new six-monthly reporting cycle for products following the granting of a full Marketing Authorisation by the Medicines Authority?

A. For those products that were initially granted a provisional Marketing Authorisation (PMA) prior to a full Marketing Authorisation, PSURs can 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 following the granting of a full Marketing Authorisation by the Medicines Authority.

Q17. To whom should PSURs be addressed at the Medicines Authority?

A. PSURs should be addressed to the Pharmacovigilance Section within the Post-Licensing Directorate using the same contact details given in response to Q6.

Q18. In what format should PSURs be submitted to the Medicines Authority?

A:

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 mutual recognition, decentralised and centralised 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 mutual recognition, decentralised and centralised 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).

Responsible Person for Pharmacovigilance

Q19. Can the responsible person for pharmacovigilance reside outside the European Community?

- A. No. In accordance with Article 5 (2) of Pharmacovigilance Regulations, 2006 (L.N. 61 of 2006) it is a legal obligation for the responsible person for pharmacovigilance to reside within the European Community.

Q20. In addition to the Europe-wide responsible person for pharmacovigilance, is it a legal requirement to have a designated individual responsible for pharmacovigilance in Malta?

- A. No. Companies are **not** legally obliged to have a designated individual responsible for pharmacovigilance in Malta.

Q21. Does the Medicines Authority require notification of the responsible person for pharmacovigilance?

- A. Yes. Pharmaceutical companies should notify the Medicines Authority of the name and contact details of the responsible person for pharmacovigilance in Section 2.4.4 of the 'Application for a Marketing Authorisation for Medicinal Products for Human Use' which can be downloaded from the following website:
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm

It is essential that any changes in the designation of this responsibility are notified immediately to the Pharmacovigilance Section within the Post-Licensing Directorate at the Medicines Authority (address as given under Q6).

Further Information

Q22. Where can I find further information/guidance?

- A. Further information is available in the Medicines Authority's "Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations & Adverse Drug Reaction (ADR) Reporting Requirements for Medicinal Products for Human Use". Any further queries related to the pharmacovigilance obligations of MAHs should be addressed to the Pharmacovigilance Section within the Post-Licensing Directorate (refer to Q6 for contact details).

Clinical Trials and ADR reporting

Q23. Does the Medicines Authority require reporting of SUSARs (Suspected Unexpected Serious Adverse Reactions) arising from clinical trials conducted in Malta?

- A. Yes, the Medicines Authority does require reporting of SUSARs arising from clinical trials conducted in Malta.

Q24. Does the Medicines Authority require reporting of SUSARs arising from clinical trials conducted outside of Malta?

- A. No, the Medicines Authority does **not** require reporting of SUSARs arising from clinical trials conducted outside of Malta **unless** these arise from multi-centre clinical trials which concern medicinal products being co-investigated in Malta.

Q25. Does the Medicines Authority require reporting of SUSARs arising from foreign clinical trials which involve products authorised in Malta?

- A. No, the Medicines Authority does **not** require reporting of SUSARs arising from foreign clinical trials which involve products authorised in Malta.

Q26. What are the Medicines Authority's SUSAR reporting requirements?

A. SUSARs which are fatal or life-threatening should be reported by the sponsor 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 not later than seven days after knowledge by the sponsor of such a case. Relevant follow-up information should be subsequently communicated within an additional eight days.

All other SUSARs should be reported to the Medicines Authority, and 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 days of first knowledge by the sponsor.

An annual listing of all suspected serious adverse reactions together with a report on the safety of the subjects participating in the clinical trial should be provided to the Medicines Authority, the Health Ethics Committee and the other competent regulatory authorities in whose territory the clinical trial is being conducted.

Q27. What are the Medicines Authority's reporting formats and systems for SUSARS arising from clinical trials?

A. 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 relevant cover letter should be addressed to the Pharmacovigilance Section within the Post-Licensing Directorate using the same contact details given in response to Q6.

(ii) Electronic format

SUSARs may be submitted electronically via EudraVigilance in E2B(M) format. Information regarding the testing of such electronic report submission can be obtained from the following 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.

Effective Date

Q28. When do these requirements come to effect?

A. These requirements are effective from July 2008.