

A Review of the National Adverse Drug Reaction (ADR) & Medication Errors Reporting System of Malta

John-Joseph Borg, Anthony Serracino Inglott, Dania Al-Haddad

Abstract

The overall objectives of Pharmacovigilance include early identification of potential safety hazards, evaluation, monitoring and where appropriate, implementation of regulatory action to maximise benefits and minimise risks associated with medicinal products. Reporting of an ADR associated with use of a medicinal product as well as medication errors is an essential source of necessary information that is required to achieve these objectives. Safety concerns that arise from spontaneous reporting contribute to assessment of the risk benefit balance and hence lead to a regulatory action which could be suspension or revocation of marketing authorization of the product or change in the product information. Furthermore, these safety concerns can be communicated to healthcare professionals through Direct Healthcare Professional Communications (DHPCs) and safety circulars and they form the basis of designing Risk Minimisation Measures (RMMs).

The establishment of a functional ADR reporting system by law since 2004, not only facilitates participation in the national and EU regulatory process, but also enables Malta to participate in the WHO Programme for International Drug Monitoring, both by contributing to and obtaining data from this extensive information resource.

Mesh Terms

Adverse Drug Reaction, Pharmacovigilance, Safety, Risk assessment

Introduction

All medicinal products in the EU including Malta are subject to strict testing and assessment of their quality, efficacy and safety before being authorised. Once placed on the market they continue to be monitored to assure that any aspect which could impact the safety efficacy profile of a medicine is detected and assessed and regulatory measures are taken as necessary. This continuous monitoring of the safety profile of a medicinal product is a core objective of Pharmacovigilance system. The ADR reporting system is an integral part of the Malta Medicines Authority's (MMA) Pharmacovigilance system through which post marketing data about medications are collected and processed to aid in the surveillance and regulation of medicinal products. The Aim of this review is to disseminate the science of pharmacovigilance amongst Maltese doctors and to encourage reporting.

The definition of ADR in the EU

Directive 2001/83/EC, defines an ADR as: A response to a medicinal product which is noxious and unintended, adverse drug reaction may arise from the use of the product within or outside the terms of the marketing authorisation or from the occupational exposure, conditions of use outside the

John-Joseph Borg BPharm (Hons), MSc (Agric Vet Pharm), PhD*

Post-Licensing Directorate Medicines Authority,
San Gwann, Malta.

Course of Pharmacy,
Department of Biology,
University of Tor Vergata,
Rome, Italy
john-joseph.borg@gov.mt

Anthony Serracino Inglott PharmD,
Pharmacy Department,
University of Malta
Msida, Malta

Dania Al-Haddad B.S.c. Pharm.,
Post-Licensing Directorate Medicines Authority,
San Gwann, Malta

*Corresponding author

marketing authorisation include off-label use, overdose, misuse, abuse and medication errors. There are multiple synonyms for an ADR: suspected adverse (drug) reaction, adverse effect, and undesirable effect.¹

A serious adverse reaction is an adverse reaction which either

- Results in death
- or is life threatening
- or requires in-patient hospitalisation
- or prolongation of existing hospitalisation
- or results in persistent or significant disability or incapacity or a congenital anomaly/birth defect.¹

The ADR reporting system established in Malta is consistent with European and Maltese legislation for the regulation of medicinal products which directs competent authorities in member states to *establish a Pharmacovigilance system where this system shall be used to collect information useful for the surveillance of medicinal products, with particular reference to adverse reactions in human beings and to evaluate such information scientifically.*²⁻³

In November 2003 the Maltese Medicines Act was published which established the regulatory framework for the MMA and lead further to the development of Pharmacovigilance subsidiary regulations.³ As part of the EU network, the MMA actively participates in the EU fora (as Rapporteur) to carry out the necessary regulatory actions mandated by law to *suspend or revoke an authorization to place a medicinal product on the market where that product proves to be harmful in the normal conditions of use, or where therapeutic efficacy is lacking, or where qualitative and quantitative composition is not declared.*²

The Role of Health Care Professionals

In all countries where Pharmacovigilance systems operate, the role of healthcare professionals is essential in recording and reporting suspected ADRs they observe in their practice in order to alert regulatory agencies to new or emerging safety concerns which facilitates timely and appropriate regulatory action to be taken. The Maltese legislation on Pharmacovigilance specifies that: *It shall be the duty of doctors and other healthcare professionals to report to the Authority any suspected serious or unexpected adverse reaction to a medicinal product.*³ National competent

authorities are also obliged to *'take all appropriate measures to encourage doctors and other healthcare professionals to report suspected adverse reactions to the competent authorities.'*² To achieve this goal the MMA has adopted a 3 year (2016-2018) strategy plan to promote ADR reporting from healthcare professionals which involves the organisation of educational seminars and promotional materials to increase awareness of ADR reporting nationally.

How to Report

For the purposes of reporting, an ADR reporting form has been developed and validated. In 2015, a unified form was designed which combines reporting of ADRs and medication errors whether they were associated with an ADR or not. Submission of a report does not mean an admission of guilt, the information contained in reports are entered in the MMA's database in a secure manner and details of the reporter are destroyed following transmission to the European database (Eudravigilance).⁴ ADR report forms can be downloaded from MMA's website: www.medicinesauthority.gov.mt/adportal.

The minimum criteria for a valid ADR report is: an identifiable reporter (e.g. doctor, pharmacist, dentist), identifiable patient (initials or age or date of birth or sex); a suspected medicinal product and a suspected ADR. However, a report should provide as much information as possible in order to facilitate evaluation e.g. for biological medicinal products ADRs should be reported by brand names and batch number ensuring the traceability. During the process MMA might request further information regarding individual ADR reports as appropriate.

How to fill ADR form:

The ADR form is composed of three sections where each section has to be filled by the reporter. Section 1 is to be filled when reporting an ADR; section 2 to be filled only when reporting a medication error while section 3 is for the reporter's details that are requested for contacting the healthcare provider for further follow up. If a medication error resulted in an ADR then both sections 2 and 3 have to be filled in by the reporter. A detailed guidance and instructions on how to fill in each section can be found at the end of the report.

Submitting a report in a timely manner along with the best possible quality of data within the

report is essential for efficient causality assessment. The higher the accuracy of the provided data the more the results of an assessment will be valid. Therefore, including the start and stop dates of an ADR and the drug treatment in terms of dd/mm/yy is more granular than in terms of mm/yy. Furthermore, availability of relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, will facilitate decisions on the causal relation between an ADR and the suspected medications, e.g. a laboratory test measuring biochemical or an immunologic marker might be helpful to explain the suspected adverse drug effect.⁵

What and When to report

Healthcare professionals are encouraged to report all suspected ADRs to MMA. It is not necessary to be certain of the casual relationship between an ADR and a medicinal product to report, but by keeping vigilance for signs and symptoms that may enhance or exclude the possibility of a medicine-induced reaction as well as following up the patient enables the reporter to provide the necessary information for regulators and marketing authorisation holder (MAH) to interpret the case, evaluate the safety issues at hand and act accordingly if required.⁶

All suspected ADRs to all drugs and vaccines must be reported. Although it is highly significant to identify previously unrecognised side effects, it is also important to emphasise the fact that well-known ADRs (particularly serious or severe) of established medicines (e.g. gastrointestinal bleeding with non-steroidal medicinal products) are highly important to report as well.

Additionally, reporting can be made where there is lack of efficacy or when suspected pharmaceutical defects are observed. This aids in improving the quality of batch released medicinal products.

Management of reports

Once a report is received by the MMA, the ADR case is validated and the information is evaluated using a causality assessment method (French imputability method) and against the product's Summary of Product Characteristics (SmPC) to identify the expectedness or not of the ADR. Feedback is sent to the reporter by email or

post and if necessary a request for follow up information is made. Reports are then inputted into Eudravigilance database and reporters' details are destroyed from the local paper-based form (to protect confidentiality of the reporter). Staff of the Authority will review safety issues arising from these received reports internally and with national experts/professional associations.

The MMA also requests modifications to be implemented to medicinal product information following safety signal detection activities by the EMA and the opinions adopted by its Committees.

How voluntary reporting of ADRs can affect the marketing authorization and labelling of medicinal products:

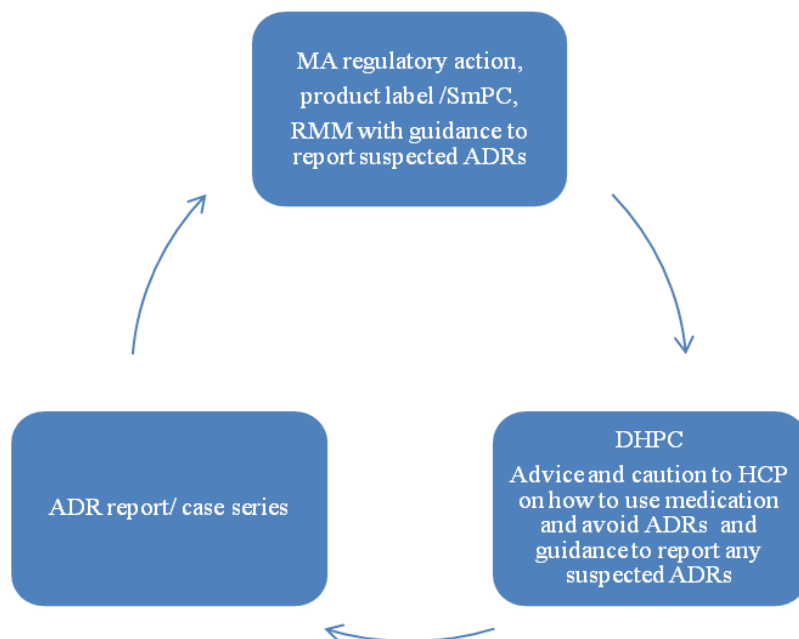
Spontaneous reporting is a system whereby case reports of adverse events are voluntarily submitted by healthcare professionals to the national Pharmacovigilance centre.⁷ Once a signal is successfully detected and confirmed from spontaneous reporting; cumulative reviews are carried out by the regulatory authorities to propose any regulatory action deemed necessary (Figure 1).

Regulatory actions can be a change in the product information like in the case of Celecoxib (Celebrex[®]); where reported cases of severe serious skin reactions and hypersensitivity reactions lead to adding a general statement in section 4.4 of the SmPC regarding these ADRs and a warning to discontinue Celecoxib at the first sign of hypersensitivity reaction.⁸ Or in other cases withdrawal from the market like suspension of Valdecoxib (Bextra[®]) -due to increased reporting of severe and unpredictable cutaneous adverse reactions- and the withdrawal of Fusafungin (Locabital[®]) in April, 2016 following reports of hypersensitivity reactions associated with its use.⁹⁻¹⁰

Risk minimisation measures (RMM) and ADRs

RMMs are a set of activities designed to guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.¹¹ RMMs are often based on specific issues identified from the pre- or post-authorisation data and from pharmacological principles.¹²

Figure 1: How ADR reports influence product labeling and SmPC, RMMs, regulatory action of Medicines Authority and trigger circulation of DHPC



Since 2009, the MMA has reviewed 505 RMMs.¹³ The approved RMMs can be found from the MMA's website: www.medicinesauthority.gov.mt/safetyinf.¹⁴

RMMs may consist of routine risk minimisation or additional risk minimisation activities. Routine RMMs are those which apply to every medicinal product and they are:¹²

- Summary of product characteristics.¹⁵
- Package leaflet.¹⁶
- Product labelling.¹⁶
- Pack size.¹²
- Legal status: controlling the conditions under which a medicinal product is prescribed or the conditions under which it is administered. For example certain medications are available only by a special medical prescriptions e.g. medicines covered by the Dangerous Drugs Ordinance CAP 101.¹⁷⁻¹⁸

For some risks a routine approach is not sufficient and “additional measures” are warranted to improve the risk-benefit balance in the approved indications, these

measures come in several forms:

- Educational materials for healthcare professionals and patients such as brochures, checklists and patient alert cards.
- Controlled access programmes: these restrict how the medicines can be prescribed or dispensed, they can be used only when prescribed by a healthcare professional with

specific expertise and patient has acknowledged that he is informed of a specific risk before receiving a medicine e.g. Thalidomide Celgene.¹⁹

- Pregnancy prevention programme: These measures aim to ensure that women are not pregnant during treatment with medicinal products that are likely to cause harm to unborn child e.g. Thalidomide Celgene Pregnancy Prevention Programme.²⁰
- DHPC: These are letters sent directly to healthcare professionals who are likely to use the medicine, to warn them of a new safety concern and to inform them of the actions to mitigate the risk. This safety information may arise from studies, clinical trials or from spontaneous ADR reporting as well. Consequently, ADR reporting is valuable in contributing to the formulation of these advices. Furthermore, DHPCs increase awareness of healthcare professionals about their role and responsibility in reporting, as the final section of a DHPC is a reminder for healthcare professionals to report and how to report. A link to the ADR form is provided along with the contact details of the MMA and MAH to send the completed form. All archived DHPCs can be accessed from MMA's website: www.medicinesauthority.gov.mt/dhpc. To date the MMA approved 201 DHPCs (Table 2).

Table 1: number of ADR reports received in the years (2010- Nov 2017)^{13,21}

Year	2010	2011	2012	2013	2014	2015	2016	Up to Nov 2017
Number of ICSR	194	150	153	150	169	122	118	228
Number of reported ADRs	403	273	300	349	741	615	613	416
% of Non-Serious ICSR	12.08%	10.7%	7.8%	7.33%	12.42%	4.88%	24.58%	27.89%
% of Serious ICSR	87.92%	89.3%	92.2%	92.66%	87.57%	95.12%	75.42%	72.11%
Most frequent system organ class	General disorders and administration site conditions	General disorders and administration site conditions	Gastrointestinal disorders	General disorders and administration site conditions	Infections and infestations	General disorders and administration site conditions	General disorders and administration site conditions	
Most frequent age criteria	18-64	18-64	12-64	20-64	20-64	20-64	18-64	18-64

When there is a potential safety concern relating to the safe and effective use of a medicinal product including warnings or alerts or product recalls, the MMA will issue a letter called safety circular to inform healthcare professionals. These safety circulars are available on MMA's website: www.medicinesauthority.gov.mt/safetycirculars.

The MMA operates a notification system where healthcare professionals can subscribe and be notified by SMS and e-mail regarding safety concern.²²

Shared responsibility

It is the responsibility of the MAH to record all the suspected ADRs reported by healthcare professionals or patients and to submit them to "Eudravigilance" database. For these reports

Where the suspected ADRs occurred in Malta, the MMA may involve the MAH in the follow-up of the reports. Together the MAH and the MMA should collaborate to detect any duplicates of

suspected ADR reports.

Conclusion

Since 2010 to date, MMA Pharmacovigilance system has received and processed 1284 of suspected ICRS reports. Through reporting, healthcare professionals make a positive contribution to the overall knowledge of the safety profile of medicines and to the national Pharmacovigilance system. All healthcare professionals are therefore encouraged to start reporting or continue to report to enhance and develop this process. MMA greatly appreciates the interest shown by healthcare professionals towards ADR reporting and acknowledges the contribution of busy healthcare professionals to the continued surveillance of the safety of medicines by contributing to the ADR reporting system.

Table 2: (Number of approved joint/DHPCs, RMMs in the period 2007- Dec 2017)²¹⁻²²

Publication Year	DHPC	RMM	Safety Circulars
Dec 2017	18	103	6
2016	19	107	17
2015	11	88	15
2014	20	91	20
2013	40	94	28
2012	31	38	15
2011	26	22	19
2010	14	11	16
2009	8	21	12
2008	16	/	10
2007	11	/	19
2006	/	/	11
2005	/	/	15
2004	/	/	4
Total	201	505	205

References

- European Medicines Agency and Heads of Medicines Agency. Guideline on good Pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3). EMA/876333/2011[Internet]. London (UK): European Medicines Agency; 2011[Cited 2016 Aug 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf
- The European Parliament and the Council of the European. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ. 2012; L299: 1-3.
- Laws of Malta. SL 458.35 Pharmacovigilance Regulations, 2012. Government Gazette of Malta 2012; 18985:12399.
- Tanti A, Serracino-Ingloft A, Borg JJ. Designing a national combined reporting form for adverse drug reactions and medication errors. East Mediterr Health J. 2015 Jan 1; 21(4):246-55.
- Reidel MA, Casillas AM. Adverse drug reactions: Types and Treatment options. Am Fam Physician .2003 Nov 1; 68(9): 1781-1791.
- Couper M. Safety of medicines- a guide to detecting and reporting adverse drug reaction- Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2016 Sep 4]. Available from: <http://apps.who.int/medicinedocs/en/d/Jh2992e/>
- Brunner M. Pharmaceutical drug safety. In: Muller M, editor. Clinical pharmacology: Current topics and case studies .Vienna: Springer-Verlag Wien; 2010 .P. 268-274.
- The European Agency for Evaluation of Medicinal Products. Committee for proprietary medicinal products (CPMP). Celecoxib -Article 31 referral –Annex I, II, III. EMEA/CPMP/1747/04A. [Internet]. London (UK) .European Medicines Agency; 2004. [cited 2016 Sep 11] Available from : http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Celecoxib/human_referral_000145.jsp

9. The European Agency for Evaluation of Medicinal Products. Post-authorisation Evaluation of Medicines for Human Use. EMEA public statement on the suspension of the marketing authorisation for Bextra (Valdecoxib) in the European Union. EMEA/358234/2005. [Internet]. London (UK): European Medicines Agency; 2005. [cited 2016 Sep 15] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018391.pdf
10. Les Laboratoires Servier. Direct Healthcare Professionals Communications. Fusafungine containing medicinal products will no longer be available on the market [Internet]. Nanterre (France): Les Laboratoires Servier; 2016 [cited 2016 Sep 16] Available from: <http://www.medicinesauthority.gov.mt/dhpc>
11. European Medicines Agency and Heads of Medicines Agencies. Guideline on good Pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators. EMA/204715/2012 Rev 1 [Internet]. London (UK): European Medicines Agency; 2014 [cited 2016 Sep 20] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf
12. European Medicines Agency and Heads of Medicines Agencies. Guideline on good Pharmacovigilance practices (GVP) Module V – Risk management systems. EMA/838713/2011 Rev 2 [Internet]. London (UK): European Medicines Agency; 2014 [cited 2016 Sep 20] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf
13. Malta Medicines Authority. Annual Reports (2004-2015). [Internet] Gzira: Malta Medicines Authority; 2016. [Cited 2016 Oct 5]. Available from: <http://www.medicinesauthority.gov.mt/annual-reports>.
14. Malta Medicines Authority. Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations for Medicinal Products for Human Use 2015. Gzira (Malta); Malta Medicines Authority; 2015. Available from: <http://www.medicinesauthority.gov.mt/safety?l=1>
15. European Commission. Enterprise and industry directorate-general consumer good pharmaceuticals. A guideline on SmPC (Summary of product characteristics), September 2009 [Internet]. Brussel: European Commission; 2008 [cited 2016 Oct 7]. Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/smcp_guideline_rev2_en.pdf
16. European Commission. Enterprise and industry directorate general consumer good pharmaceuticals. Guideline on the readability of the labelling and package leaflet of medicinal products for human use, 2009. ENTR/F/2/SF/jr (2009) D/869 [Internet]. Brussel: European Commission; 2009. [cited 2016 October 11] Available from: http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf
17. Government of Malta. Medicines Act Subsidiary legislation 31.18 Drugs (Control) regulations: Legal notice 22 of 1985 Drug (control) regulations. Government Gazette of Malta 1985.
18. Government of Malta. Medicines Act Subsidiary legislation 31.18 Drugs (Control) regulations: Legal notice 34 of 1989 Drug (control) (amendments) regulations. Government Gazette of Malta 1989.
19. European Medicines Agency. Thalidomide Celgene-Annex I summary of product characteristics, Annex II.D Conditions and restrictions with regards to the safe and effective use of the medicinal product. EMEA/H/C/000712-PSUSA/2919/201510-3427. [Internet]. European Medicines Agency ; 2009 [cited 2016 Oct 12] Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000823/WC500037050.pdf
20. Celgene Corporation: Risk Minimisation Measures. Thalidomide Celgene Pregnancy Prevention Programme; RMM L04AC02_EU108443001_21052015. [Internet]. Gzira (Malta): Malta Medicines Authority; 2014. [Cited 2016 Oct 12]. Available from : <http://www.medicinesauthority.gov.mt/rmm>
21. Tanti A, Benjamin M, Serracino-Inglott A, Borg JJ. A review of the national Pharmacovigilance system in Malta-implementing and operating a Pharmacovigilance. Expert opin Drug saf. 2016 Oct 10; 16(1): 65-76.
22. Malta Medicines Authority [internet]. San Gwann: Malta Medicines Authority; c2017 [cited 2017 Apr 3]. Safetyinformation. Available from: <http://www.medicinesauthority.gov.mt/safetyinfo>.