

Towards the use of safer medicines: why is it important to support the national pharmacovigilance system?

Post-Licensing Directorate

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Educational aims

- To enhance the reader's knowledge on the legal obligations for the reporting of ADRs in Malta
- To have a more thorough understanding of how the Medicines Authority handles ADRs and reports them across the EU pharmacovigilance network.
- To recognise the value of reporting ADRs in the identification of post-authorisation safety signals through established data analysis programmes and analysis techniques
- To be able to appreciate how aggregated pharmacovigilance information is the rationale behind regulatory action on a medicines' marketing authorisation.
- To be informed of the recently published EU directive 2010/84/EC on the community code relating to medicinal products for human use, focusing on the changes that are of interest to healthcare professionals, which are expected to occur with the implementation of this new directive in 2012.

Key words

Pharmacovigilance, Adverse Drug Reactions, Regulatory affairs

All medicinal products carry an inevitable and unpredictable potential for harm that cannot always be detected at the pre-authorisation stage. Pharmacovigilance comprises the science and activities relating to the assessment, understanding and prevention of adverse effects of medicines. The main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions. With the new directive 2010/84/EC (amending 2001/83/EC) on the community code for medicinal products in the EU it is important that healthcare professionals are refreshed on the need to support pharmacovigilance systems in order to maximise efforts to maintain the safest and most effective medicines on the market.

Introduction

Advances in the process of approval of medicines in Malta and the rest of Europe over the last decade have meant that medicines are approved simultaneously in many countries. In light of the increasing range and potency of medicines, all of which carry an inevitable and sometimes unpredictable potential for harm, supporting the national pharmacovigilance system today is now more important than ever. Pharmacovigilance comprises the science and activities relating to the assessment, understanding and prevention of adverse effects of medicines.¹

The ultimate goal of pharmacovigilance is to contribute to a safer use of medicines. Through this activity:

- Public health is safeguarded, fostering a sense of trust among patients in the medicines they use that extends to confidence in the health service in general.
- Healthcare professionals have evidence-based knowledge on which to base their practise, and so ensuring that risks from medicines use are anticipated and managed.
- Regulators have a solid basis on which regulatory action can be taken.

Mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital.² In practise this means having in place a well-organised pharmacovigilance system³. Pharmacovigilance is an umbrella term used to describe processes for monitoring the safety of medicines. However the main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions (ADRs).

The Legal basis for Adverse Drug Reaction Reporting in Malta

The Medicines Act of 2003⁴ and subsequent subsidiary legislation, provide the regulatory framework for the Medicines Authority's operations. The Medicines Act as laid out in 2003, required the establishment of a national system for the reporting of ADRs occurring in Malta. In 2006, subsidiary legislation to the Medicines Act, S.L. 458.35 was published under the title "Pharmacovigilance Regulations" stipulating that it is the duty of doctors and other healthcare professionals to immediately report any serious or unexpected adverse reaction to a medicinal product in Malta.⁵ Unexpected ADRs are those ADRs that are

not mentioned in sections 4.4 - 4.9 of the Summary of Product Characteristics (SmPCs). SmPCs and Patient Information Leaflets (PILs) are available online on the medicines authority websites (www.medicinesauthority.gov.mt and www.maltamedicineslist.com).

In December 2010 a new directive by the European Parliament and the Council of the European Union relating to pharmacovigilance was published in the Official Journal of the European Union. This directive (Directive 2010/84/EC) amends directive 2001/83/EC on the community code relating to medicinal products for human use and is applicable to all member states in July 2012.⁶ The introduced legislation will induce changes in the European Union in terms of evaluation of risk associated with medicinal products as well as the framework on how the Union takes harmonised regulatory action on drug safety. The following points are especially relevant to practising healthcare professionals, the pharmaceutical industry and also to patients. The new legislation will bring into force⁷:

- Widening of the legal definition of adverse events to capture medication errors
- Enabling direct patient reporting of suspected Adverse Drug Reactions;
- The inclusion of patients and health-care professionals in the decision-making process.
- The creation of a new European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) based at the European Medicines Agency (EMA) whose work will focus solely on the assessment and communication of safety issues with medicines. The PRAAC will replace the Pharmacovigilance working party and has the added capability of issuing public hearings which would enhance transparency in decision making. The role of the new committee at the EMA will be to carryout:
 - Evaluation of pharmacovigilance data submitted during all pre- and post-authorisation activities at the EMA and issuing of recommendations
 - Periodic Safety Update Reports (PSURs); evaluation and approval
 - Adverse Drug Reactions signal detection from the EU database of Adverse Drug Reactions, (the Eudravigilance data warehouse) and assessment of identified signals
 - Risk management plans (RMPs) assessment and approval

- Imposition of temporary measures (through the European Commission) to be implemented by Member States to protect patients if the PRAAC considers that a product may not be safe anymore or that a product will not provide any significant therapeutic benefit;
- Assessment of Post-Authorisation Safety Studies (PASS) protocols to be carried out within the Member States as required.
- Further harmonisation with respect to the creation and maintenance of a single frequency date for the submission of Periodic Safety Update Reports (PSURs) by Marketing Authorisation Holders
- Establishing and making public a list of medicinal products for human use under additional monitoring

Medication Errors and Adverse Drug Reactions

As mentioned previously, the definition of the term 'adverse drug reaction' will now be extended to cover not only noxious and unintended effects resulting from the authorised use of a medicinal product at normal doses, but also those arising from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product. For the purpose of pharmacovigilance, any medication errors that result in an adverse drug reaction must be reported.

Reporting an Adverse Drug Reaction

The first step in ADR reporting is when a healthcare professional either sends a yellow card (in paper format or electronically) to the Medicines Authority, or directly reports the ADR to the marketing authorisation holder or their local representative. The national ADR form is available at <http://www.medicinesauthority.gov.mt/pub/adr.doc>.

The national ADR form consists of four sections detailing the patient, the adverse reaction, the suspect drug and the reporter. The more information provided, and the more detailed the report the better one can analyse the ADR within a realistic context. Patient details consist of identifiers such as initials, age, gender, weight and height as well as medical history. Information on the medicinal product must be given, ideally both generic and trade names are given, (even for generic medicines, a brand in the form of company name must be given)

as well as dates (even approximate) for starting and stopping the therapy as well as indications for use. The batch number of the product is also very useful information, especially in relation to quality short-falls.

A good description of the adverse drug reaction that is suspected to be related to the medication should follow; describing affected area(s), the severity of the event, the outcome, course of events, and time relationship between therapy and ADR. Information on challenge, dechallenge and rechallenge is also important together with laboratory data if any. Challenging in medicine is when a therapeutic agent is administered in order to observe its outcome. Conversely, dechallenge is when the outcome is observed upon stopping the medicine, and rechallenge is when therapy is restarted after an initial challenge.

The last section details the reporter. This is primarily there to enable reporter and assessor to be in contact in case of the need to follow up a case. It also serves as a means of discouraging fraudulent reporting by individuals. The contact information provided will also be used to send an acknowledgment that the Medicines Authority has received an ADR report.

What happens to reports once they are submitted to the Medicines Authority?

ADR reports may be received by the Medicines Authority either directly from the health care professional (HCP), the public, or indirectly via secondary reporting by the product's Marketing Authorisation Holder. Incoming ADRs are reviewed, evaluated and logged into a database. The receiver analysing the ADR must contextualise the information and if there are any points that require clarification, or more information is required for the analysis of the ADR then the reporter is contacted. The first step of the analysis is checking whether the ADR is expected or not according to the Summary of Product Characteristics. The medicine is then coded by Anatomical and Therapeutic Classification (ATC) and the product's registration status is listed. The next step is checking for the seriousness of each ADR within a safety report against the International Conference for Harmonisation ICH⁸ guidelines for seriousness criteria, since these criteria determine whether a report is transmitted in a normal or expedited way. Expedited reporting is a legal obligation for marketing authorisation holders and competent authorities where any suspected

serious adverse reactions that have been reported to them by healthcare professionals, must be relayed within fifteen calendar days. For a marketing authorisation holder this means that a serious ADR report must reach the Medicines Authority within 15 days, and for the Medicines Authority this means that the report must be given to the European Medicines Agency in 15 days. ADRs are subsequently analysed for a potential biological explanation for the event, taking into account concomitant medications, alternative explanations for the ADR and temporality association.

Distinguishing between the effects of a medicine and the 'normal' course of events within a disease/condition may not always be straight forward. Moreover background incidence of any event is a key consideration and ascribing causality may sometimes prove to be difficult. For example in the case of rofecoxib, a selective COX-2 inhibitor marketed as Vioxx that was withdrawn due to an excess risk for myocardial infarctions (MIs) and strokes. This withdrawal was

based on the results of the clinical trial, 'APPROVe', in patients with intestinal polyps, which had shown an increased risk of confirmed serious thrombotic events (including myocardial infarction and stroke) compared to placebo, following long-term use (over 18 months).⁹ Therefore, in the clinical setting a clear-cut ADR may be one of few, with uncertainty being associated with many reports, especially if the adverse drug reaction at that stage is unknown and unexpected. Uncertainty of whether an event is actually an ADR or not should not be a deterrent from reporting the adverse event.

The minimum criteria for reporting are:

- 1 **a patient with at least one identifier** which may be initials, gender, age, weight, ethnicity, area, the more information that is given the better
- 2 a **medicinal product** name and active ingredient
- 3 **an adverse drug reaction** that is suspected to be related to the drug
- 4 **a contactable reporter.**

The outcome of reporting

The primary incentive for this massive data collection and collation is to extract information on medicines when they are used within the broader clinical context, rather than within the restricted environment of clinical trials. To harmonise and facilitate data collection and collation across the EU, in 2001, the first operating version of EudraVigilance was launched. Eudravigilance is a processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products.

EudraVigilance supports in particular the:

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the European Medicines Agency (EMA), national Competent Authorities, marketing authorisation holders, and sponsors of clinical trials in the EEA;
- Early detection of possible safety signals associated with medicinal products for Human Use;

Table 1: Examples of medicines that have been withdrawn in the last decade

Medicine	Active ingredient	Date of withdrawal	Comments
Propulsid	Cisapride	2000	Withdrawn due to risk of cardiac arrhythmias
Dexatrim	Phenylpropanolamine	2000	Withdrawn due to risk of stroke in women under 50 years of age when taken at high doses for weight loss.
Trovan	Trovafloxacin	2001	Withdrawal due to due risk of unpredictable liver injury
Baycol	Cerivastatin	2001	Withdrawn due to risk of rhabdomyolysis
Vioxx	Rofecoxib	2004	Withdrawn due to risk of myocardial infarction
Distalgesic	Co-proxamol	2004	Withdrawn in the UK due to overdose dangers, will be withdrawn EU wide in end 2011
Melleril	Thioridazine	2005	Withdrawn due to cardiotoxicity
Exubera	Inhaled insulin	2007	Withdrawn voluntarily following restrictions on prescribing, doubts over long term safety
Prexige	Lumiracoxib	2007–2008	Withdrawn due to liver damage
Acomplia	Rimonabant	2008	Withdrawn around the world effected due to risk of severe depression and suicide
Raptiva	Efalizumab	2009	Withdrawn effected due to increased risk of progressive multifocal leukoencephalopathy
Reductil	Sibutramine	2010	Suspended in Europe, due to increased cardiovascular risk
Avandia	Rosiglitazone	2010	Suspended in Europe due to increased risk of heart attacks and death.

- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions;
- Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the frame of Risk Management.

Coupled with Eudravigilance is the Eudravigilance Data Analysis System (EVDAS), a programme that statistically analyses the data within the data-warehouse for signal detection. Through this mining of electronic records, the result is generation of signals of specific events that are then investigated, qualitatively and quantitatively through numerous techniques such as Disproportionate Analysis, Proportional Reporting Ratios (PRR), Bayesian Confidence Propagation Neural Networks amongst others. The methodology used by the Medicines Authority within EVDAS is the PRR ratio which is a statistical aid to signal generation developed in the UK. In PRR ratios, the proportion of all reactions to a drug for a particular medical condition of interest are compared to the same proportion for all drugs in the database, in a 2 by 2 table.¹⁰ Additionally, national competent authorities and the EMA evaluate information from supplementary sources such as past and novel medical literature, official company data and international databases to consider the impact on the benefit/risk assessment and thereby allow for proper and timely regulatory action to be taken.

Regulatory safety measures may take the form of the following outcomes:

- Direct Healthcare Professional Communications known as the 'Dear Doctor' Letters where information relating to safety is disseminated across the medical community
- Safety circulars on the medicines authority website which give the latest alerts on medicines
- Media statements by the Medicines Authority when appropriate
- Personal feedback to reporters
- An adjustment to a section/s of the Summary of Product Characteristics which are then submitted as variations to the marketing authorisations
- Urgent safety restrictions, which are interim changes to the product literature, concerning in particular one or more of the following items in the summary of product characteristics: therapeutic

indications, posology, contraindications, warnings, target species and withdrawal periods.¹¹

- Change in Patient information leaflets
- Suspension of a Marketing Authorisation pending further information that alters benefit-risk balance,
- Withdrawal of a Marketing Authorisation

Discussion

Not all hazards can be identified under the limited and restricted environment of testing in clinical trials, before a medicinal product is marketed. Since patients, consumers and healthcare professionals have expectations that medicinal products available are 'safe', they are, from time to time, surprised when regulatory action is taken to restrict their use, introduce new warnings in the product information, or withdraw medicines as a result of the emergence of new data regarding safety issues affecting the positive benefit-risk assessment of the product. Numerous examples can be identified in the literature. Table 1 is a collation of the majority of withdrawals in Europe that occurred in the last decade. In the case of Vioxx in 2004, which was withdrawn due to an increased risk of confirmed serious thrombotic events (including myocardial infarction and stroke), this withdrawal took place after 5 years of extensive marketing. The recent suspension of rosiglitazone, a blockbuster anti-diabetes drug is another example of how a widely prescribed drug showed a degree of toxicity in the post-marketing phase¹⁰. Regulatory action was taken in the EU following a review of new studies questioning the cardiovascular safety of the medicine by the EMA's committee for human medicinal products. Since its first authorisation, rosiglitazone has been recognized to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety has always been kept under close review.

The sibutramine case is another example of why pharmacovigilance is key in the process of maintaining the safest most effective medicines on the market.

Sibutramine gained initial EU approval in 1999. In 2009, preliminary results of a cardiovascular outcomes trial indicated that sibutramine increased the relative risk for major adverse cardiac events by 16% in a population of older over-weight and obese individuals. This outcomes trial (SCOUT) was conducted as a post-marketing

requirement to evaluate the safety of long-term sibutramine, after EU approval of the medicine. The need for this trial came through an accumulation of cardiovascular adverse drug reactions related to sibutramine. Through this trial the EU EMA could conclude that the risk for an adverse cardiovascular event from sibutramine in the population studied outweighed any benefit from the modest weight loss observed with the medicine, and so the marketing authorisation was withdrawn. Pharmacovigilance communications to doctors and pharmacists ensued advising to stop the prescribing and dispensing of sibutramine, while patients taking sibutramine were told to seek alternative weight-loss and weight maintenance programmes.

Conclusion

Proper management and recording of spontaneous ADR reports comprises a critical pharmacovigilance tool useful in identifying unexpected side effects or indicating whether certain adverse effects occur more commonly than previously believed, or whether some patients are more susceptible to ADRs than others. Such findings can lead to changes in the marketing authorisation of the medicine, e.g. restrictions in use, changes in the dose of the medicine and introduction of specific warnings or side effects in the Summary of Product Characteristics. In order to achieve this, the proposed new legislation will strengthen the EudraVigilance database and its data warehouse (the EMA's signal detection software) as the sole EU database. The legislation will also direct National Competent Authorities and MAHs to accept reports sent to them by patients, care givers, families and consumers as well as healthcare professionals. The definition of an adverse drug event will be broadened to also incorporate medication errors. The widening of the definition of an ADR to include and capture adverse events from off-label use and abuse, as well as the introduction of the possibility that the public can also submit ADR reports to the competent authority, is envisaged to strengthen spontaneous reporting systems.

In line with new Pharmaceutical Legislation, a more proactive conduct of Pharmacovigilance will be carried out across Europe, homing onto emerging issues with intensive monitoring in a clinical or academic setting on a large number of

patients. In conclusion it is important to highlight that all medicinal products have benefits as well as risks associated with them. Furthermore not all pharmacological effects of active substances are known, hence vigilant participation of healthcare professionals for new emergent safety issues with long term exposure to medicines is required in order to support the efforts made to maintain safe and effective medicines on the market.

Abbreviations

ADR(s) – Adverse Drug Reactions

MAH(s) - Marketing Authorisation Holders

PRAAC - Pharmacovigilance Risk Assessment Advisory Committee

HCPs – Healthcare professionals

EMA – European Medicines Agency

CHMP – Committee for Human Medicinal Products

SmPC – Summary of Product Characteristics

Key points

- 1 All medicinal products carry an inevitable and unpredictable potential for harm that cannot always be detected at the pre-authorisation stage.
- 2 The main underlying component of all pharmacovigilance activities is the reporting of Adverse Drug Reactions (ADRs) by companies and Health Care Professionals.
- 3 The new pharmacovigilance legislation will widen the legal definition of ADRs, enable patient reporting, increase transparency and enable greater participation by stakeholders.

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