The essentials and challenges of today

Supporting the National Pharmacovigilance System in 2011

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An important aspect of the regulation of medicines by the Medicines Authority in Malta is Pharmacovigilance

'The science and activities relating to the detection, assessment, understanding and prevention of adverse effects of medicines'
(WHO 2002)

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Objectives:

- To highlight the need for drug safety monitoring through pharmacovigilance
- To give an overview of the national pharmacovigilance system today
- To identify the role of the healthcare professional in pharmacovigilance
- To make clear the process of spontaneous reporting
- To give an update of the data in the national pharmacovigilance system as of 2010

Aims of Pharmacovigilance

- To improve public health and safety through the early identification of potential safety hazards
- To contribute to the assessment of benefit, harm, effectiveness and risk of Medicines
- Implementation of regulatory action to maximise benefit and minimise risks associated with medicinal products
- To promote effective communication to the public
- To promote rational and safe use of medicines

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Development of ADR Reporting Systems

The Thalidomide trigger;

Thalidomide tragedy of 1961-1962, when thalidomide caused major birth defects in an estimated 10 000 children in the countries in which it was widely used for the treatment of nausea and vomiting in early pregnancy. The thalidomide disaster led to the establishment of drug regulation in many countries around the world.

World Health Assembly resolution lead to the (WHO) Programme for International Drug Monitoring of 1968.

Pharmacovigilance today:

Today we have moved from a reactive to a pro-active approach where we are striving towards the anticipation of major pharmaceutical safety issues rather than deal with issues reactively.

As drug consumption has increased and the public has grown to expect higher levels of drug safety, the traditional reactive approach has proved largely incapable of addressing shifts in public expectations and media scrutiny

The Need for Drug Safety Monitoring

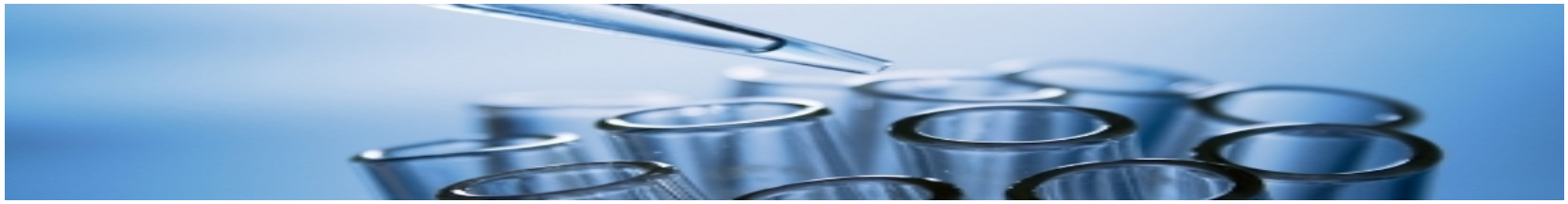
Not all hazards can be established before a medicinal product is marketed.

Information collected during the pre-marketing phase of a medicinal product is incomplete with regard to the medicinal safety profile because:

- Animal testing is insufficiently predictive of human safety

- Data from clinical trials is limited by their size, duration and controlled environment

- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available and will only become manifest after the drug is released, maybe after several years



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Adverse Drug Reaction (ADR)

‘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.’

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ADRs may or may not be serious. A serious ADR is one that:

- Is fatal
- Is life threatening
- Causes or prolongs hospitalization
- Causes a congenital abnormality
- Causes disability or incapacity
- Causes some other medically significant condition

Non-serious ADRs now have the same legal requirement to be reported. On a population level, non-serious ADRs give valuable information, often uncovering new, unexpected reactions to drugs, necessitating the update of product information.

The Legal basis for Pharmacovigilance and ADR reporting:

- The Medicines Act of 2003 provides the regulatory framework for the Medicines Authority

- Further subsidiary legislation to the Medicines Act for pharmacovigilance activities published in Legal Notice 61 of 2006 for health care professionals

'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'

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The new Pharmacovigilance legislation:

Following adoption by the Council and the European Parliament, a new legislation on pharmacovigilance was published on 31 December 2010 in the Official Journal of the EU and will become applicable in July 2012

‘ The new legislation will strengthen and rationalise the current system for monitoring the safety of medicines on the European market. The strengthened legislation on Pharmacovigilance will improve patient safety and public health through better prevention, detection and assessment of adverse reactions to medicines’ (European Commission 2010)

Of importance to Healthcare Professionals, the new legislation will bring into force;

- Widening of the legal definition of adverse events to capture medication errors and overdoses
- Enabling direct patient reporting of suspected ADRs
- The inclusion of patients and heath-care professionals in the decision-making process at an EU level

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Adverse Drug Reaction (ADR)

The new definition of the term ‘adverse reaction’ now covers not only the noxious and unintended effects resulting from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

The suspicion of an adverse drug reaction, meaning that there is at least a reasonable possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting

This also means that there is now a legal obligation to report medication errors, as well as to report the misuse and abuse of medicinal products.

The Role of Healthcare Professionals

‘The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions’

This system of reporting is based on a NO BLAME culture

ADVERSE DRUG REACTION (ADR) REPORT FORM

ALL CONSUMER/PATIENT AND REPORTER INFORMATION WILL REMAIN CONFIDENTIAL

Please complete as much information as possible

PATIENT DETAILS

INITIALS _____ SEX ❑ MALE ❑ FEMALE AGE (at time of reaction) _____ WEIGHT (in kg, if known) _____

ETHNICITY _____ AREA _____

SUSPECTED DRUG(S) / VACCINE(S) / BLOOD PRODUCT(S)

Brand name and form of drug and batch no. (if known)	Dosage	Prescribed for	Date started	Date stopped

SUSPECTED REACTION(S) (Description of Toxic/Side Effects/Interaction)	Date started	Date stopped

OTHER DRUGS (including self-medication & herbal medicinal products)

Brand name and form of drug and batch no. (if known)	Dosage	Prescribed for	Date started	Date stopped

How serious do you consider this ADR?

- ❑ Fatal
- ❑ Life threatening
- ❑ Caused or prolonged hospitalisation
- ❑ Congenital abnormality
- ❑ Caused disability or incapacity
- ❑ Other medically significant condition

_____

- ❑ Not Serious

Outcome from ADR:

- ❑ Recovered
- ❑ Recovering
- ❑ Symptoms Continuing
- ❑ Long-term effects
- ❑ Death related to the ADR
- ❑ Death not related to ADR
- ❑ Not known

For this ADR:	**YES**	**NO**
Drug was discontinued	❑	❑
Improvement noted on discontinuation	❑	❑
Patient was rechallenged	❑	❑
Manufacturer notified	❑	❑
Treatment required	❑	❑

If yes, which _____

If pregnant, state age: _____weeks

ADDITIONAL RELEVANT INFORMATION (medical history, test results, known allergies, suspected drug interactions)

❑ Liver disease ❑ Kidney disease	Allergy (please describe):
Other illnesses (please describe):	

REPORTER

	Reporter Stamp
Type (please circle): doctor/dentist/pharmacist/other health worker	
Name:	
Address:	
Telephone/Mobile:	
E-mail address:	
Registration number:	

Signature _____ **Date** _____

An electronic version of the ADR reporting card can be downloaded from: www.medicinesauthority.gov.mt	❑ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ❑ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

Patient

- Initials
- Age
- Sex
- Weight
- Medical history

Adverse event

- Description: aspect, place, severity, diagnosis
- Outcome, course, time relationship (‘challenge, dechallenge, rechallenge’)
- Laboratory data

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Suspected drug

- Name (product, generic, ingredients, batch no.)
- Dose, route, dates (interval, duration)
- Indication

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Case follow-up

- Missing data
- Laboratory data, pathology
- Outcome data (if not yet recovered)
- Underlying disease
- Verification of findings

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What should be reported?

- Unknown and unexpected ADRs
- ADRs with new drugs
- Serious (also when known) ADRs
- Non serious ADRs
- Medication errors
- Medication abuse
- Unexpected beneficial effects
- Unexpected ineffectiveness

It is important that ADRs for OTCs are reported too.

Because:

- Less healthcare professional input
- Absence of records per se
- Absence of linkage to other medical records
- Direct-to-consumer advertising often allowed
- Inappropriate expectations, demand and use of OTC medicines
- Limited opportunity for ongoing patient follow-up and monitoring of safety

How do we identify ADRs?

- Patients may tell healthcare professionals about symptoms they have experienced since taking a new medicine.

- Some ADRs may not be apparent to the patient and therefore healthcare professionals need to be alert to the possibility of suspected ADRs and link signs or symptoms to either current drug therapy or previous therapy.

- Healthcare professionals should be alert for abnormal clinical findings and laboratory results.

All medicines have the potential to cause ADRs. Published literature estimates that ADRs cause admission to hospitals in as much as 2% to 6% of all cases. Furthermore, ADRs contribute to an increased attendance at primary care and may complicate hospital in-patient stay in as much as 10% to 20% of patients. (Andrews and Mann 2002)

- ADRs cause mortality and morbidity
- ADRs increase the length of hospital stay and increase the cost of patient care.
- ADRs may adversely affect quality of life and may cause patients to lose confidence in healthcare professionals.
- ADRs also mimic disease and result in unnecessary investigations and/or delay in treatment.
- ADRs are a major economic burden.

Occurrence of toxicity in a minority of patients might preclude use of a medicinal product in the majority of patients, if predisposing factors cannot be identified and appropriate regulatory measures implemented to appropriately manage their risks.

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The definition of spontaneous reporting is;

“a system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national pharmacovigilance centre.”

The role of Healthcare Professionals is vital in recording and reporting suspected ADRs in order that regulatory agencies are alerted of emerging safety concerns and thereby facilitating timely and appropriate action.

To detect the full spectrum of complications from pharmaceutical treatment and to gain a representative picture, all sectors of the health-care system need to be involved. This includes public and private hospitals, general practice, government and retail pharmacies, nursing homes, and providers of traditional medicine.

Wherever medicines are being used, there should be a readiness to observe and report unwanted and unexpected medical events.

Advantages of the ADR Reporting System

- It is an inexpensive method for monitoring the safety of a medicinal product throughout its lifetime
- Reports are based on unbiased observations made by vigilant HCPs
- It is an essential method for detecting signals of rare ADRs
- It remains the primary method of data-collection used in most countries
- Participation of Healthcare Professionals is therefore essential for the effective functioning of a pharmacovigilance system.

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The Medicines Authority is responsible for:

- Collecting case reports of adverse reactions (ICSRs)
- Clinically evaluating case reports it receives
- Collating, analysing and evaluating patterns of adverse reactions
- Distinguishing signals of adverse reactions from “noise”
- Recommending or taking regulatory action in response to findings supported by good evidence
- Initiating studies to investigate significant suspect reactions
- Alerting prescribers, manufacturers and the public to new risks of adverse reactions and
- Sharing their reports with the WHO Programme for International Drug Monitoring programmes and transmitting ICSRs to the European Database (Eudravigilance)

The Medicines Authority is responsible for:

- Reviewing of Dear Healthcare Professional letters – which are written in response to National, European or International signals obtained through PhV. For example; DHPCs on topical Ketoprofen, Sutent, Avandia, Sibutramine

- Regularly issuing Safety Circulars on ongoing medical concerns or safety issues. These are uploaded onto the Medicines Authority website on a monthly basis.

- Risk Management Plan review and implementation according to national need, for example through issuing reminders of an ADR that may be experienced in a particular season ex. a reaction to a medication that is sun induced where reminders are sent preceding the summer months.

- Periodic Safety Update Reports (PSUR) data review of medicinal products to contribute to their safety assessment.

What happens to reports once they are submitted to the MA?

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ADR reports may be received electronically or by post

(1) Date stamped

(2) Reviewed for essential information (minimum criteria) and entered into a database
- an identifiable patient
- a medicinal product
- an ADR suspected to be related to the drug
- a contactable reporter

What happens to reports once they are submitted to the MA?

(3) Evaluation

- Expectedness – is it listed in the SPC?
- ATC classification
- Product registration status
- Seriousness of ADR - determines expedited reporting
- Analysis of event - temporality association, concomitant medication, alternative explanations. May require the use of the French Tool of Causality assessment

What happens to reports once they are submitted to the MA?

(4) If there are any points that require clarification, or more information is required for the analysis of the ADR then the reporter is contacted

(5) The reports are then sent to EudraVigilance post-authorisation module. The cumulative data is used for identification of new or emerging safety concerns or new information on recognized adverse effects to be evaluated.

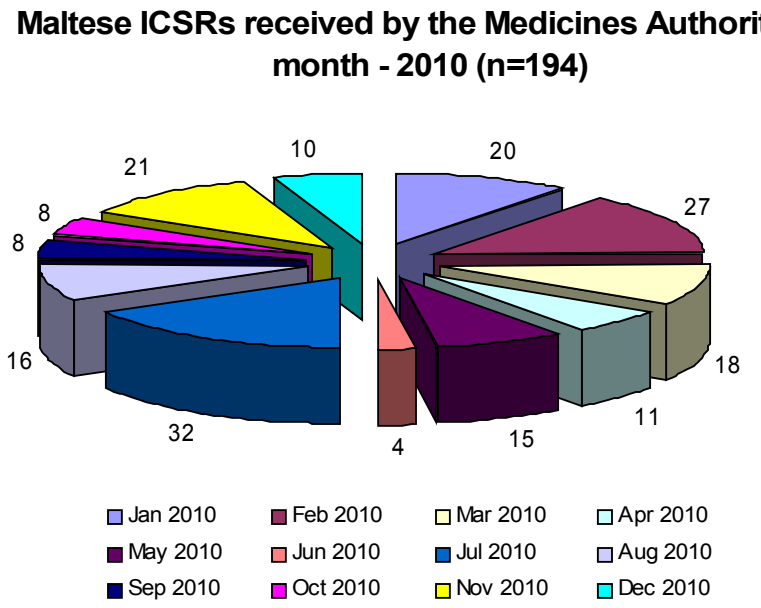
(6) Periodically sent to WHO

(7) The MA will also evaluate information from additional sources such as the medical literature, official company data and international databases to consider their impact on the benefit/risk assessment and thereby allow for proper and timely regulatory action to be taken.

What happens to reports once they are submitted to the MA?

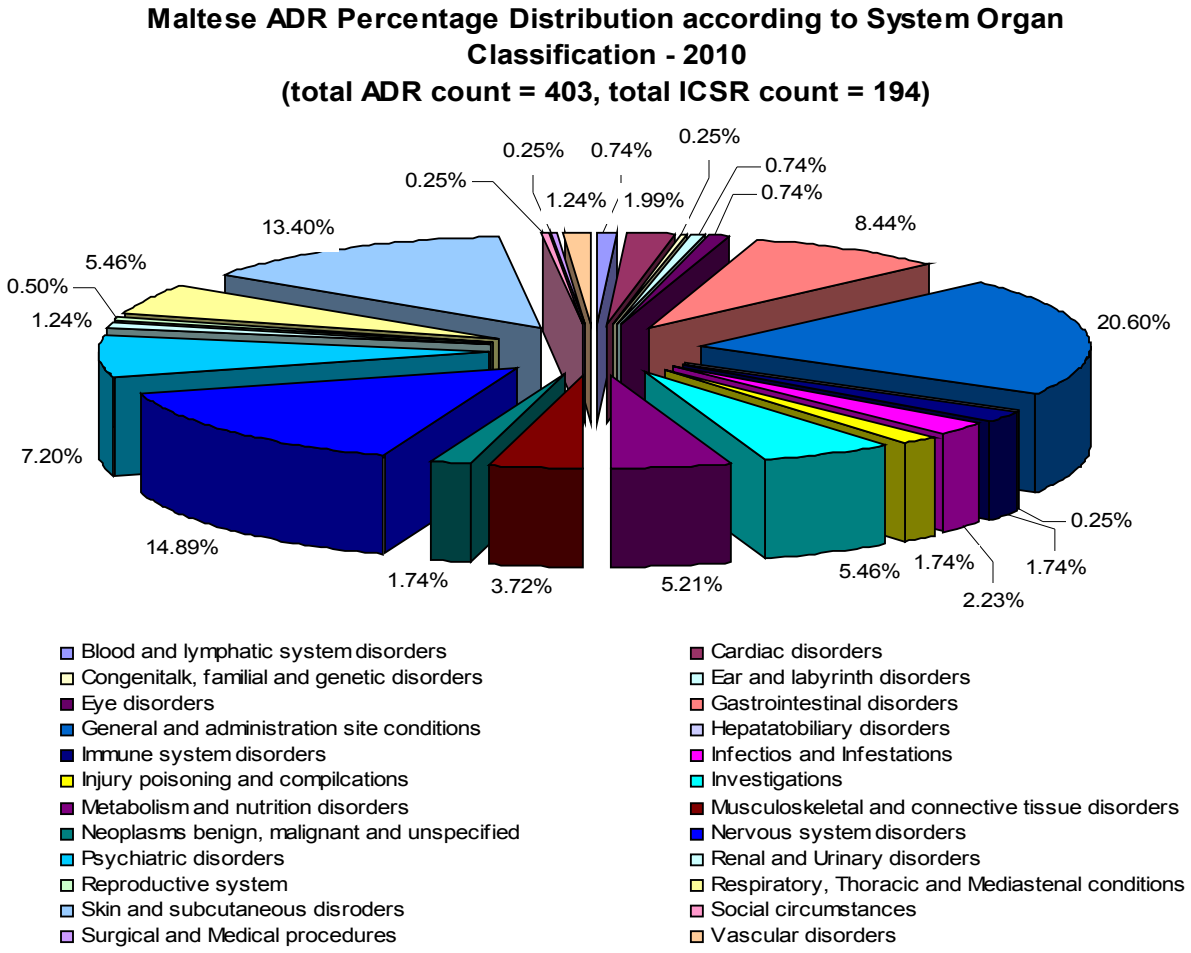
In 2010 the Medicines Authority received a total of one hundred and ninety four (194) adverse drug reaction case reports (ICSRs). Each of these cases detailed at least one adverse drug reaction to the medicinal product concerned thus resulting in a total of four hundered and three (403) individual adverse drug reactions.

The receipt distribution of ICSRs in 2010;



What happens to reports once they are submitted to the MA?

Breakdown of ADRs according to system organ classification (SOC);



Maltese ADR Percentage according to Seriousness - 2010
(Total ADR count 403, total ICSR count 194)

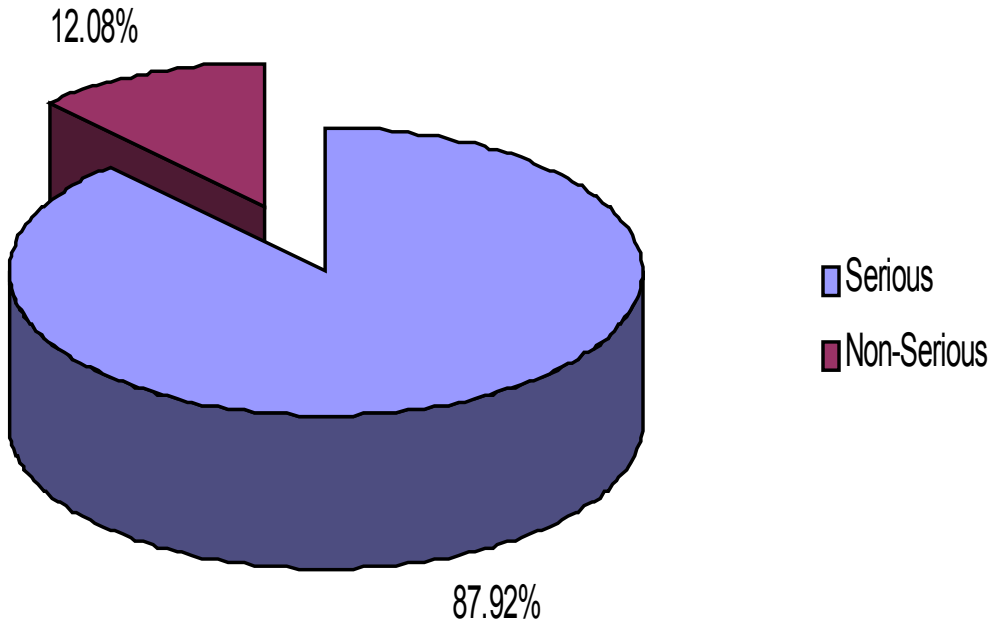


Table 1: Changes to the Marketing Authorisation and/or product literature through Pharmacovigilance

Medicine	***Outcome***	***Reason***
Altargo (retapamulin),	*Update to SPC*	*Epistaxis*
Humira (adalimumab)	*Update to SPC*	*Pleural effusion*
Clopidogrel	*Update to SPC*	*Interaction with PPIs*
Protelos (strontium ranelate)	*Update to SPC*	*Alopecia*
Revlimid (lenalidomide	*Update to SPC*	*Arterial thromboembolic events and risk of thromboembolic events*
Valdoxan (agomelatine),	*Update to SPC*	*Agitation*
Avandia, Avandamet Avaglim	*Withdrawal*	*Cardiovascular effects*
Co-proxamol	*Withdrawal*	*Overdose and lack of efficacy*
Sibutramine	*Suspension of marketing authorisation*	*Cardiovascular effects*

‘ Everything that happens once will never happen again. But everything that happens twice will surely happen a third time.’

Paulo Coelho

Please Report!!

Thank You

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