APRIL 2015

MADRAC

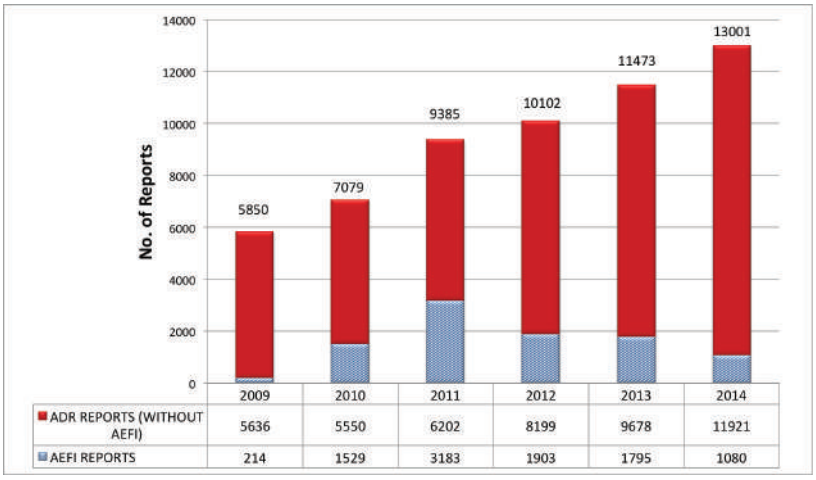
Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my

ANNUAL REPORT FOR 2014

SPONTANEOUS ADVERSE DRUG REACTIONS REPORTED IN MALAYSIA (2014)

The number of ADR reports received by the National ADR Monitoring Centre, NPCB, in 2014 was 13.4% higher than the previous year, totaling 13,001 reports ***(Figure 1)***. After processing, 674 reports were found to be either follow-up reports to cases sent in earlier, duplicates, or reports that had to be rejected, leaving **12,327** new individual ADR reports for 2014. These included 1,069 reports of Adverse Events Following Immunisation (AEFI), 908 (84.9%) involving the Human Papilloma Virus (HPV) vaccine as active surveillance is conducted for this vaccine.

Figure 1: Total Number of ADR Reports Received in Malaysia (2009-2014)



	2009	2010	2011	2012	2013	2014
ADR REPORTS (WITHOUT AEFI)	5636	5550	6202	8199	9678	11921
AEFI REPORTS	214	1529	3183	1903	1795	1080

CONTENT

To join the NPCB Safety Information Mailing List, please send an email to fv@bpfk.gov.my

To report an adverse drug reaction:
1. Visit www.bpfk.gov.my
2. Click on the red box: 'Reporting Medicinal Problems'.
3. Go to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Alternatively, please contact:
The Drug Safety Monitoring Centre,
National Pharmaceutical Control Bureau,
Ministry of Health
PO Box 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.
Tel : +603 78835550
Fax : +603 79567151

Quality of ADR Reports

As can be seen in ***Figure 1,*** Malaysia has successfully increased the quantity of ADR reports received each year. Efforts are also being taken to improve the quality of ADR reports in Malaysia. The World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, measures report quality using the 'Documentation Grading - Completeness Score' system. This is a score between 0.07 (poorly documented case) to 1 (well-documented), measuring the amount of information provided in a report.

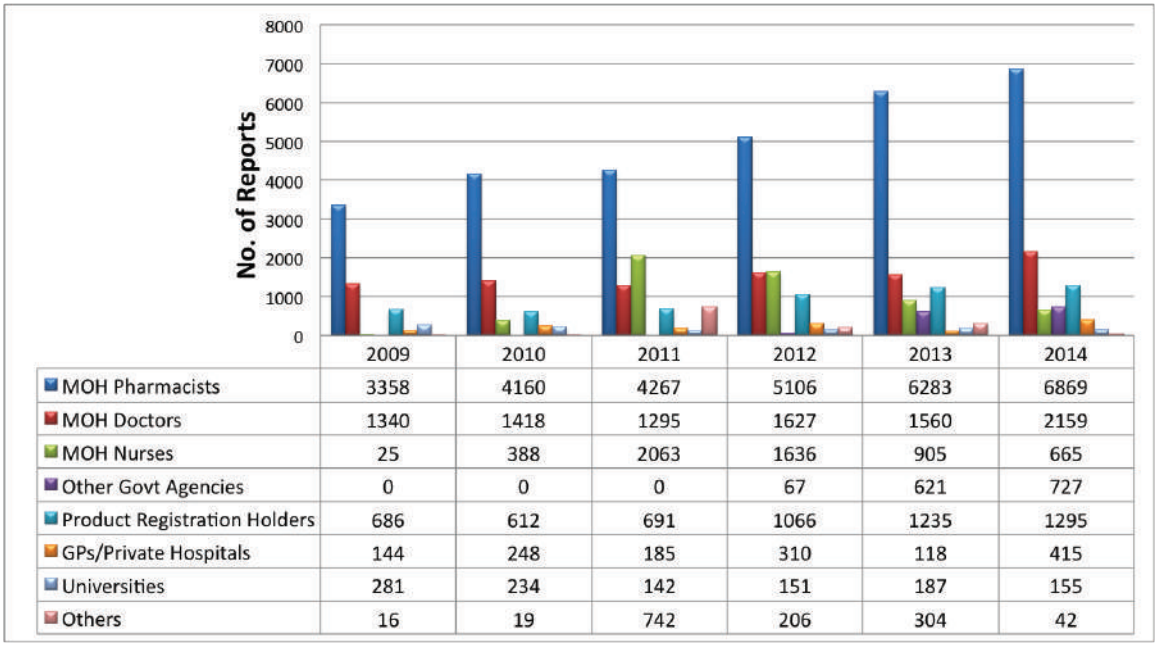
Malaysia obtained an average score of 0.45 from 2010 to 2013, and has successfully increased this to 0.63 by the end of 2014. NPCB will continue to educate reporters on the importance of providing complete and accurate information in order to ensure usefulness of reports.

ADR Reporters

More than half of the reports (55.7%) were submitted by Ministry of Health (MOH) pharmacists, as shown in ***Figure 2***. MOH doctors were the next highest reporters, followed by product registration holders. Reports submitted by private healthcare professionals remained very low, contributing to less than 4% of the total ADR reports received. Only three (3) reports were received from retail pharmacists, while 11 consumers submitted complaints on adverse reactions to the NPCB. Although reports from general practitioners (GPs) and private hospitals showed an encouraging increase to 416 reports in 2014, there are still thousands of ADRs that go unreported. This will delay or prevent detection of drug safety issues.

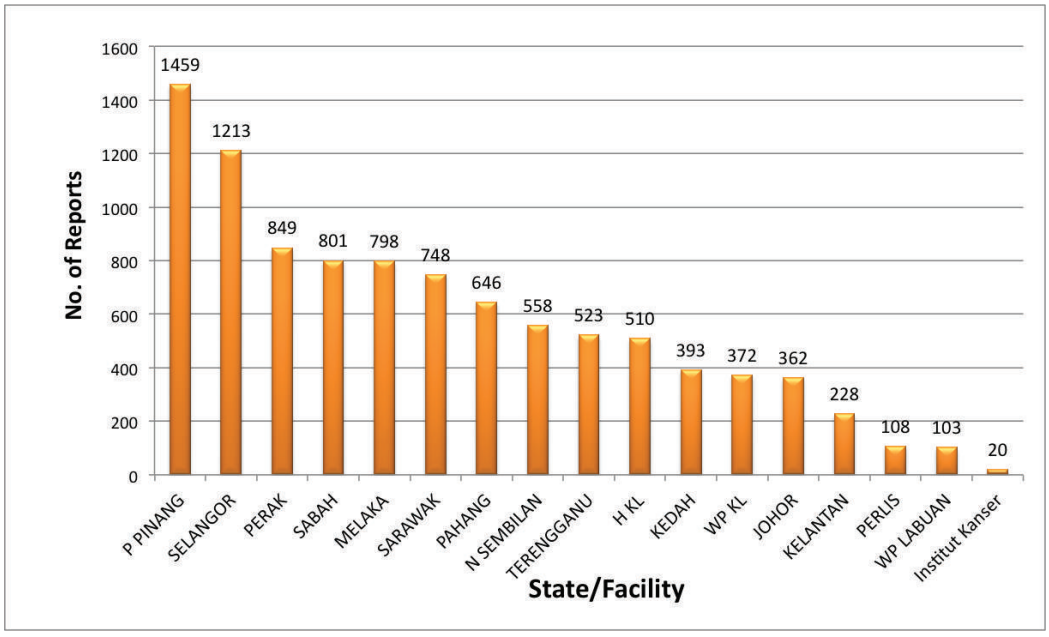
A breakdown of ADR reports received from MOH facilities according to state is shown in ***Figure 3.***

Figure 2: ADR Reports by Reporter Category (2009-2014)



	2009	2010	2011	2012	2013	2014
MOH Pharmacists	3358	4160	4267	5106	6283	6869
MOH Doctors	1340	1418	1295	1627	1560	2159
MOH Nurses	25	388	2063	1636	905	665
Other Govt Agencies	0	0	0	67	621	727
Product Registration Holders	686	612	691	1066	1235	1295
GPs/Private Hospitals	144	248	185	310	118	415
Universities	281	234	142	151	187	155
Others	16	19	742	206	304	42

Figure 3: ADR Reports Received from MOH Facilities According to State (2014)

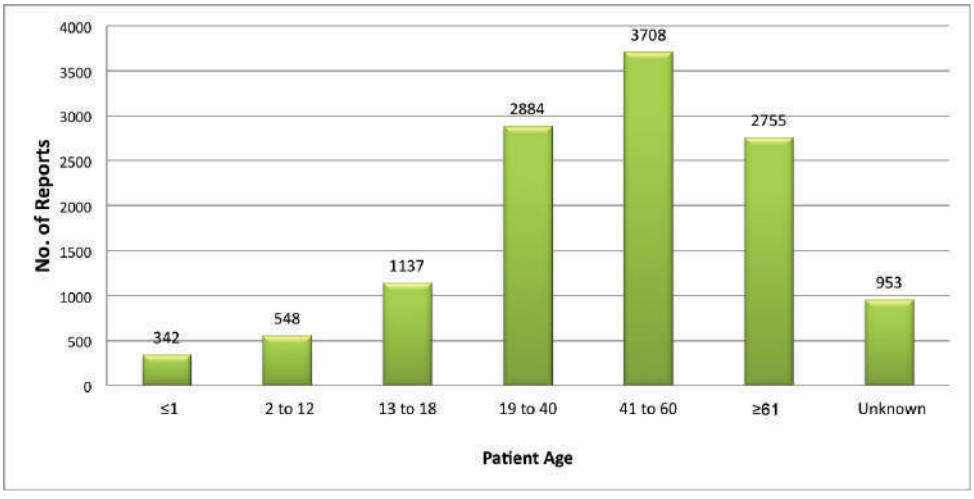


Patient Age

Figure 4 shows the breakdown of ADR reports received according to patient age group. About 53% of the reports involved adults aged between 19-60 years, 22% involved the elderly aged above 60 years, and about 7.2% reported ADRs in children aged 12 years and below.

Several studies have shown that elderly and paediatric patients are at higher risk of ADRs because drug absorption and metabolism are more variable and less predictable in both of these groups[1,2]. Drugs are also less likely to be studied extensively in these extremes of age, while a large proportion of drugs are used "off-label" (outside their license) in paediatric patients, thus increasing the risk of ADRs[3].

Figure 4: ADR Reports by Patient Age Group



Types of Reactions and Suspected Drugs

Overall, there were 21,158 adverse events reported in 2014. Skin and Appendages Disorders contributed the most reports by WHO System Organ Class (SOC), namely 28% (as seen in ***Figure 5***).

The highest number of reports by pharmacological group for 2014 was received for cardiovascular drugs (excluding antihyperlipidemics and anticoagulants) (19.6%) and anti-infectives (excluding anti-tuberculosis and antiviral drugs) which contributed 19.3% (***Figure 6***).

Figure 5: Top Ten System Organ Classes of Adverse Events Reported

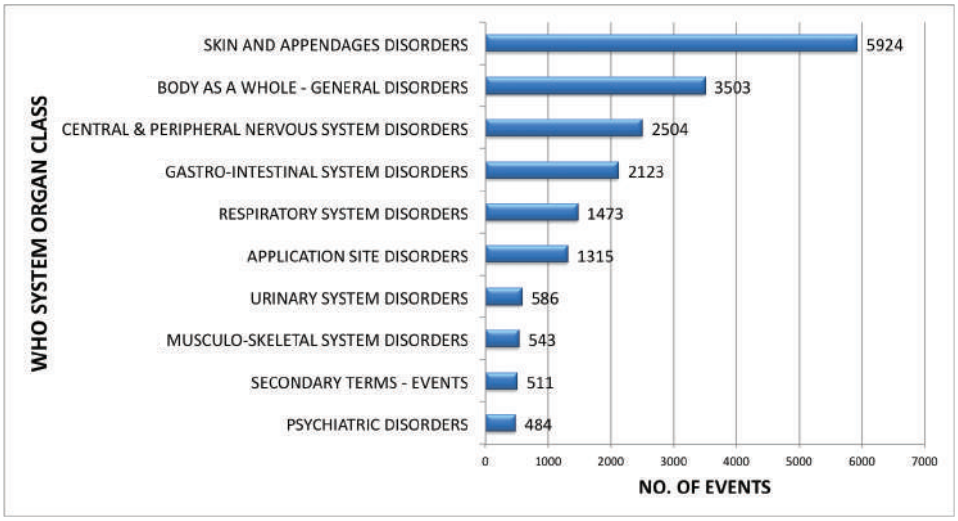
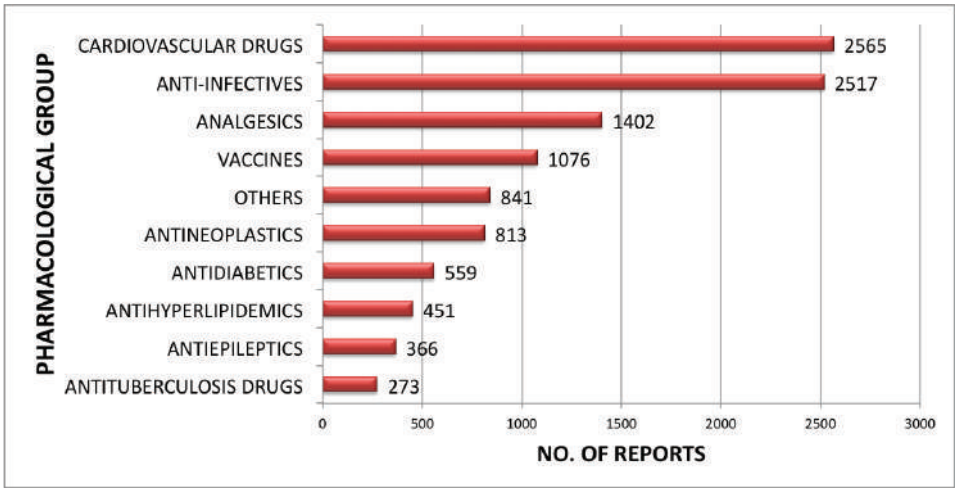


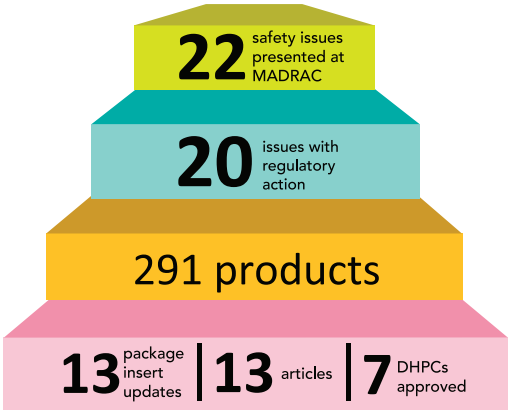
Figure 6: Top Ten Pharmacological Groups of Suspected Drugs in ADRs Reported



References:

1. Bégaud, B., Martin, K., Fourrier, A., & Haramburu, F. (2002). Does age increase the risk of adverse drug reactions? *British Journal of Clinical Pharmacology*, 54(5), 550–552.
2. Alomar, M. J. (2014). Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharmaceutical Journal: SPJ*, 22(2), 83–94.
3. Patel, H., Bell, D., et. al (2007). Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998–2005. *BMC Clinical Pharmacology 2007*, 7:9.

DRUG SAFETY ISSUES DISCUSSED IN 2014



In 2014, a total of 76 drug safety issues were identified through environmental screening. Following review, 22 issues were presented at MADRAC meetings to determine the appropriate risk minimisation measures ***[Table 1]***. The majority of these issues resulted in updates to the package insert safety information, such as tightening of indications or additional contraindications. Regulatory actions for ten (10) of these issues were proposed to the DCA, resulting in DCA directives issued to ensure package inserts of all generic products containing the affected active ingredients are updated with the required safety information.

Table 1: Drug Safety Issues Discussed by MADRAC in 2014 and Resulting Risk Minimisation Actions

MADRAC Meeting Date	Product name (active Ingredient) & Safety Issue	MADRAC Recommendation/Resulting Actions				
		DCA Directive	PI Update	DHPC	Publication of article	Further review
20/2/2014	Trivastal® (piribedil): Restriction of indication to the treatment of Parkinson's Disease		√			
	New oral anticoagulants - (dabigatran, rivaroxaban, apixaban): Association with bleeding risk				√	√
	Synthetic salmon calcitonin: Restriction of indication and duration of use due to evidence of increased risk of cancer	√	√		√	
17/4/2014	Ondansetron: Updates to prescribing information due to risk of clinically significant QT interval prolongation which may lead to a serious and potentially fatal heart rhythm	√	√	√	√	
	Mefloquine: Updated safety information regarding neuropsychiatric adverse effects and visual disturbances	√	√		√	
	Cyproterone acetate & ethinyl estradiol: Restriction of indication and strengthening of warnings related to the risk of thromboembolism	√	√		√	

MADRAC Meeting Date	Product name (active Ingredient) & Safety Issue	MADRAC Recommendation/Resulting Actions				
		DCA Directive	PI Update	DHPC	Publication of article	Further review
17/4/2014	Erbitux® (cetuximab) and Vectibix® (panitumumab): Update of package information to highlight the importance of establishing wildtype RAS status before treatment in metastatic colorectal cancer		√	√	√	
12/6/2014	Risperidone and paliperidone: Updated warnings on the increased risk of intraoperative floppy iris syndrome (IFIS) in patients undergoing cataract surgery	√	√	√	√	
21/8/2014	All statins: Updated package information regarding risk of cognitive adverse effects, increases in HbA1c and fasting blood glucose, and the risk of myopathy	√	√		√	
	Temozolomide: Updated warnings on the risk of hepatic injury	√	√		√	
	Methylphenidate: Updated warning on the risk of priapism	√	√	√	√	
	Filgrastim and pegfilgrastim: Updated information on the risk of capillary leak syndrome in patients with cancer (both drugs) and in healthy donors (filgrastim only)		√	√		
21/8/2014 & 9/10/2014	Metoclopramide: Tightening of indication and restriction of dose due to the risk of neurological adverse effects	√	√		√	
	Domperidone: Restriction of use due to cardiac adverse effects					√
9/10/2014	Cytotec® (misoprostol): Review into the product safety due to evidence of widespread off-label use					√
	Topiramate: Updated warning related to the risk of visual field defects	√		√	√	
18/12/14	Artrodar® (diacerein): Restriction of use to limit the risks of severe diarrhoea and effects on the liver		√	√	√	

REGULATORY MATTERS

PROLIA® AND XGEVA® (DENOSUMAB): MINIMISING THE RISK OF SEVERE SYMPTOMATIC HYPOCALCAEMIA (SSH) AND OSTEONECROSIS OF THE JAW (ONJ)

Denosumab is a human IgG2 monoclonal antibody that inhibits the activity of osteoclasts, the cells responsible for bone resorption. There are currently two denosumab products of different strengths registered in Malaysia since 2012 for different indications, as follow:

(i) Prolia® (60mg) is indicated for the treatment of postmenopausal osteoporosis, male osteoporosis, and bone loss in patients undergoing hormone ablation for cancer;
(ii) Xgeva® (120mg) is indicated for the prevention of skeletal related events in patients with bone metastases from solid tumours.

The prescribing information for both Prolia® and Xgeva® have recently been updated with additional safety information on reducing the risk of SSH and ONJ.

Hypocalcaemia

Through inhibition of osteoclast bone resorption, denosumab causes decreased release of calcium from bone into the bloodstream. Hypocalcaemia is a documented side effect of denosumab, and the risk increases with the degree of renal impairment. Cases of severe symptomatic hypocalcaemia (SSH) have been reported in clinical trials, usually occurring in the first weeks of initiating denosumab therapy.

Osteonecrosis of the Jaw (ONJ)

ONJ is a condition in which the jawbone becomes necrotic, exposed, and does not heal within 8 weeks. Cases of ONJ are commonly reported in patients with advanced cancer receiving Xgeva® (120mg every 4 weeks), but rarely in osteoporosis patients receiving Prolia® (60mg every 6 months). Known risk factors for ONJ include invasive dental procedures, poor oral hygiene, pre-existing dental disease, advanced malignancies, smoking, and previous treatment with bisphosphonates.

Local ADR Reports

In Malaysia, over the past three years since these products were registered, the NPCB has received five (5) ADR reports all involving Prolia® used to treat post-menopausal osteoporosis. The adverse events reported were low back pain, rash, sore mouth, urticaria, tingling skin and vertigo. All the reports were assigned causality C3 (possibly-related to the drug) by MADRAC.

Advice to Healthcare Professionals

- **Monitoring of calcium levels** should be conducted:
  - Prior to the initial dose of denosumab
  - Throughout treatment, especially during the first few weeks
  - If suspected symptoms of hypocalcaemia occur
  - More frequently in patients with risk factors for hypocalcaemia (e.g. creatinine clearance <30ml/min)
- Pre-existing hypocalcaemia must be corrected prior to initiating therapy.
- **Supplementation** with calcium and vitamin D is required in all patients unless hypercalcaemia is present.
- Before starting treatment, patients should be **evaluated for risk factors** of ONJ and a dental examination with appropriate preventive dentistry is recommended.
- **Counselling points:** Tell patients to report symptoms of hypocalcaemia, maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility,pain or swelling.

GUIDE FOR ADR REPORTERS

Access information on global ADR reports at www.vigiaccess.org

VigiAccess™ by the WHO

VigiAccess™ is a public gateway that allows anyone to access information on reported cases of adverse events related to over 150,000 medicines and vaccines, as sourced from the WHO international database of ADRs (VigiBase®).

VigiBase® contains data on over 10 million reports dating back to 1968, from more than 120 countries which participate in the WHO Programme for International Drug Monitoring. VigiBase® may only be accessed by WHO officials and regulatory authorities of member countries, therefore VigiAccess™ has now been created to promote open access, timely sharing of information, and transparency.

Sharing of information is vital in pharmacovigilance, to identify drug-related problems, new or unexpected adverse effects, medication errors and misuse of medication as quickly as possible. This will ensure risk minimisation measures can be put in place. Besides that, Marie-Paule Kieny, WHO Assistant Director General for Health Systems and Innovation said, "By promoting open access and transparency, we hope that we will also promote medicine awareness and save lives."

However, it is important to note that information on suspected ADR should not be interpreted as meaning that the medicinal product in question, or the active substance(s), generally causes the observed effect or is unsafe for use. Any robust conclusion with regard to benefits and risks of a specific medicinal product always requires detailed evaluation and scientific assessment of all available data. The balance between benefit and risk of a specific medicinal product also varies between individual patients.

VigiAccess™ presents search results by active ingredient(s), with a breakdown by type of ADR, geographical distribution, age group, patient sex, and the number of reports per year. Great care has been taken to ensure privacy of the patient and reporter is protected.