NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING, NPCB
ANNUAL REPORT 2014

1. The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC)

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) was established in 1987 under the DCA to perform the function of monitoring safety profiles of drugs registered for use in Malaysia.

During MADRAC meetings held once in two months, causality verification is done for all local ADR reports, and all pertinent drug safety issues are discussed to provide DCA with information and recommendations if required.

A total of six (6) MADRAC meetings were held in 2014, with 11953 adverse drug reaction (ADR) reports presented for verification of causality.

Table 1: List of MADRAC Members (Jan- Dec 2014)

No.	Name and Designation
Ex-officio	
1	**Chairman** En. Tan Ann Ling Director of NPCB
2	**Secretary** Cik Sameerah Shaikh Abdul Rahman Deputy Director, Centre for Post-Registration of Products, NPCB
3	Pn. Noorizam Ibrahim Secretary of the Drug Control Authority
Committee Members *(Alternate Members)*	
1	Prof. Datuk Dr. Jeyaindran Tan Sri Sinnadurai, PJN, DSSA Deputy Director General of Health (Medical) Ministry of Health Malaysia. *(Dr. Hjh. Rosaida Mohd. Said)*
2	Datuk Dr. Roshidah Baba Head of Dermatology Services Head of Department and Senior Consultant Dermatologist, Hospital Melaka. *(Dr. Rohna Ridzwan)*
3	Dato' Dr. Gun Suk Chyn Head of Department and Senior Medical Consultant (Rheumatology) Hospital Tuanku Ja'afar. *(Dr. Azmillah Rosman)*
4	Dr. G.R. Letchuman Ramanathan Head of Department and Senior Medical Consultant (Endocrinology) Hospital Taiping. *(Dr. Padmini Menon)*

No.	Name and Designation
5	Dr. Lim Chong Hum Head of Department and Senior Consultant Psychiatrist, Hospital Ampang. *(Dr. Siti Nor Aizah Ahmad)*
6	Dr. Norzila Mohamed Zainudin Senior Consultant Paediatrician, Hospital Kuala Lumpur. *(Dato' Dr. Hussain Imam bin Hj. Muhammad Ismail)*
7	Dr. Sunita Bavanandan Consultant Nephrologist, Hospital Kuala Lumpur. *(Dato' Dr. Tan Chwee Choon)*
8	Accosiate Prof. Datin Dr. Zoriah binti Aziz Pharmacy Department, Medical Faculty, Universiti Malaya. *(Professor Dr. Mohamed Mansor bin Manan)*
9	Dr. Rohani Jahis Senior Principal Assistant Director, Prevention of Disease Vaccine/ Food & Water Borne Sector Disease Control Division Ministry of Health Malaysia *(Dr. Jamiatul Aida Md. Sani)*
10	Pn. Anis Talib Deputy Director, Formulary and Pharmacoeconomics Section, Pharmaceutical Services Division. *(Pn. Azuwana Supian/ Pn. Azuana Ramli)*
11	Dr. Koh Kar Chai Malaysian Medical Association (MMA) *(Dr. Azizan binti Abdul Aziz)*
12	Dr. Steven Chow Federation of Private Medical Practitioners' Association Malaysia (FPMPAM) *(Dr. G. Shanmuganathan)*
13	Ms. Wendy Khor Hooi Chin Malaysian Pharmaceutical Society (MPS) *(Mr. Lam Kai Kun, RPH, MMPS)*
14	Ms. Eliza Basir Association of Private Hospitals of Malaysia (APHM) *(Ms. Lee Seng Dee)*

2. ANALYSIS OF ADR REPORTS

The National Centre received **13,001** ADR reports in 2014, with **12,067** reports sent to the WHO Uppsala Monitoring Centre for inclusion into the WHO database. This figure includes 1,069 **Adverse Events Following Immunisation** (AEFI) reports received by NPCB in 2014. More than 80% of the AEFI reports involved the Human Papilloma Virus (HPV) vaccine as active surveillance is conducted for this vaccine. Through this programme, majority of the adverse events reported have been non-serious and HPV vaccination in Malaysia has been found to be safe.

Efforts are also being taken to increase the **quality of ADR reports** by educating reporters on the importance of providing complete and accurate information in order to ensure usefulness of reports. Malaysia obtained an average score of 0.45 from 2010 to 2013, and has successfully increased this to 0.63 in 2014.

Detailed analysis of the ADR reports received in 2014 is shown in **Appendix 1**.

3. TESTING OF SUSPECTED ADULTERATED PRODUCTS

The NPCB receives ADR reports with samples of products, mainly for traditional medicines, food and cosmetics, sent in by consumers or healthcare professionals who suspect adulteration. The NPCB conducts tests on these samples to identify suspected adulterants including steroids, antihistamines, NSAIDs, or slimming agents.

Among the ADR reports presented at MADRAC meetings in 2014, a total of 93 products were sent for laboratory testing and 31 (33%) tested positive for various adulterants. These were all unregistered traditional products or products classified as food, and information on the adulterants detected was conveyed to the Pharmacy Enforcement Division for further action. **Table 2** shows the list of products and adulterants detected.

Table 2: Adulterants Detected in Samples of Products Suspected to Cause ADRs

No.	Product Name	Adverse Reactions Reported	Adulterants Detected
1	100% Natural Pure Herbal (Acti Fast)	Unexpected therapeutic benefit, moon face, hypertension, gastritis, weight gain	Dexamethasone
2	Al Taqwa Resdong	Pancytopenia	Chlorpheniramine
3	Al Taqwa Tonic	Rhabdomyolysis, dizziness, delirium	Dexamethasone
4	Bella Formula Har One Cy Nus Capsules	Adrenal insufficiency	Dexamethasone, chlorpheniramine
5	Creative Health Resources Creative Herbs	Moon face, nosebleed, weight increase	Dexamethasone, chlorpheniramine
6	D' raja Urat Saraf	Acute renal failure	Dexamethasone
7	Dakupap	Skin discolouration	Econazole
8	Dong Mai Tan	Maculo-papular rash, pruritis	Dexamethasone, chlorpheniramine
9	Eucommia Herbal Pill	Non-inflammatory swelling, cortisol decrease, weight increase, tiredness	Dexamethasone
10	Extra Slim	Papular rash, joint pain, oedema of the legs	Fluoxetine
11	Garcinia 15d	High blood pressure, palpitation, feeling cold, excessive perspiration	Sibutramine
12	German Sore Eyes and Throat Capsule	Aggravated convulsions	Prednisolone, paracetamol
13	Hydroxycut Hardcore Elite	Palpitation, sweating increased, shortness of breath	Yohimbine
14	Jamu Ajaib	Cortisol decrease, acute renal failure	Dexamethasone

No.	Product Name	Adverse Reactions Reported	Adulterants Detected
15	Natural Herbal Antipyretic	Non-inflammatory swelling, cortisol decrease, weight increase, tiredness	Paracetamol
16	Pil Tupai Jantan Asli	Lower limb oedema	Dexamethasone
17	Red White Cap	Weight increase, purple striae, moon face	Paracetamol
18	Ren Sem To Chon Chin Kuo Pill	Cushing's Syndrome	Dexamethasone, chlorpheniramine
19	Skyline Al Taqwa Gaut Asam Urat	Unexpected therapeutic benefit	Dexamethasone
20	Skyline Al Taqwa Juice	Moon face, hypertension, unexpected therapeutic benefit, gastritis, weight gain	Dexamethasone
21	Skyline Al Taqwa Sakit Pinggang & Lutut	Moon face, unexpected therapeutic benefit	Dexamethasone
22	Surut Ayu	Bradycardia, complete heart block	Sibutramine
23	Susuk Dara Coklat Love Habibi	Hepatitis	Metformin
24	TCM HKL1931787	Thrombocytopenia, fever, purpura	Dexamethasone
25	TCM HRPB KOK 2a	Epigastric pain (not food-related), cataract, glaucoma, weight increase, ascites	Dexamethasone, chlorpheniramine
26	TCM HRPB KOK 2b	Epigastric pain (not food-related), cataract, glaucoma, weight increase, ascites	Dexamethasone, chlorpheniramine
27	TCM HRPB KOK 4	Epigastric pain (not food-related), cataract, glaucoma, weight increase, ascites	Chlorpheniramine
28	TCM HRPB KOK 5	Epigastric pain (not food-related), cataract, glaucoma, weight increase, ascites	Chlorpheniramine
29	Thoo Tzon Hukut Chuang Yaw Wan	Moon face, hypertension, unexpected therapeutic benefit, gastritis, weight gain	Indomethacin
30	Traditional Chinese Medicine A	Face oedema	Dexamethasone, chlorpheniramine
31	Za'faran	Unexpected therapeutic benefit	Dexamethasone, chlorpheniramine

4. MONITORING DRUG SAFETY ISSUES

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 3**]. The majority of these issues resulted in updates to the package insert safety information, such a 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.

MADRAC also discussed the safety issue of **allopurinol related to severe skin reactions**. Through analysis of the Malaysian ADR database (2000-2013), the top drugs suspected to cause serious skin reactions were identified. MADRAC proposed the implementation of auxiliary warning labels as shown in **Table 4.** These labels have been implemented in Ministry of Health as well as private healthcare facilities, with the aim of preventing the development of serious skin reactions.

Table 3: Drug Safety Issues Discussed by MADRAC

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	✓	✓		✓	
	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	✓	✓	✓	✓	

MADRAC Meeting Date	Product name (active Ingredient) & Safety Issue	MADRAC Recommendation/ Resulting Actions				
		DCA Directive	PI Update	DHPC	Publication of article	Further review
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		✓	✓	✓	

Table 4: Auxiliary Warning Label for Drugs Commonly Associated with causing Severe Skin Reactions

Drugs in Pilot Project	**Allopurinol, Co-trimoxazole, Diclofenac, Mefenamic acid**	**Phenytoin, Carbamazepine**
Suggested wording for warning	If you have side effects such as a rash, fever, sore throat, or eye irritation, **stop using this medication IMMEDIATELY** and consult your doctor/ pharmacist.	If you have side effects such as a rash, fever, sore throat, or eye irritation, **seek medical advice** from your doctor/ pharmacist **IMMEDIATELY.**
Cadangan pernyataan amaran	*Sekiranya anda mengalami kesan sampingan seperti ruam, demam, sakit tekak, atau iritasi mata,* ***hentikan pengambilan ubat ini SERTA-MERTA*** *dan rujuk dengan doktor/ ahli farmasi.*	*Sekiranya anda mengalami kesan sampingan seperti ruam, demam, sakit tekak, atau iritasi mata,* ***dapatkan nasihat*** *doktor/ ahli farmasi dengan* ***SERTA-MERTA****.*

5. DRUG SAFETY COMMUNICATION

In 2014, the NPCB published and distributed four (4) issues of the MADRAC Bulletin and eight (8) issues of Reaksi drug safety newsletter to highlight drug safety issues to local healthcare professionals and international regulatory agencies

An electronic mailing list was also established in 2014 for all healthcare professionals in an effort to ensure wider and faster spread of the information. This mailing list currently consists of more than 400 individuals, including doctors, pharmacists, nurses, assistant medical officers and assistant pharmacists.

Five (5) early safety issue communications were distributed in 2014 containing important safety updates involving erythropoietin stimulating agents, hydroxyethyl starch products, strontium ranelate, and the combination product cyproterone acetate + ethinylestradiol (2mg/0.035mg).

The NPCB also prepared 24 press releases or media statements in 2013, while eight (8) were prepared in 2014. These were regarding recall of adulterated products or cosmetics, and unregistered traditional products linked to recurrent ADR reports. Drug safety communication was also carried out through product alerts or circulars, and feedback to ADR reporters.

Besides that, Consumer Medication Information Leaflets (RiMUPs) are reviewed and approved by the Pharmacovigilance Section, to be uploaded on the NPCB website for use by consumers or healthcare professionals. As of the end of 2014, there are RiMUPs for 1,030 products available for download from the website.

6. OTHER ACTIVITIES

Training

Throughout the year 2014, there were 15 training programmes conducted or presentations delivered, with the aim of improving the quality of ADR reporting, training reporters to perform causality assessment, and increasing awareness on the importance of reporting.

These included three (3) training sessions on ADR report analysis and causality assessment held in Johor, Perak and Kelantan, involving more than 100 pharmacists. Such training is in-line with the future plan for causality assessment to be done by reporters themselves, for verification by the NPCB.

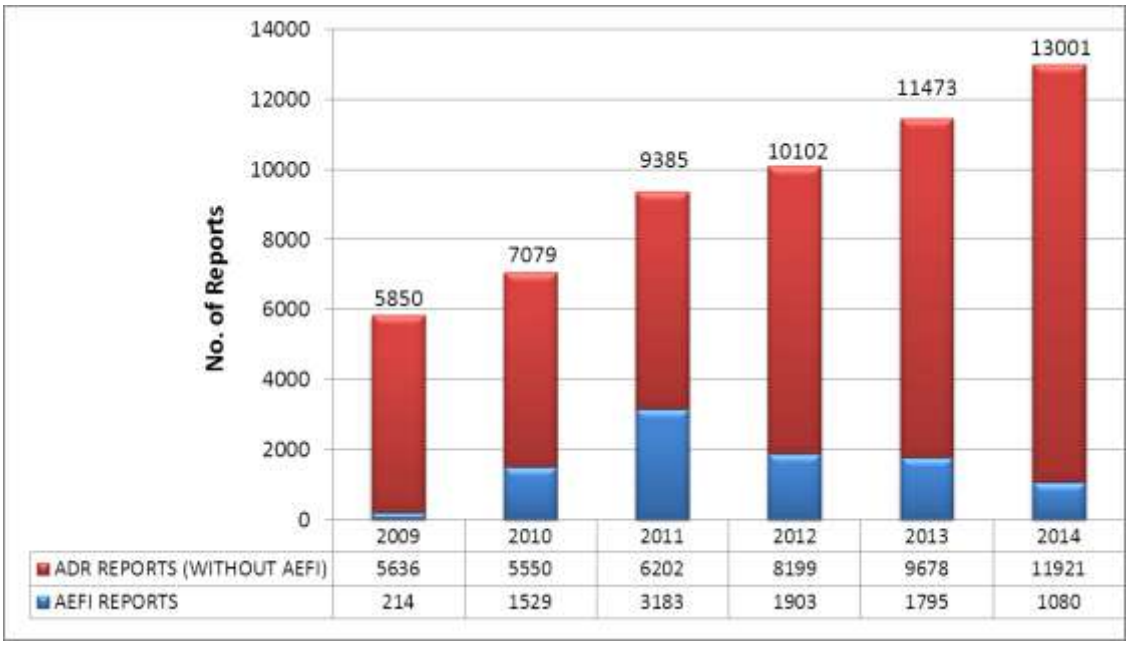
In March 2014, a group of eight representatives from the Uganda National Drug Authority were also given a briefing on Pharmacovigilance in Malaysia. Besides that, almost 200 other healthcare professionals attended the presentations on pharmacovigilance and ADR reporting held in Melaka and Selangor.

Research Collaboration

The National Centre carried out collaboration with local universities for research projects, particularly involving Masters and PhD students. Among the publications arising from this collaboration include the topics ‘Signal Detection’, ‘ADRs related to Antihypertensives’, ‘Adverse Events of Anti-tetanus Toxoid’, ‘Drug-induced Blurred Vision’, ‘ADRs Related to DPP-4 Inhibitors’, and ‘ADRs Related to Alopecia’.

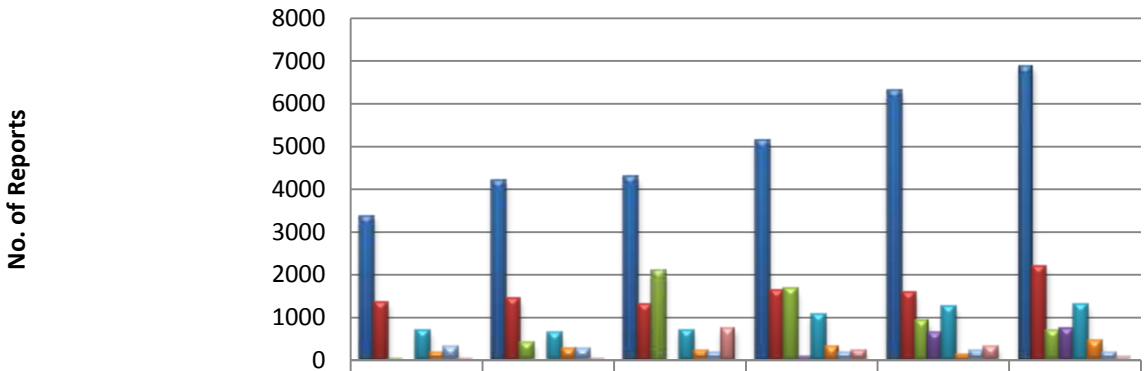
APPENDIX 1

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

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



	2009	2010	2011	2012	2013	2014
MOH Pharmacist	3358	4160	4267	5106	6283	6869
MOH Doctors	1340	1418	1295	1627	1560	2159
MOH Nurse	25	388	2063	1636	905	665
Other Govt Agency	0	0	0	67	621	727
Product Registration Holder	686	612	691	1066	1235	1295
GP/Private Specialist	144	248	185	310	119	416
University	281	234	142	151	187	155
Others	16	19	742	206	303	41

Figure 3: ADR Reports by State from MOH Facilities 2014

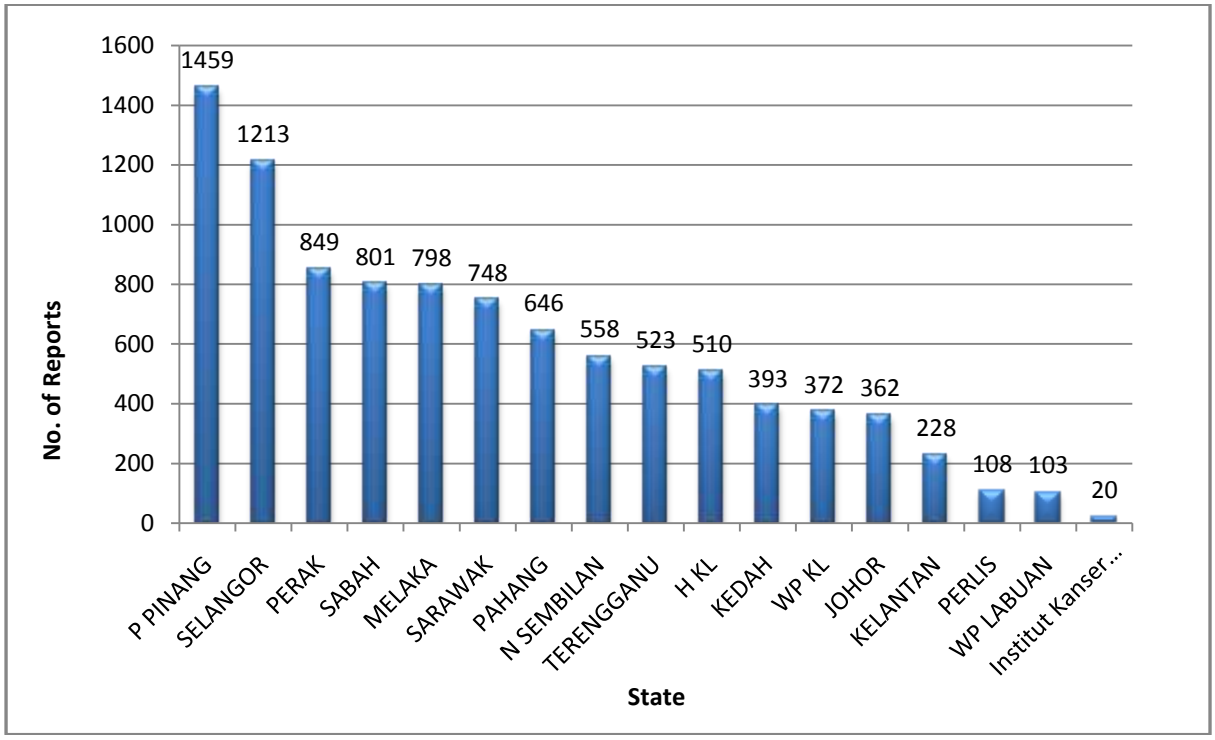


Figure 4: ADR Reports by Age Group of Patient

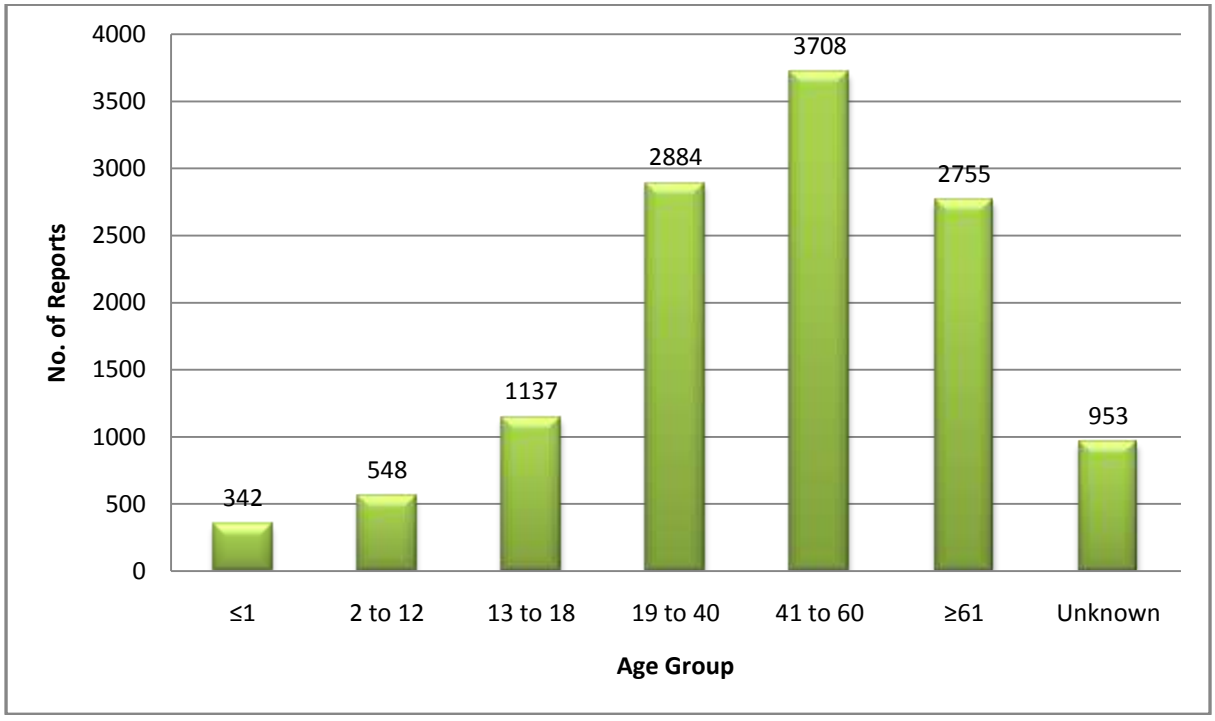


Figure 5: ADR Reports by Race of Patients

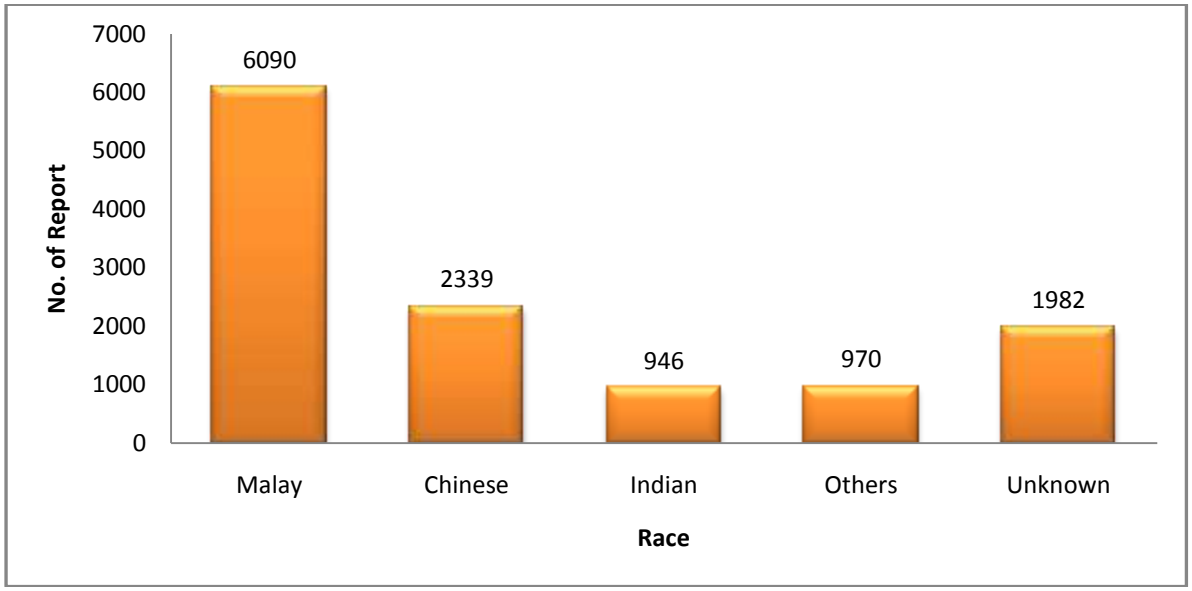


Figure 6: ADR Reports by Gender of Patients

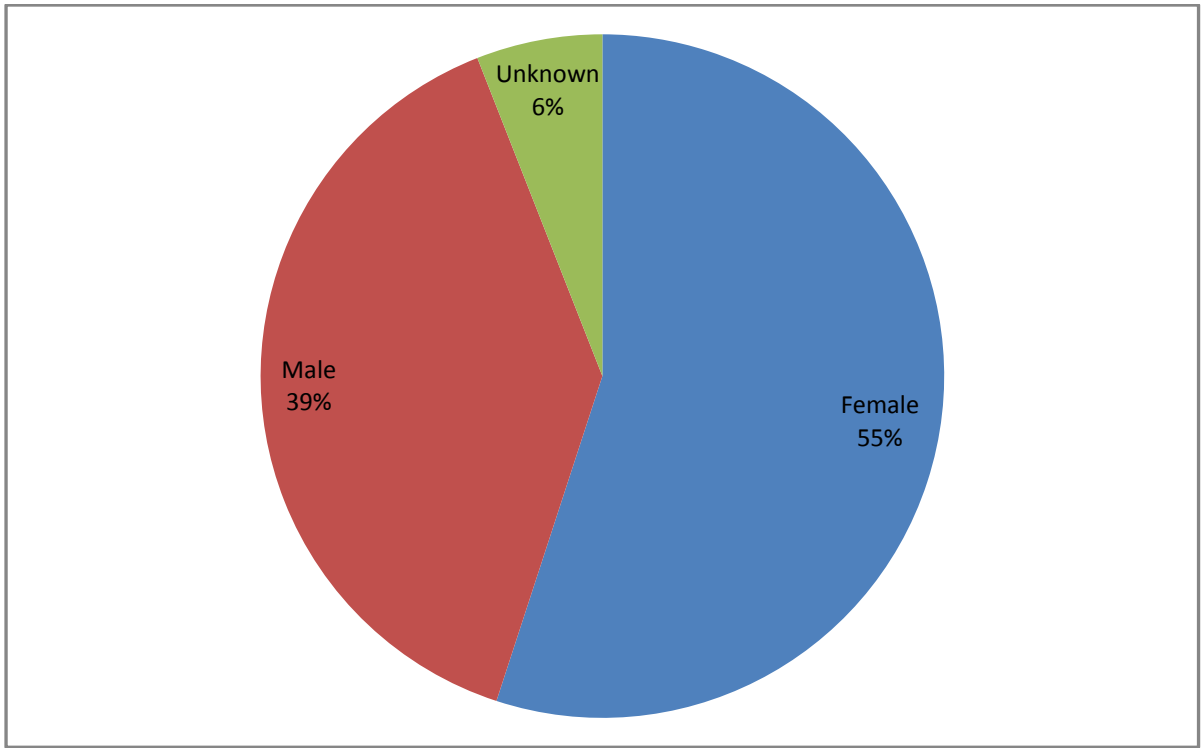


Figure 7: ADR Reports by Severity

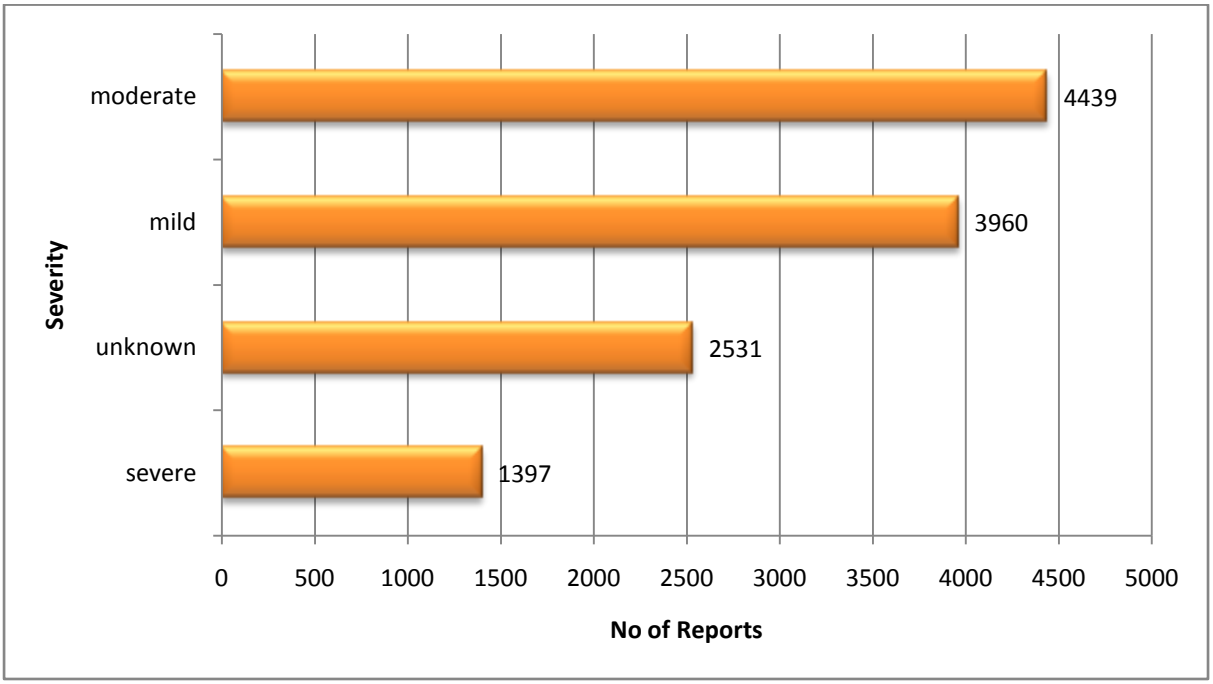


Figure 8: ADR Reports by Product Category

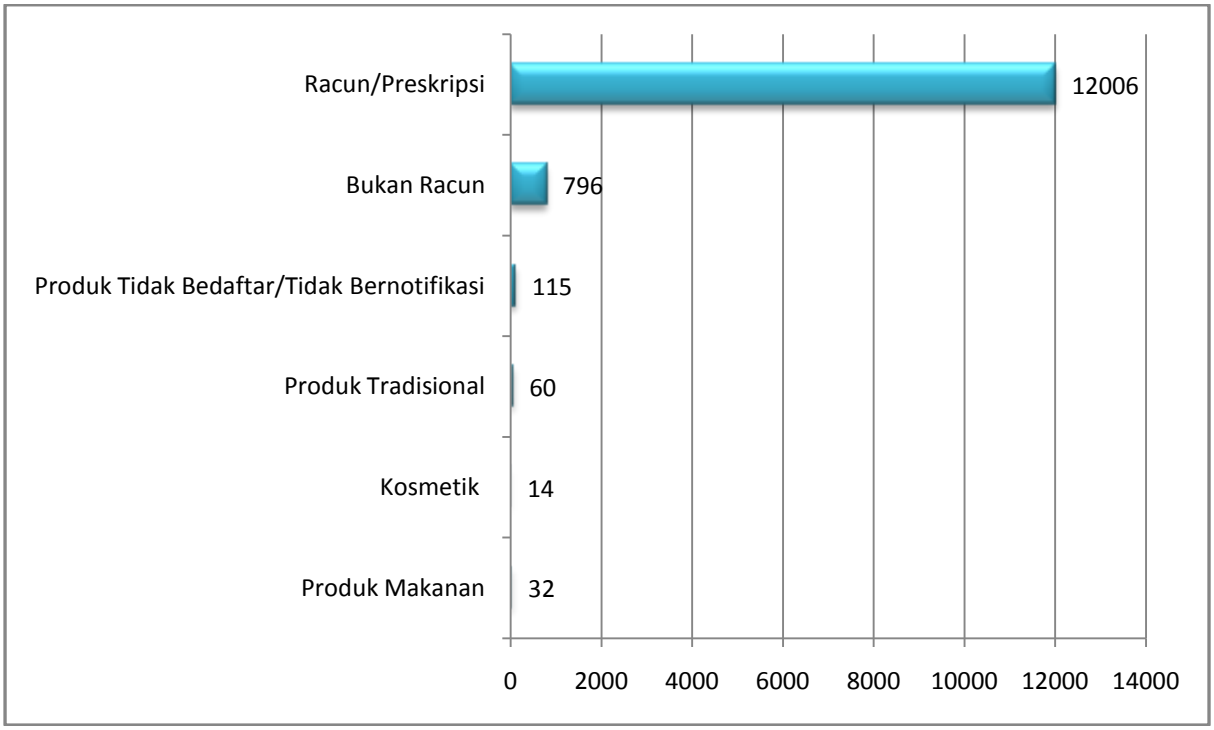


Figure 9: Number of Adverse Drug Reactions by Pharmacological Group

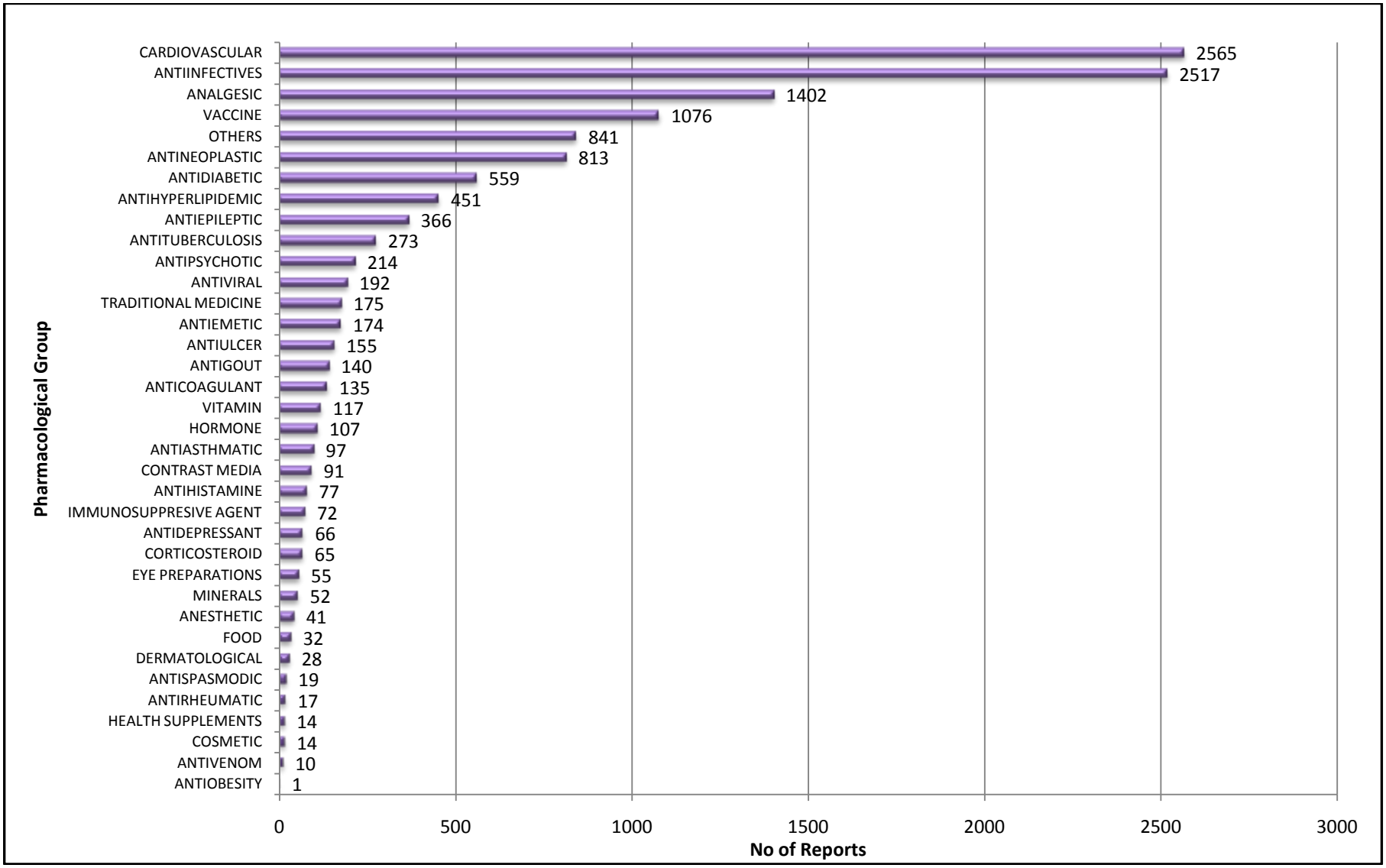


Figure 10: Number of Adverse Drug Reactions by System Organ Class