ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) 2009

1. i) Previous Membership of MADRAC

MADRAC Members/*(Alternate members)*	
En Selvaraja Seerangam Director of National Pharmaceutical Control Bureau.	Chairman
Dr. Sarfraz Manzoor Hussein Consultant Psychiatrist, Hospital Kuala Lumpur	Committee Member
Tan Sri Dato Dr R. P. Lingam Representative of the Malaysian Medical Association.	Committee Member
Prof Jamiyah Hassan Medical Faculty, University Malaya.	Committee Member
Prof Madya Dr Rahmat b Awang/*(Dr. Abdul Fatah Hj. Abdul Rahman)* National Poisons Centre, Universiti Sains Malaysia.	Committee Member
Prof. Dr. Nik Aziz b Sulaiman/*(Prof. Dr. Ima Nirvana Soelaiman)* Cyberjaya University College of Medicine	Committee Member
Dr G.R. Letchuman Ramanathan/*(Dr. Padmini Menon)* Consultant Physician, Hospital Taiping.	Committee Member
Dr Rosaida Mohd Said Consultant Physician, Hospital Ampang.	Committee Member
Dr. Norzila Mohamed Zainudin Consultant Paediatrician, Hospital Kuala Lumpur	Committee Member
Pn Abida Haq Syed M. Haq Secretary, Drug Control Authority, Ministry of Health	Committee Member
Pn. Rosminah Mohd. Din Senior Principal Assistant Director, Pharmaceutical Services Division, Ministry of Health.	Committee Member
Pn Tan Lie Sie Senior Principal Assistant Director Centre for Post Registration, NPCB, Ministry of Health	Committee Member
Pn Fuziah Abdul Rashid Principal Assistant Director (Pharmacovigilance), Centre for Post Registration, NPCB, Ministry of Health	Secretary

ii) Current Membership of MADRAC

MADRAC Members/*(Alternate members)*	
En Selvaraja Seerangam Director of National Pharmaceutical Control Bureau.	Chairman
Cik Sameerah Shaikh Abdul Rahman Deputy Director of Centre for Post Product Registration Centre National Pharmaceutical Control Bureau	Secretary
Pn Siti Aida Abdullah Secretary, Drug Control Authority, Ministry of Health	Committee Member
Dato' Dr Jeyaindran Tan Sri Dr. Sinnadurai DSSA / *(Dr. Hjh Rosaida Mohd Said)* Head of Department and Senior Consultant (Medical), Hospital Kuala Lumpur	Committee Member
Dr. Sarfraz Manzoor Hussein / *(Dr. Siti Nor Aizah Ahmad)* Head of Department and Senior Consultant Psychiatrist, Hospital Kuala Lumpur	Committee Member
Dr G.R. Letchuman Ramanathan/*(Dr. Padmini Menon)* Head of Department and Senior Consultant Physician, Hospital Taiping.	Committee Member
Dr. Roshidah Baba/*(Dr. Rohna Ridzwan)* Head of Dermatology Services Head od Department and Consultant (Dermatology).	Committee Member
Dr. Gun Suk Chyn*/(Dr. Muhaini Othman)* Senior Consultant Physician (Rheumatology), Hospital Hospital Tuanku Ja'afar	Committee Member
Dr Hussein Imam Bin Hj. Muhammad Ismail / *(Dr. Norzila Mohamed Zainudin)* Head of Department and Consultant Paediatrician, Hospital Kuala Lumpur	Committee Member
Dr. Tan Chwee Choon / *(Dr. Sunita Bavanandan)* Head of Department and Senior Consultant Physician (Nefrology), Hospital Tuanku Ampuan Rahimah	Committee Member
Dr. Rohani Jahis / *(Dr. Nor Zahrin Hasran)* Principal Assistant Director	Committee Member
Pn. Zawiyah Mat Johor / *(Pn. Rosminah Mohd. Din)* Deputy Director, Pharmaceutical Services Division, Ministry of Health.	Committee Member

2. MEETINGS

The committee met six times over the year and a total of 5615 adverse drug reactions reports were reviewed.

Meeting No.	107	108	109	110	111	112
Date	5/02/2009	12/03/2009	14/05/2009	23/07/2009	10/09/2009	10/12/2009
No. of reports	987	542	811	1091	1147	1037

3. ANALYSIS OF ADVERSE DRUG REACTIONS REPORTS

A detailed review and analysis of the adverse drug reactions (ADR) reports received during the year 2009 was conducted (Appendix 1).

4. REGULATORY ACTIONS

During the course of the year, the following recommendations were proposed by MADRAC and accepted by the Drug Control Authority (DCA):

NO.	MADRAC MEETING	PRODUCT	RECOMMENDATIONS	DCA MEETING
1.	108	Cough & Cold	**Additional Warning on Cough & Cold Products** - To include the following information in the product label and information leaflet under "Warnings" and "Precautions" for cough and cold oral liquid preparation (single or combination):- a. "not to be used in children less than 2 years of age"; b. "to be used with caution and doctor's advice in children 2 to 6 years of age"; - Only applicable for poison containing products while Guaifenesin & Ipecac/Ipecacuanha (non-poison) should be reviewed later.	215 30/04/2009
2.	110	Propylthiouracil	**Additional Warning on "Potential For an Increase in Risk of Hepatotoxicity"** To include the following information in the product information leaflet under "Warnings" and "Precautions":- **WARNINGS AND PRECAUTIONS** *Potential risk of serious hepatotoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiouracil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy.* *Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available.*	218 30/07/2009

3.	110	Clopidogrel	**Additional Warning on "Possible Interaction Between Clopidogrel And Proton Pump Inhibitors"** The DCA has agreed to MADRAC's proposal on the following amendment in the product information leaflet:- **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE** *Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.* **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** *Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g., proton pump inhibitors) should be discouraged.* **PHARMACOKINETIC PROPERTIES** *The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6, 3A4, 1A1, 1A2 and 2C19.*	218 30/07/2009
4.	110	Antiepileptics	**Additional Warning on Potential for an Increase in Risk of Suicidal Thoughts or Behaviours** - There are 100 antiepileptic products registered with Drug Control Authority (DCA) in Malaysia but only several marketing authorization holders update the warning of increased risk of suicidal thoughts and behaviors (suicidality) into their product information leaflet. - The DCA has agreed to MADRAC's proposal that all marketing authorization holders of antiepileptic products are requested to include the following information in the product information leaflet under "Warnings"	218 30/07/2009

			and "Precautions":- **"Potential for an increase in risk of suicidal thoughts or behaviours"**	
5.	111	Colchicine	**Additional Warning on "Severe Drug Interaction Between Colchicine And P-Glycoprotein Or Strong CYP3A4 Inhibitors"** To include the following information in the product containing clochicine information leaflet under "Warnings":- **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** *Potential risk of severe drug interactions, including death, in certain patients treated with colchicines and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g. verapamil and diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone.* *P-glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine.* *A dose reduction or interruption of colchicines treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required.* *Avoid consuming grapefruit and grapefruit juice while using colchicines.*	220 01/10/2009
6.	111	Immunosupressant	**Additional Warning On "Increased Risk for Opportunistic Infections such as Activation of Latent Viral Infections Including BK Virus-Associated Nephropathy"** To include the following information in the product information leaflet under "Warnings" and "Precautions":- **WARNINGS AND PRECAUTIONS**	220 01/10/2009

			Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppresants. These infections may lead to serious, including fatal, outcomes.	
7.	112	Ceftriaxone	**Update to the Previous Warning on "Potential Risk Associated with Concomitant Use of Ceftriaxone with Calcium-Containing Intravenous Solutions"** - Previously additional warning regarding the interaction of ceftriaxone with calcium-containing products in all product information leaflet of Ceftriaxone was done in the 196th Drug Control Authority (DCA) meeting. - *Health Canada, U. S. Food and Drug Administration (USFDA)* and *Medicines and Healthcare Products Regulatory Agency (MHRA)* notified healthcare professionals of an update to a previous alert that addresses the interaction of ceftriaxone with calcium-containing products. - The DCA has agreed to MADRAC's proposal on the dissemination of information through circular to notified healthcare professionals on the updates and also the following amendment in the product information leaflet:- **CONTRAINDICATION** *Ceftriaxone is contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.* **WARNINGS** *In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.* *Diluents containing calcium, such as Ringer's solution or Hartmann's solution,*	223 24/12/2009

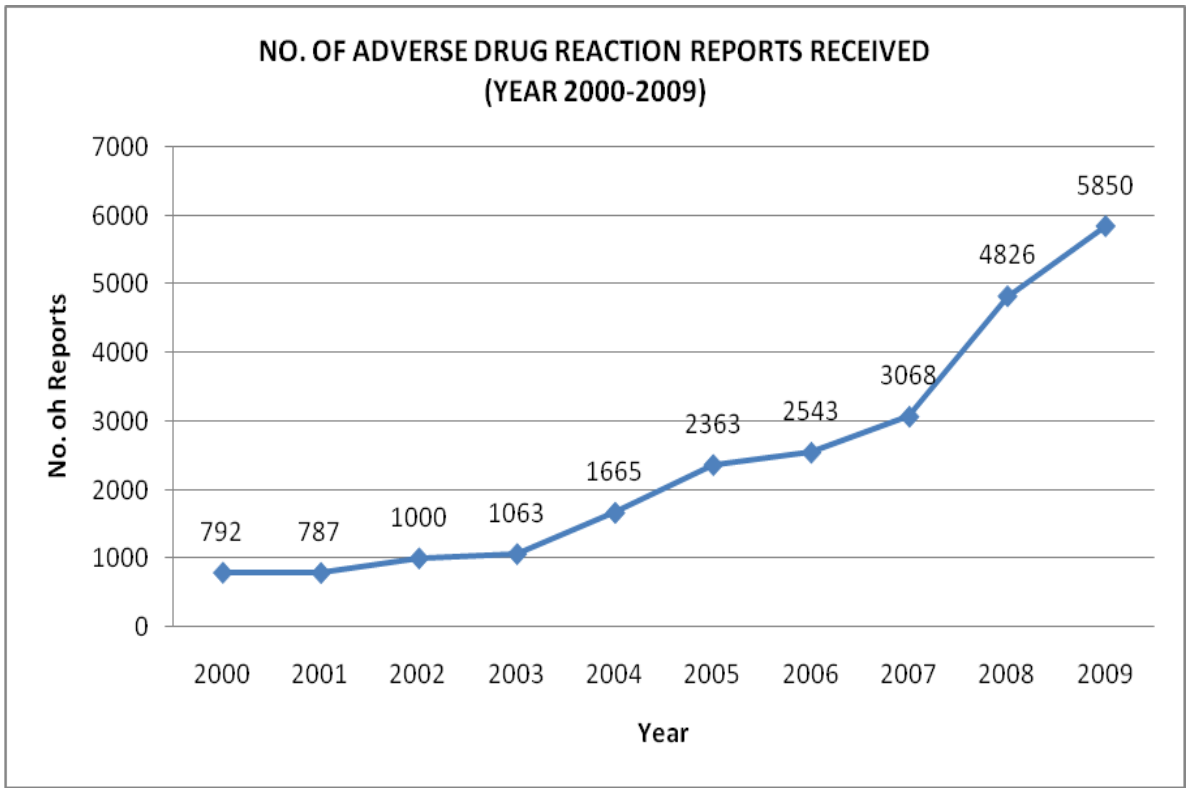
			are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.	
8.	112	Hydroxycut MAL06061641TC	**Lifted the Suspension of Registration** - On 1st May 2009, USFDA warned consumers to immediately stop using Hydroxycut products because they are associated with serious liver injuries. The decision was based on a report from *Health Hazard Evaluation Board* - Based on action taken by USFDA, Hydroxycut® marketing authorization in Malaysia voluntarily suspended Hydroxycut® registration until further investigations and safety information received. - Based on the safety data evaluation there are some differences between Hydroxycut® products marketed in US compared to Malaysia such as active ingredients and this product did not contribute to any adverse reactions and safe to be use as health supplement in the normal daily dose. - Screening on the Hydroxycut® sample shows that it is free from adulteration but might contain naturally producing caffeine. Therefore, it could be conclude that is free from quality and safety issues. - To date, there are no adverse drug reactions reports received by MADRAC relating to Hydroxycut®. - The DCA has agreed to MADRAC's proposal on lifting the suspension of Hydroxycut® registration.	223 24/12/2009
9.	112	Cardiamed Injection 1mg/1ml (4ml Ampoule) MAL20051326A	**Lifted the Suspension of Registration** - In the 206th DCA meeting, Cardiamed Injection 1mg/ml (MAL20051326A) which is a tender item had been suspended and withdraw from the market until further investigation duly to the several serious adverse reactions of gangrene and cyanosis peripheral reported to MADRAC.	223 24/12/2009

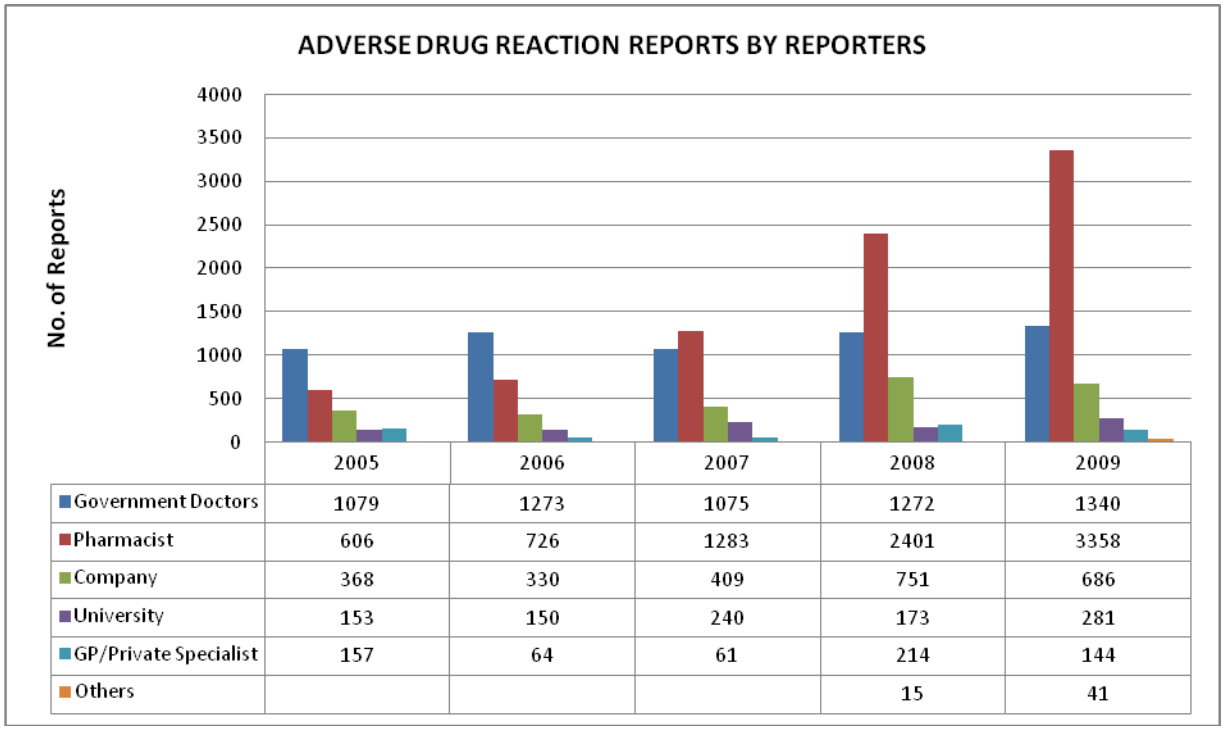
			- Therefore, other alternative Noradrenaline injection (Levophed) is under closed monitoring and the serious adverse drug reactions also presented with the used of Levophed. - The proposal was presented in the 223rd DCA meeting (24/12/2009), but the decision was put on hold waiting for recommendation and feedback regarding a standard protocol on Noradrenaline injection with other potent vasoconstrictor from specialist in reducing adverse reactions. - In the 224th DCA meeting, DCA was satisfied with the feedback and the suspension of registration had been lifted.	

6. ACTIVITIES

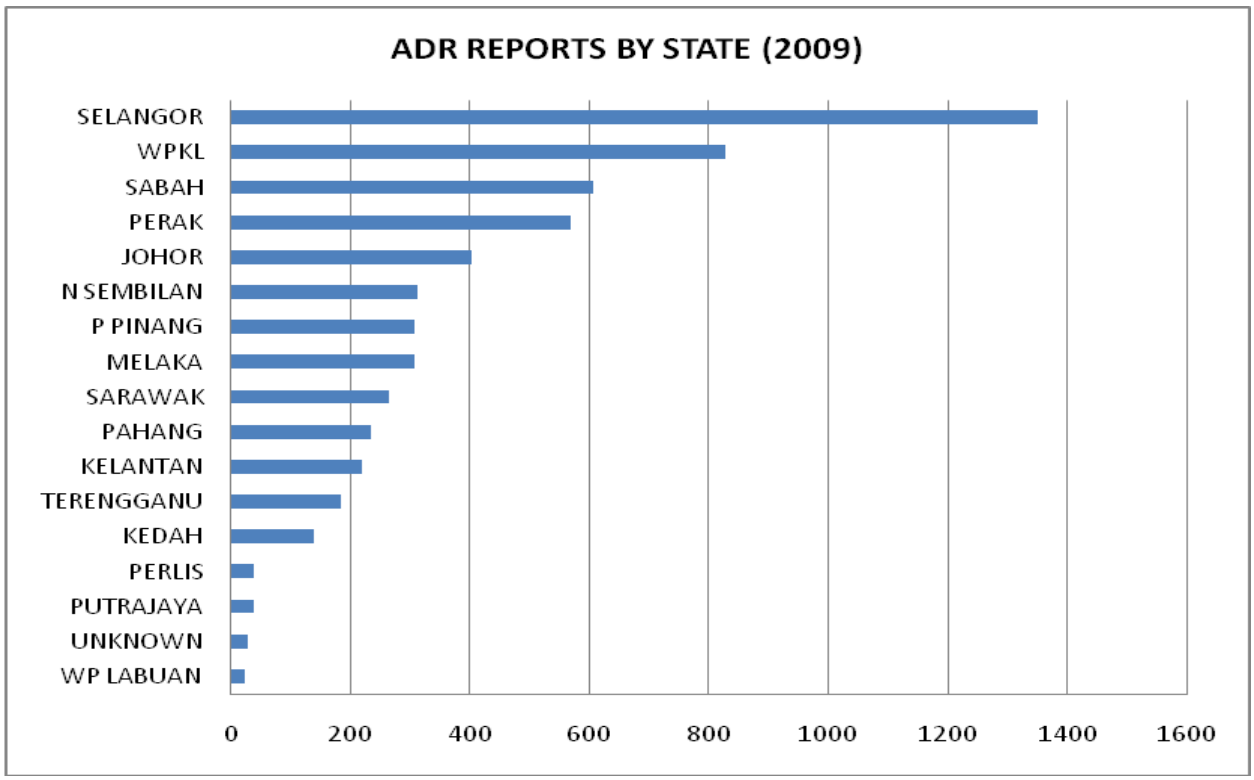
NO.	FORUM	PLACE	TITLE OF PRESENTATION
1.	Bengkel Kesan Advers Ubat-ubatan dan Vaksin	1) Hotel The Palace, Kota Kinabalu, Sabah 2) Alor Setar, Kedah 3) Kuala Terengganu 4) Hotel Allson Klana Putra, Nilai, Negeri Sembilan 5) National Pharmaceutical Control Bureau (2 times)	Background to Product Registration and Overview of Current System of Post-Market Surveillance
			Pharmacovigilance: Ensuring the Safe Use of Medicines/Vaccines and Role of Pharmacists
			Current Reporting System for ADR
			How Reporting of ADR can Improve the Safety Profile of Medicines
			Recognizing, Reporting and Reducing ADR
			Causality Measurement of Suspected ADR
			Adverse Events Following Immunization (AEFI)
			Consumers Medicines Surveillance
2.	Bengkel Penyediaan Garispanduan Kejadian Kesan Advers Berikutan Imunisasi (AEFI)	Pharmaceutical Services Division	Adverse Events Following Immunization (AEFI)
3.	Pembentangan Garispanduan Pengendalian Kejadian Kesan Advers Berikutan Immunisasi	National Pharmaceutical Control Bureau	Adverse Events Following Immunization (AEFI)
4.	Continuous Medical Education	Hospital Port Dickson	Adverse Drug Reaction Reporting & Monitoring
5.	Pharmacovigilance-Keselamatan Vaksin	Jabatan Hal – Ehwal Orang Asli	Pharmacovigilance – Adverse Event Following Immunization
6.	Introduction of Pharmacovigilance For Student	IMU, Cyberjaya	Pharmacovigilance in Malaysia
7.	Sesi Dialog Bersama Ahli Farmasi WP KL dan Putrajaya	JKWP, KL	Managing ADR Effectively
8.	Kursus Perundangan dan Regulatori	Jabatan Kesihatan Negeri Pulau Pinang	Adverse Drug Reaction

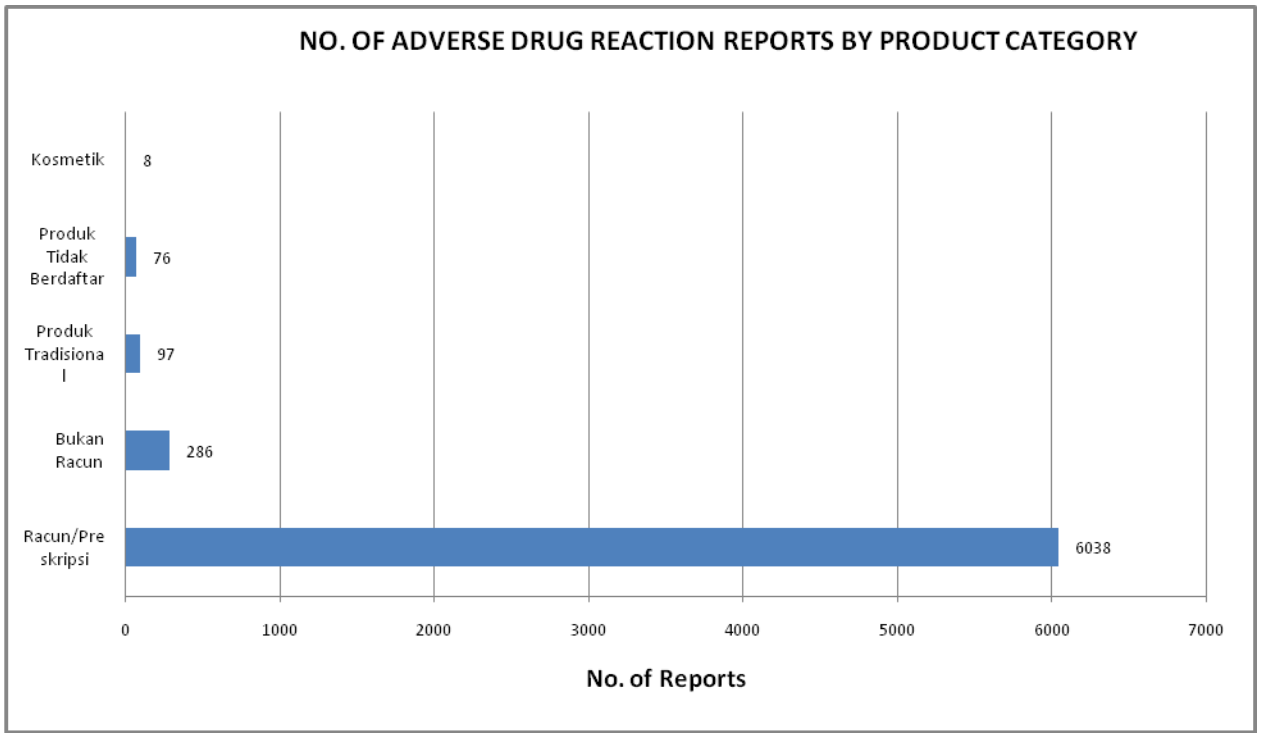
APPENDIX 1

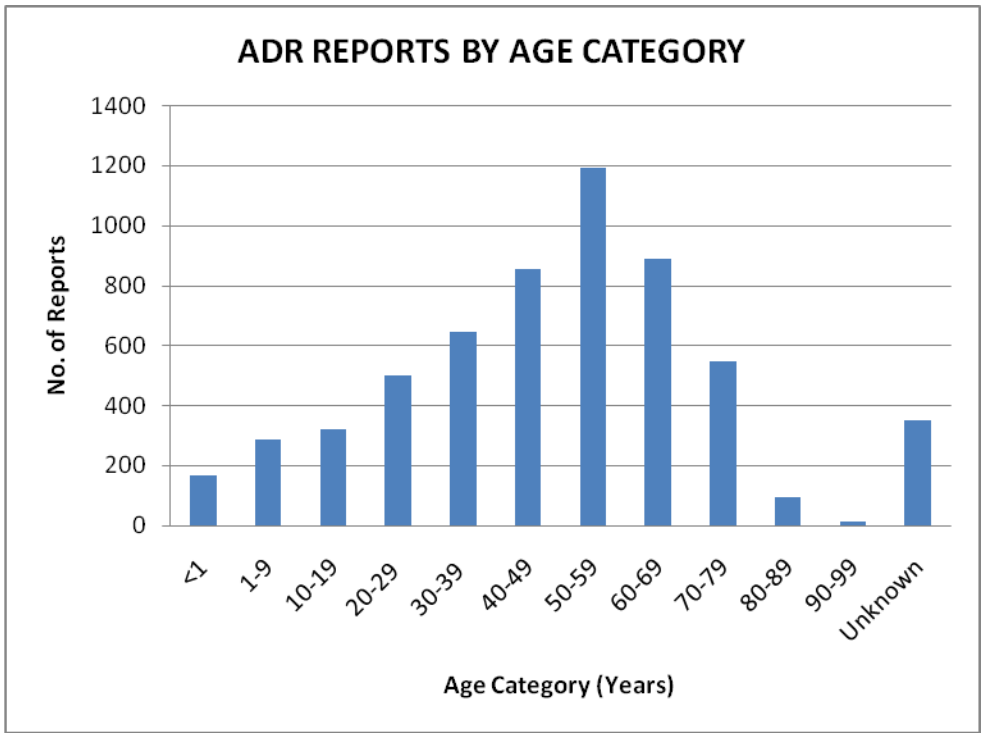


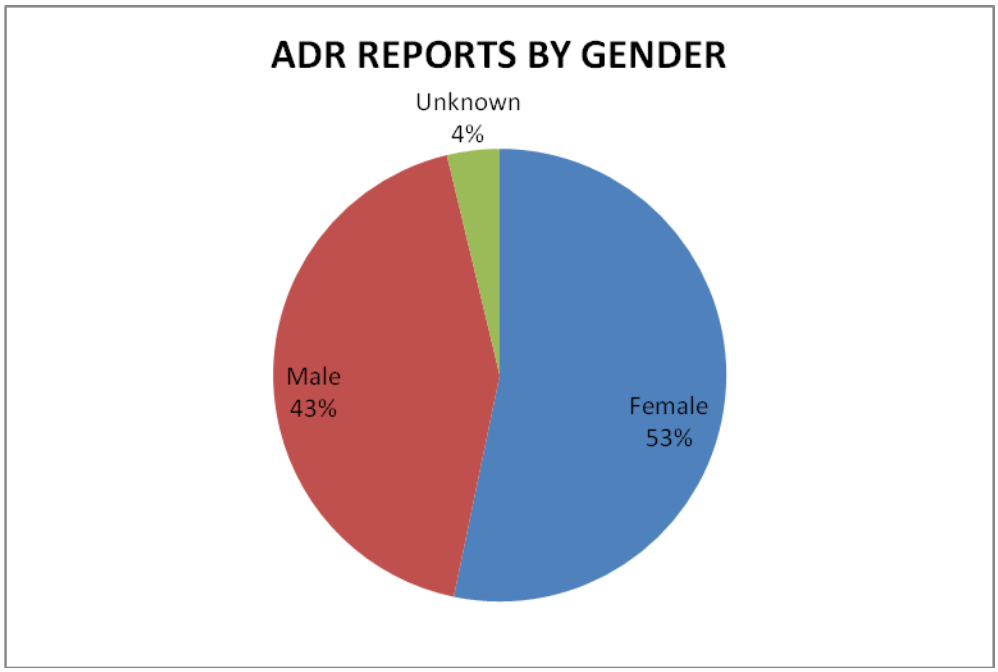


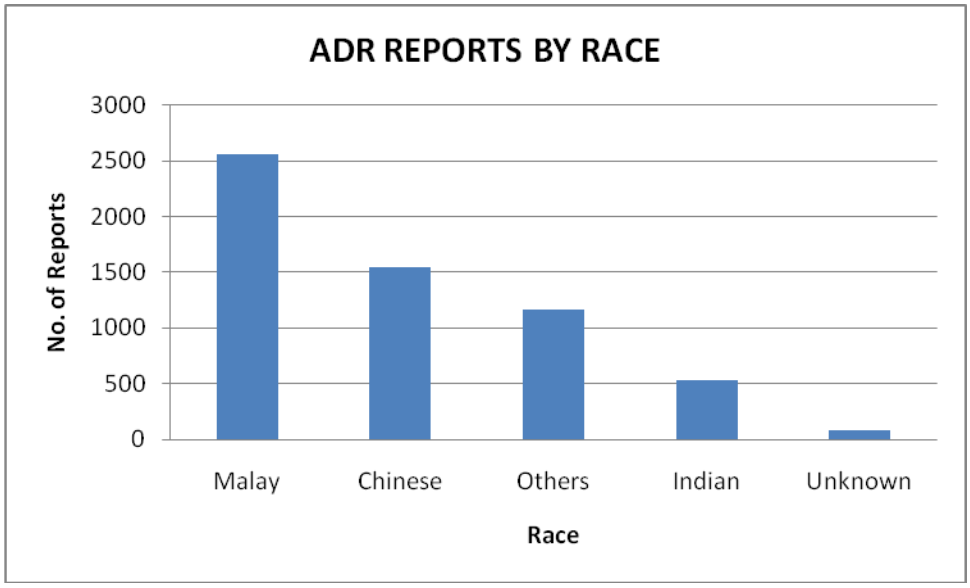
	2005	2006	2007	2008	2009
Government Doctors	1079	1273	1075	1272	1340
Pharmacist	606	726	1283	2401	3358
Company	368	330	409	751	686
University	153	150	240	173	281
GP/Private Specialist	157	64	61	214	144
Others				15	41

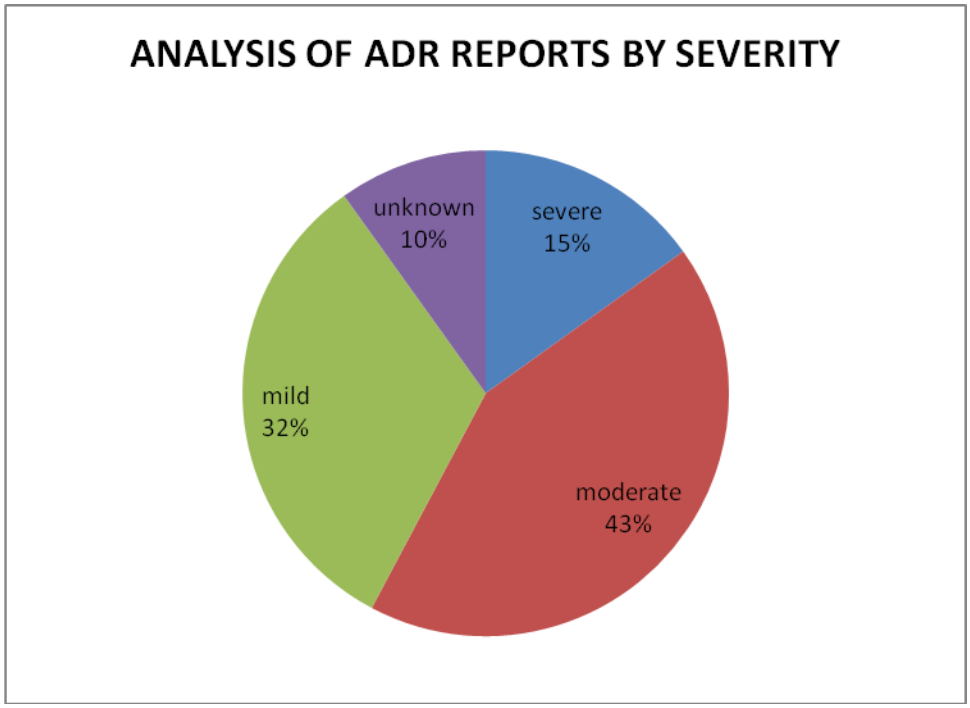

ADR REPORTS BY STATE (2009)
SELANGOR
WPKL
SABAH
PERAK
JOHOR
N SEMBILAN
P PINANG
MELAKA
SARAWAK
PAHANG
KELANTAN
TERENGGANU
KEDAH
PERLIS
PUTRAJAYA
UNKNOWN
WP LABUAN
0
200
400
600
800
1000
1200
1400
1600

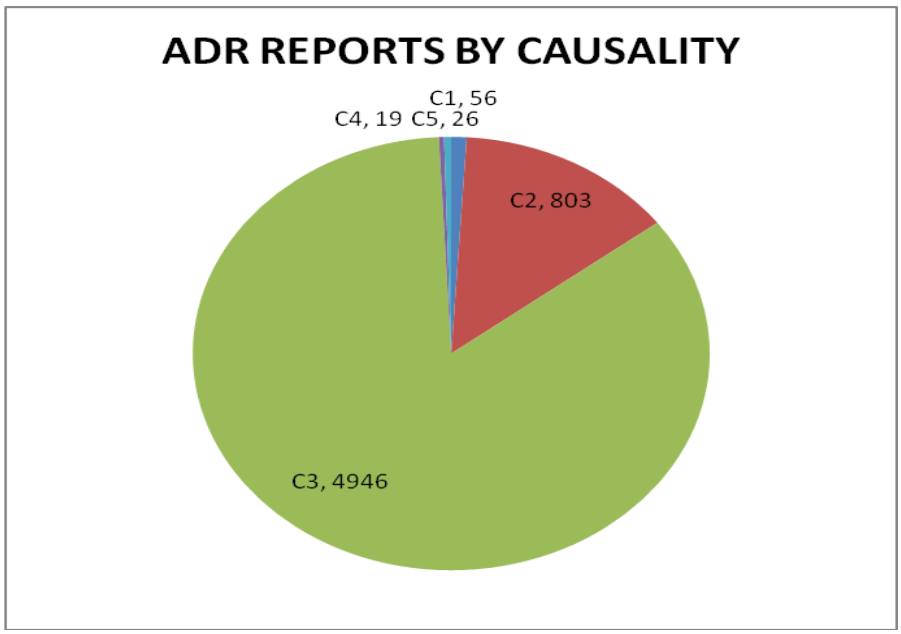

NO. OF ADVERSE DRUG REACTION REPORTS BY PRODUCT CATEGORY
Kosmetik
8
Produk Tidak Berdaftar
76
Produk Tradisional
97
Bukan Racun
286
Racun/Preskripsi
6038
0
1000
2000
3000
4000
5000
6000
7000
No. of Reports

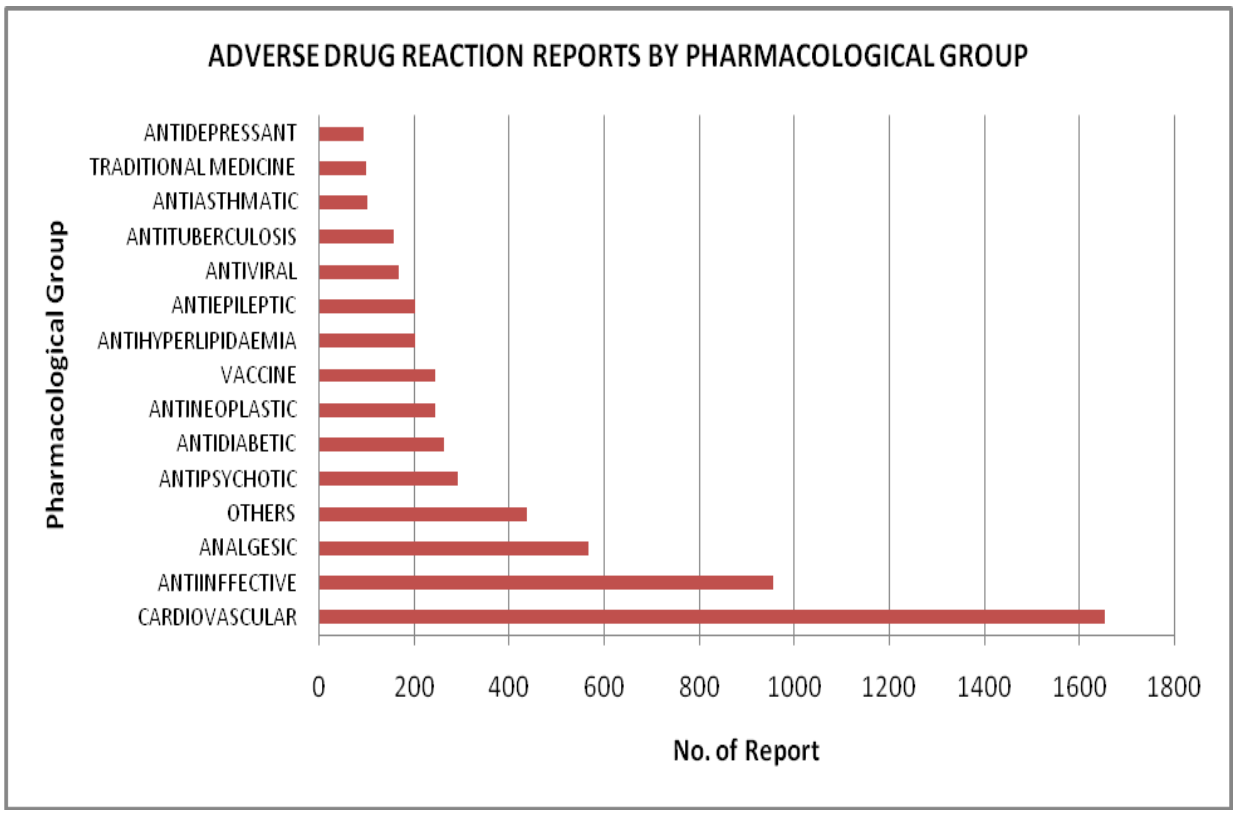

ADR REPORTS BY AGE CATEGORY
No. of Reports
1400
1200
1000
800
600
400
200
0
<1
1-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
90-99
Unknown
Age Category (Years)

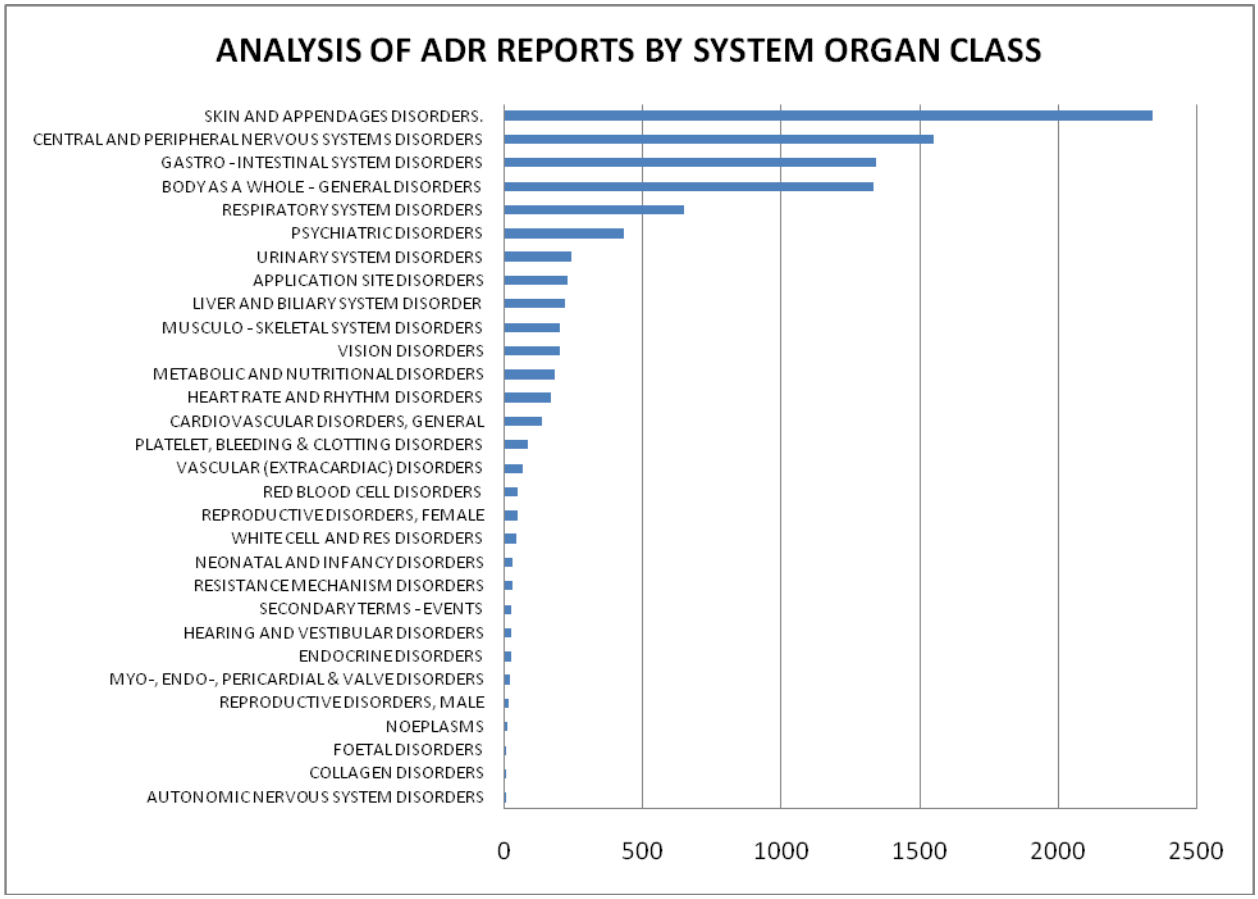

ADR REPORTS BY GENDER
Unknown
4%
Male
43%
Female
53%


ADR REPORTS BY RACE
No. of Reports
3000
2500
2000
1500
1000
500
0
Malay
Chinese
Others
Indian
Unknown
Race


ANALYSIS OF ADR REPORTS BY SEVERITY
unknown
10%
severe
15%
mild
32%
moderate
43%


ADR REPORTS BY CAUSALITY
C1, 56
C4, 19
C5, 26
C2, 803
C3, 4946


ADVERSE DRUG REACTION REPORTS BY PHARMACOLOGICAL GROUP
Pharmacological Group
ANTIDEPRESSANT
TRADITIONAL MEDICINE
ANTIASTHMATIC
ANTITUBERCULOSIS
ANTIVIRAL
ANTIEPILEPTIC
ANTIHYPERLIPIDAEMIA
VACCINE
ANTINEOPLASTIC
ANTIDIABETIC
ANTIPSYCHOTIC
OTHERS
ANALGESIC
ANTIINFFECTIVE
CARDIOVASCULAR
0
200
400
600
800
1000
1200
1400
1600
1800
No. of Report


ANALYSIS OF ADR REPORTS BY SYSTEM ORGAN CLASS
SKIN AND APPENDAGES DISORDERS.
CENTRAL AND PERIPHERAL NERVOUS SYSTEMS DISORDERS
GASTRO - INTESTINAL SYSTEM DISORDERS
BODY AS A WHOLE - GENERAL DISORDERS
RESPIRATORY SYSTEM DISORDERS
PSYCHIATRIC DISORDERS
URINARY SYSTEM DISORDERS
APPLICATION SITE DISORDERS
LIVER AND BILIARY SYSTEM DISORDER
MUSCULO - SKELETAL SYSTEM DISORDERS
VISION DISORDERS
METABOLIC AND NUTRITIONAL DISORDERS
HEART RATE AND RHYTHM DISORDERS
CARDIOVASCULAR DISORDERS, GENERAL
PLATELET, BLEEDING & CLOTTING DISORDERS
VASCULAR (EXTRACARDIAC) DISORDERS
RED BLOOD CELL DISORDERS
REPRODUCTIVE DISORDERS, FEMALE
WHITE CELL AND RES DISORDERS
NEONATAL AND INFANCY DISORDERS
RESISTANCE MECHANISM DISORDERS
SECONDARY TERMS - EVENTS
HEARING AND VESTIBULAR DISORDERS
ENDOCRINE DISORDERS
MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS
REPRODUCTIVE DISORDERS, MALE
NOEPLASMS
FOETAL DISORDERS
COLLAGEN DISORDERS
AUTONOMIC NERVOUS SYSTEM DISORDERS
0
500
1000
1500
2000
2500

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2003-2009)

NO	2003 (No. of Reports)	2004 (No. of Reports)	2005 (No. of Reports)	2006 (No. of Reports)	2007 (No. of Reports)	2008 (No. of Reports)	2009 (No. of Reports)
1	ALLOPURINOL (33)	ALLOPURINOL (37)	CAPTOPRIL (52)	TRADITIONAL MEDICINE (68)	PERINDOPRIL (97)	PERINDOPRIL (217)	AMLODIPINE (351)
2	CLOXACILLIN (30)	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC (65)	ALLOPURINOL (75)	ASPIRIN (134)	PERINDOPRIL (335)
3	MEFENAMIC ACID (25)	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)	CLOXACILLIN (71)	DICLOFENAC (111)	HYDROCHLORO - THIAZIDE (172)
4	DICLOFENAC (24)	NIFEDIPINE (28)	DICLOFENAC (44)	NIFEDIPINE (58)	DICLOFENAC (71)	AMLODIPINE (92)	DICLOFENAC (122)
5	CHLOROTHIAZIDE (22)	CO – TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)	METFORMIN (69)	METFORMIN (91)	ASPIRIN (114)
6	CARBAMAZEPINE (19)	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)	ASPIRIN (67)	TRADITIONAL MEDICINE (80)	METFORMIN (105)
7	TRADITIONAL MEDICINE (18)	AMOXYCILLIN (23)	PARACETAMOL (38)	CO – TRIMOXAZOLE (55)	TICLOPIDINE (50)	ALLOPURINOL (80)	LOVASTATIN (99)
8	AMOXYCILLIN (18)	MEFENAMIC ACID (21)	CO – TRIMOXAZOLE (37)	ASPIRIN (41)	RIFAMPICIN (46)	CO – TRIMOXAZOLE (73)	AMOXYCILLIN /CLAVULANATE (84)
9	PENICILLIN G SODIUM (15)	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)	PHENYTOIN (44)	HEPARIN (70)	TRADITIONAL MEDICINE (81)
10	VANCOMYCIN (15)	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)	AMOXYCILLIN (43)	LOVASTATIN (66)	CLOXACILLIN (80)

TEN BEST REPORTERS (HOSPITAL)

NO.	NAME OF HOSPITAL	NO. OF REPORTS
1.	HOSP. SELAYANG	242
2.	HOSP. KUALA LUMPUR	210
3.	HOSP. DUCHESS OF KENT	150
4.	HOSP. TUANKU JAAFAR	143
5.	HOSP. SULTANAH AMINAH	142
6.	HOSP. RAJA PEREMPUAN ZAINAB II	131
7.	HOSP. SERI MANJUNG	120
8.	HOSP. MELAKA	120
9.	HOSP. PAKAR SULTANAH FATIMAH	118
10.	HOSP. PULAU PINANG	112

TEN BEST REPORTERS (KLINIK KESIHATAN)

NO.	NAME OF CLINIC	NO. OF REPORTS
1.	KLINIK KESIHATAN SHAH ALAM	49
2.	KLINIK KESIHATAN PUCHONG	49
3.	KLINIK KESIHATAN SANDAKAN	44
4.	KLINIK KESIHATAN LUYANG	41
5.	KLINIK KESIHATAN MEDAN MAJU JAYA	33
6.	KLINIK KESIHATAN SERI KEMBANGAN	32
7.	KLINIK KESIHATAN KELANA JAYA	32
8.	KLINIK KESIHATAN AMPANGAN	25
9.	KLINIK KESIHATAN NIBONG TEBAL	24
10.	KLINIK KESIHATAN SEREMBAN	23

TEN BEST REPORTERS (OTHER HEALTH INSTITUTION)

NO.	NAME OF HOSPITAL	NO. OF REPORTS
1.	PUSAT PERUBATAN UNIVERSITI MALAYA	178
2.	SUBANG JAYA MEDICAL CENTRE	104
3.	PUSAT PERUBATAN UKM	98
4.	HOSP. FATIMAH	61
5.	HOSP. PAKAR PERUBATAN JOHOR (KPJ JOHOR)	23
6.	GLENEAGLES MEDICAL CENTRE	19
7.	HOSP. UNIVERSITI SAINS MALAYSIA	16
8.	PENANG ADVENTIST HOSPITAL	9
9.	KLINIK DR. TONG AND PATNERS	7
10.	COLUMBIA ASIA MEDICAL CENTRE	7