ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE
2006

1. MADRAC MEMBERS

Members of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) were as follows:

MADRAC Members/*(Alternate members)*	
Pn Eishah Binti A. Rahman Director of National Pharmaceutical Control Bureau. Ministry of Health Malaysia	Chairperson
Puan Sri Dr Suraiya H. Hussein*/(Dr. Gangaram Hemandas)* Consultant Dermatologist, Hospital Kuala Lumpur.	Committee Member
Dr. Sarfraz Manzoor Hussain Consultant Psychiatrist, Hospital Kuala Lumpur	Committee Member
Tan Sri Dato Dr R. P. Lingam Representative of the Malaysian Medical Association.	Committee Member
Prof Madya Jamiyah Hassan Ikhtisas Deputy Director 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)* Clinical Pharmacologist Medical Faculty, Universiti Kebangsaan Malaysia.	Committee Member
Dr G.R. Letchuman Ramanathan/*(Dr. Padmini Menon)* Consultant Physician, Hospital Ipoh.	Committee Member
Dr. S Ganesanathan Consultant Physician, Hospital Kuala Lumpur.	Committee Member
Dr. Mardziah Alias/*(Dr. Norzila Mohamed Zainudin)* Consultant Paediatrician, Hospital Kuala Lumpur	Committee Member
Pn Hasnah Ismail / *(Pn. Rosminah Mohd. Din)* Head of Assistant Director, Pharmaceutical Services Division, Ministry of Health.	Committee Member
Mr. Selvaraja Seerangam Secretary, Drug Control Authority, Ministry of Health	Committee Member
Puan Abida Syed Haq Head, Centre for Post Registration, NPCB, Ministry of Health	Secretary

2. MEETINGS

The committee met six times over the year and a total of 2583 adverse drug reaction reports were reviewed.

Meeting	89 01/06	90 03/06	91 05/06	92 07/06	93 09/06	94 11/06
No Of Reports	456	307	386	450	540	444

3. ANALYSIS OF ADR REPORTS

A detailed review and analysis of the ADR reports received during the year 2006 was conducted (Ref: Appendix 1)

4. REGULATORY ACTIONS

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

PRODUCTS	REGULATORY ACTIONS IMPLEMENTED	DCA MEETING
IRESSA	The DCA at its 165th meeting made a decision to disallow the promotion of IRESSA in Malaysia based on the findings of IRESSA Survival Evaluation Study (ISEL). The study showed that IRESSA failed to significantly prolong survival in comparison to placebo in the overall population or in patients with adenocarcinoma. <Signal> on safety was also reported in Japan on the risk of Interstitial Lung Disease (ILD) in patients who have been treated with IRESSA. Following that decision, AstraZeneca forwarded an appeal to the DCA to support the use of IRESSA as a monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies and to support the lifting of the current restriction on promotion of IRESSA in Malaysia. The appeal was based on efficacy and safety aspects. Efficacy aspect: *i. In the ISEL study, IRESSA has demonstrated a statistically significant and clinically relevent survival advantage to best supportive care in a pre-planned subgroup of patients of Asian racial origin in a second/third line treatment setting* *ii. The IRESSA Expanded Access Programme in Malaysia has shown that IRESSA benefits patients across races in Malaysia* Safety aspect : *i. As of January 2006, of the 827 patients who were treated with IRESSA, only 2 cases of ILD were reported in Malaysia. (reporting rate*	**181 (May 2006)**

	0.24%. Reporting rate in the rest of the world :other South East Asian countries excluding Japan : 0.23%)) *MADRAC has agreed to the comprehensive monitoring programme of adverse events of IRESSA proposed by AstraZeneca (pharmacovigilance activities and risk mitigation strategies).* Based on this review, the DCA lifted the restriction on promotion of IRESSA in Malaysia.	
Promethazine In Children	The US FDA, after reviewing the safety profile of Promethazine has announced that all medications containing promethazine hydrochloride should not be used for children less than two years old due to the potential for fatal respiratory depression . The US FDA has received reports of serious adverse events including seven deaths in children under two. Based on this information, the DCA has decided that the following warning statement should be included in the package inserts of all products containing promethazine hydrochloride: ***"It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression".***	**DCA 181 (May 2006)**
Gatifloxacin	Following the serious cases of both hypoglycaemic and hyperglycaemia reported with gatifloxacin during post marketing surveillance, the US FDA has directed the labeling of all products containing gatifloxacin to be reviewed. The updates include labeling changes to strengthen the existing WARNING on hypoglycaemia and hyperglycaemia and add a CONTRAINDICATION for use in diabetic patients. Due to these safety concerns, the DCA has decided to cancel the registration of all products containing gatifloxacin. For products which have been registered and marketed, a period of 6 months is given to the product holder to withdraw all relevant products from the market. Meanwhile, the product holder is required to issue a 'Dear Healthcare Professional' letter to inform of this safety issue. The DCA will not consider any new registration of products containing gatifloxacin in the future.	**DCA 181 (May 2006)**
Black Cohosh	The "Medicines and Healthcare Products Regulatory Agency" (MHRA) and "European Medicines Agency" (EMEA) have been made aware of a number of case reports of hepatoxicity in patients using *Cimicifugae Racemosae.* Based on a review done, MHRA has decided to include a safety warning about 'serious hepatic reactions' to the labels of black cohosh products whereas EMEA issued precautionary advice to patients and healthcare professionals. In Malaysia, Black Cohosh has been classified as a traditional	**DCA 183 (July 2006)**

	medicine which can be bought without prescription and is easily accessible. Therefore, the DCA agreed with MADRAC's proposal that all black cohosh products should carry the following precautionary statement: • ***Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately.*** • ***Patients using herbal medicinal products should tell their doctor about it.***	
Arginine	The Journal of the American Medical Association (JAMA) has published the results of a study on L-Arginine Therapy in Acute Myocardial Infarction (AMI). The study was investigating the possible benefits of L-Arginine on cardiovascular parameters following AMI but was stopped as a result of six deaths. In view of the finding that L-Arginine did not improve cardiovascular circulation after the first heart attack but could increase the risk of death if used after a heart attack, Health Canada and TGA have decided all L-Arginine products must carry a warning on their labels that reflects the current safety information. Therefore, the DCA at its 185th meeting agreed that the following warning must be included on labels and package inserts of oral health supplement products containing L-Arginine: ***"Arginine is not recommended for patients following a heart attack"***	**DCA 185 (September 2006)**
ACE Inhibitors	The New England Journal of Medicine published the results of a cohort study on the association between exposure to ACE Inhibitors in 1st trimester of pregnancy and the risk of congenital malformations. The results reported that exposure to ACE inhibitors during the 1st trimester cannot be considered safe and should be avoided. Based on this new finding, USFDA and Health Canada have directed that all ACE Inhibitors should carry a statement of this safety warning and recommend discontinuation of the affected drugs as soon as possible if a patient becomes pregnant. Following the safety concern, the DCA made the decision to strengthen the labeling of ACE inhibitors in Malaysia. All ACE inhibitors products should carry the following statement under "Warning" and "Use in Pregnancy" section :- ***"Increased risk of birth defects, fetal and neonatal morbidity and death when used throughout pregnancy".***	**DCA 186 (October 2006)**

4.2 Review of Periodic Safety Update Reports (PSURs)

Over the year, the Periodic Safety Update Reports (PSURs) submitted by the industry for the New Chemical Entities registered by the DCA were reviewed and where necessary, the product registration holders were instructed to update the package inserts to reflect new safety data and findings.

5. ACTIVITIES

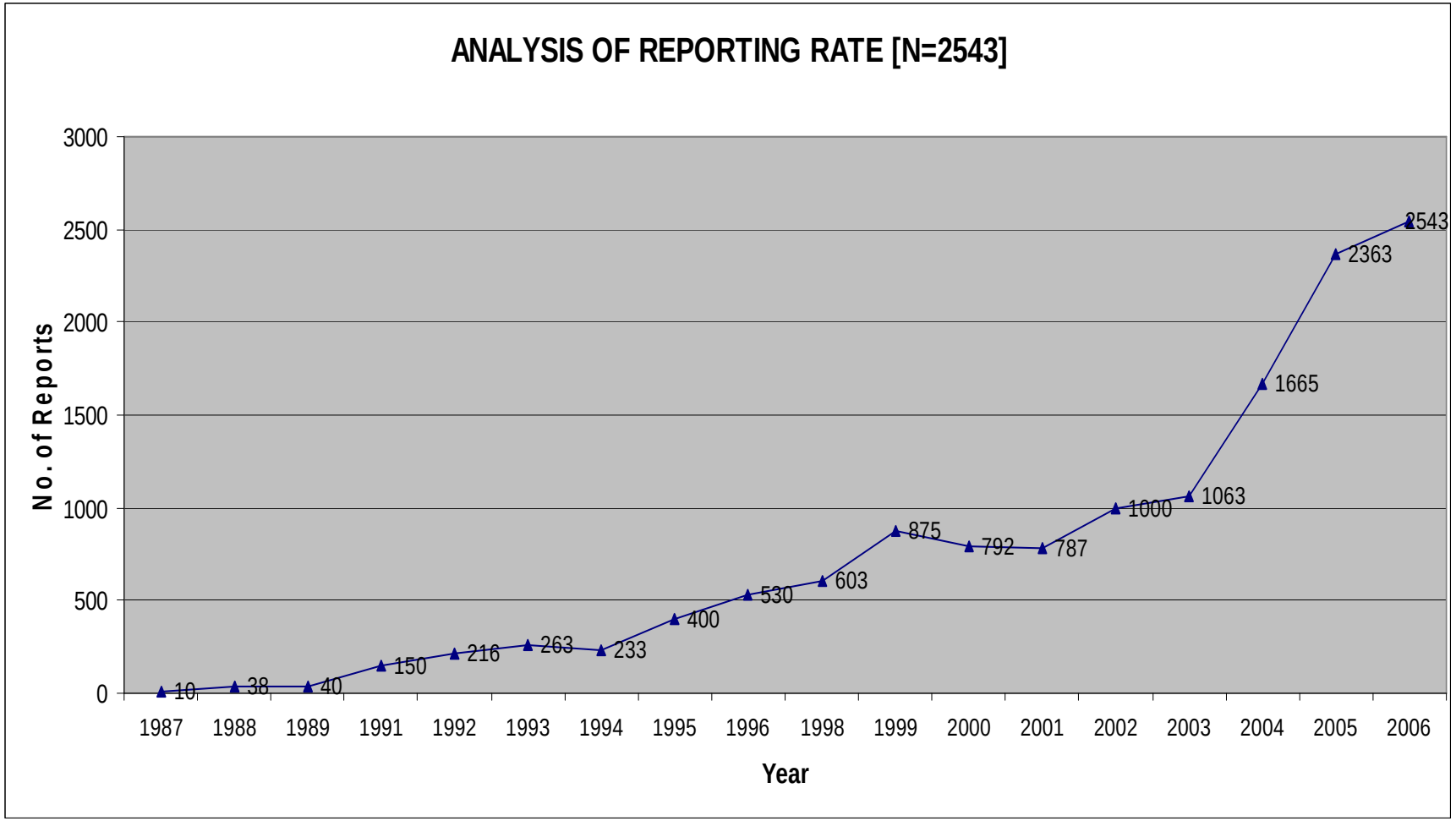
MADRAC members conducted several talks over the year in an effort to promote ADR reporting as well as to update health professionals on issues related to drug safety

NO.	TITLE OF PRESENTATION	FORUM	PLACE	DATE
1.	ADR Monitoring	CPD Programme	Kuala Lumpur	3 Mac 2006
2.	ADR Monitoring	CPD Programme	Sarawak	7 April 2006
3.	ADR Monitoring and Product Complaint	GSP Seminar	Alor Setar, Kedah	24 April 2006
4.	ADR Monitoring	PTK6 Seminar	Kuala Lumpur	9 June 2006
5.	Quality & Safety of Cosmetic	International Symposium on Food and Drug Regulations	Riyadh, Saudi Arabia	22 May 2006
6.	Pharmacovigilance in Emerging Nations	Future Perspectives on Pharmacovigilance	Italy	30 June 2006
7.	Pharmacovigilance and ADR Monitoring	PTK6 Seminar	Kuala Lumpur	4 Jualy 2006
8.	Talk for Pharmacist (Master Student)	Masters Program for Clinical Pharmacists	Kuala Lumpur	21 July 2006
9.	ADR Monitoring – The Role of Pharmacist Assistant	Pharmacist Assistant Seminar	Taiping, Perak	3 Sept. 2006
10.	Case Study on Product Recall	KPDN Seminar	Kuala Lumpur	28 Nov.2006
11.	R&D in Pharmacy Practice – Smart Partnerships with Industry	National Pharmacy R&D Conference	Melaka	30 Nov. 2006
12.	Pharmacovigilance and ADR Monitoring	CPD Program	Putrajaya	8 & 15 Dec 2006

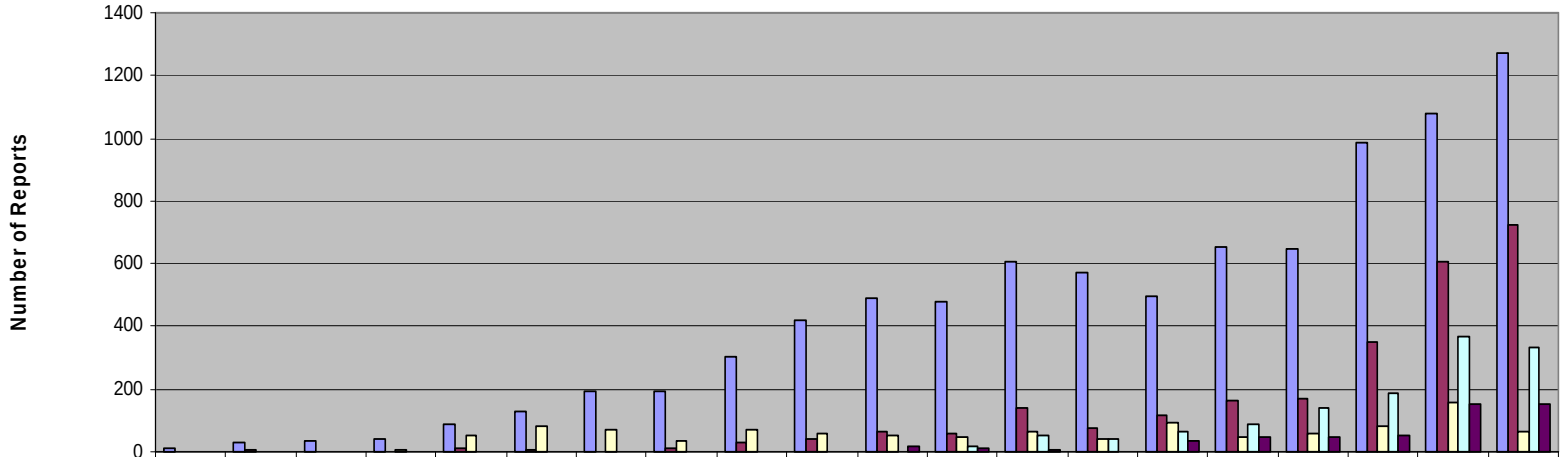
6. WORLD HEALTH ORGANISATION

2491 ADR reports reviewed by MADRAC were submitted to the International Centre for Drug Monitoring (WHO) in Upssala, Sweden.

APPENDIX 1

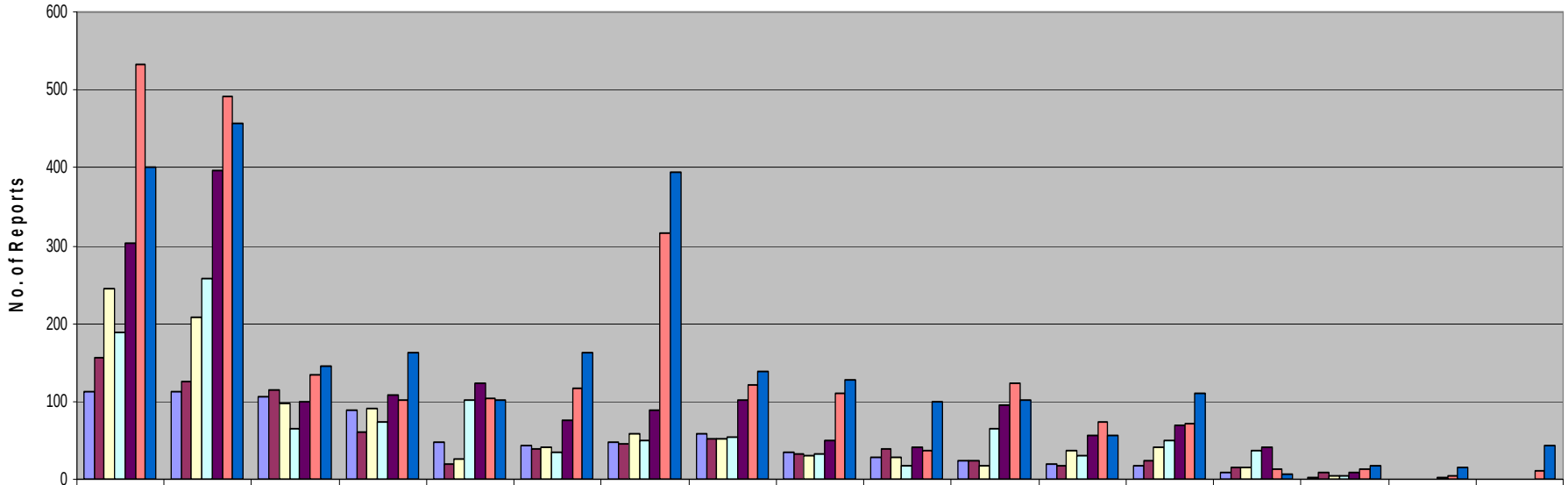

ANALYSIS OF REPORTING RATE [N=2543]
No. of Reports
3000
2500
2000
1500
1000
500
0
10
38
40
150
216
263
233
400
530
603
875
792
787
1000
1063
1665
2363
2543
1987
1988
1989
1991
1992
1993
1994
1995
1996
1998
1999
2000
2001
2002
2003
2004
2005
2006
Year

ADR REPORTS BY REPORTER (N=2543)



	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Government Doctors	10	32	36	39	87	129	193	191	303	419	489	480	608	573	496	651	646	988	1079	1273
Others (Pharmacist, Dentist)	0	3	2	1	12	6	2	9	27	40	62	61	141	74	118	162	169	352	606	726
GP/Private Specialist	0	1	2	4	51	81	68	33	70	61	51	44	66	38	94	49	60	83	157	64
Company	0	0	0	0	0	0	0	0	0	0	1	18	54	43	67	90	141	188	368	330
University	0	0	0	0	0	0	0	0	0	0	16	11	7	0	36	47	47	54	153	150

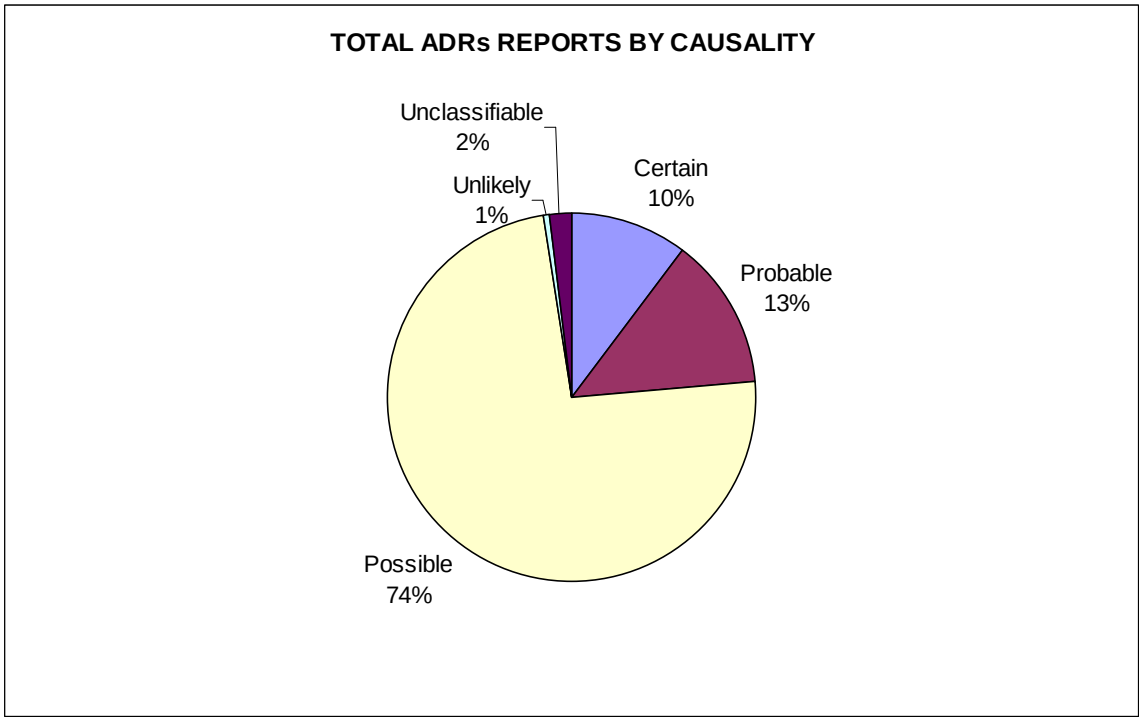
TOTAL ADRs REPORT BY STATE [n=2543]

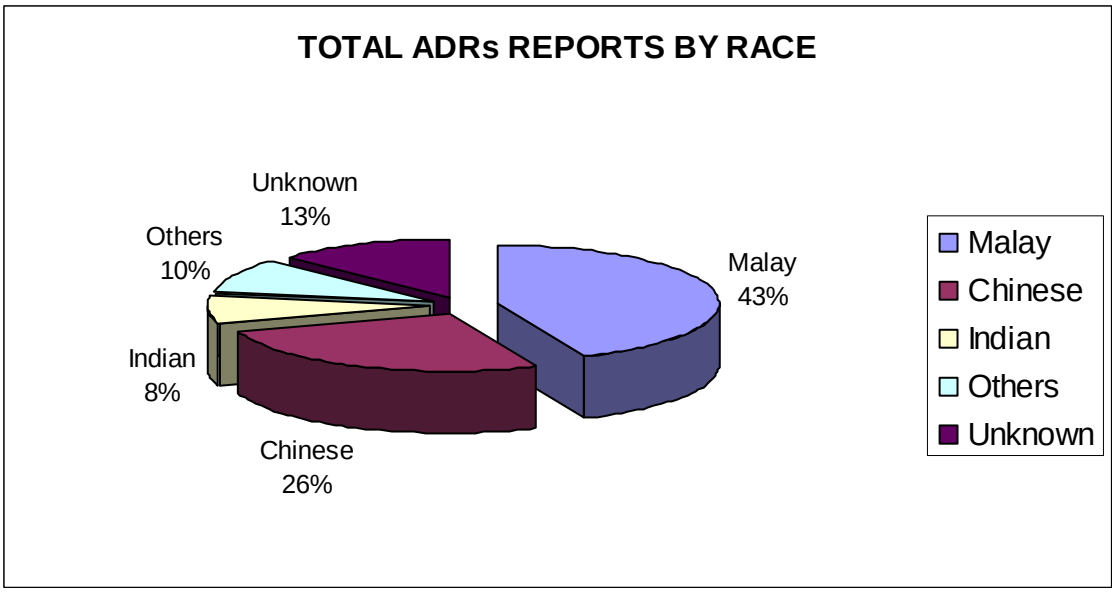


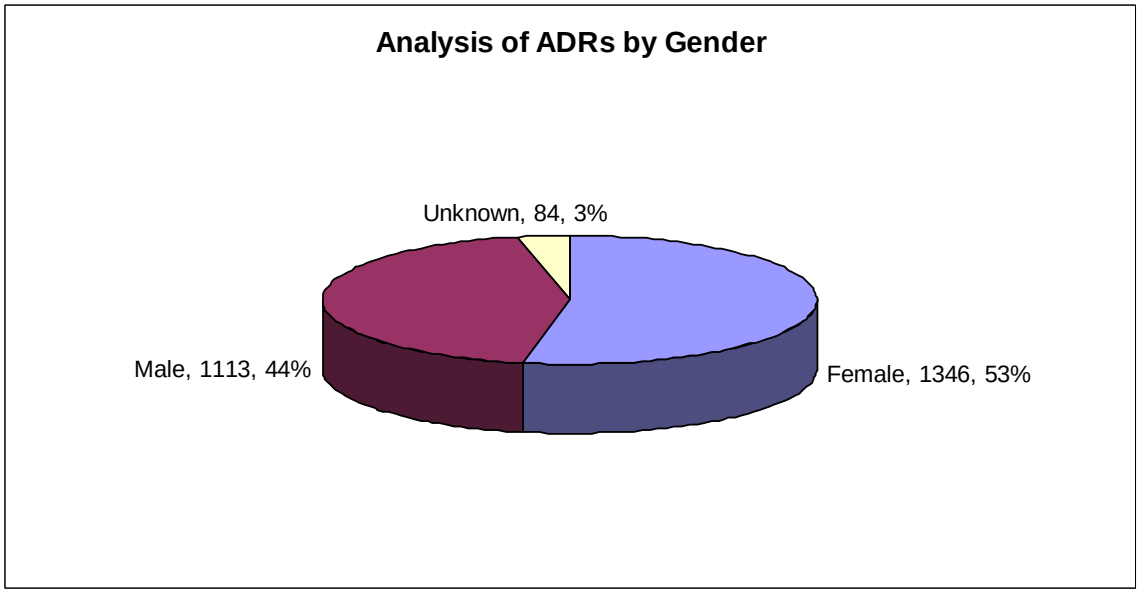
	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N SEMBILAN	P PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	39	46	53	32	38	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0
2003	188	257	66	74	102	34	50	54	33	17	65	30	50	36	5	1	1
2004	304	397	100	109	124	76	88	102	49	42	96	56	69	42	8	3	1
2006	532	491	134	101	105	116	316	121	110	36	123	73	72	14	13	5	11
2006	401	456	146	163	102	162	394	138	128	100	101	57	110	7	18	16	44

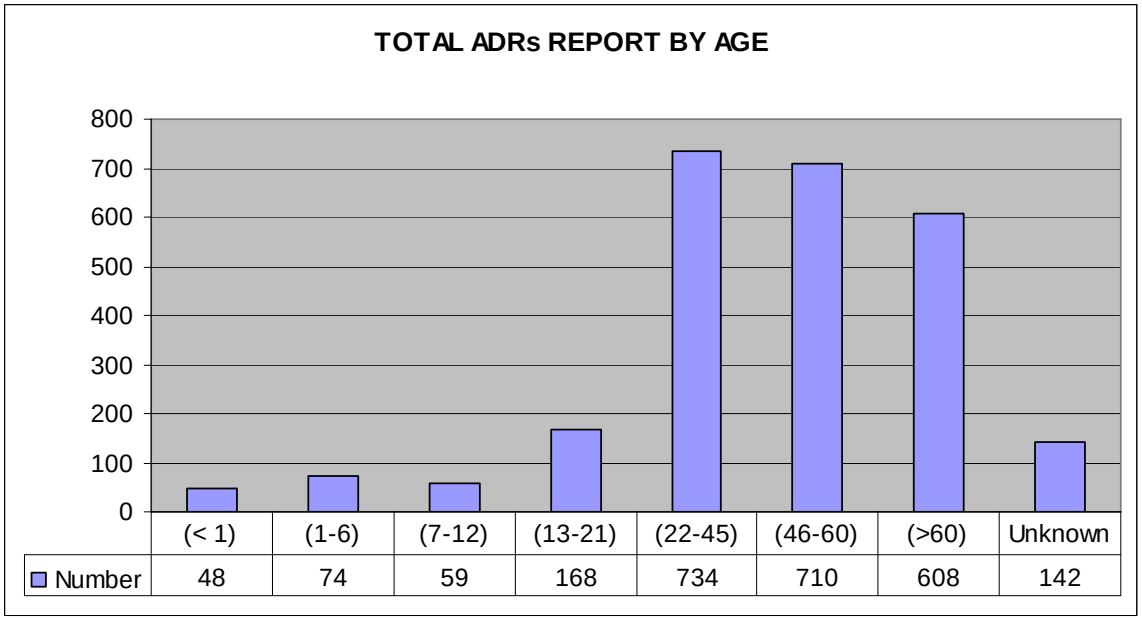
TOP TEN REPORTERS (INSTITUITION) – 2006

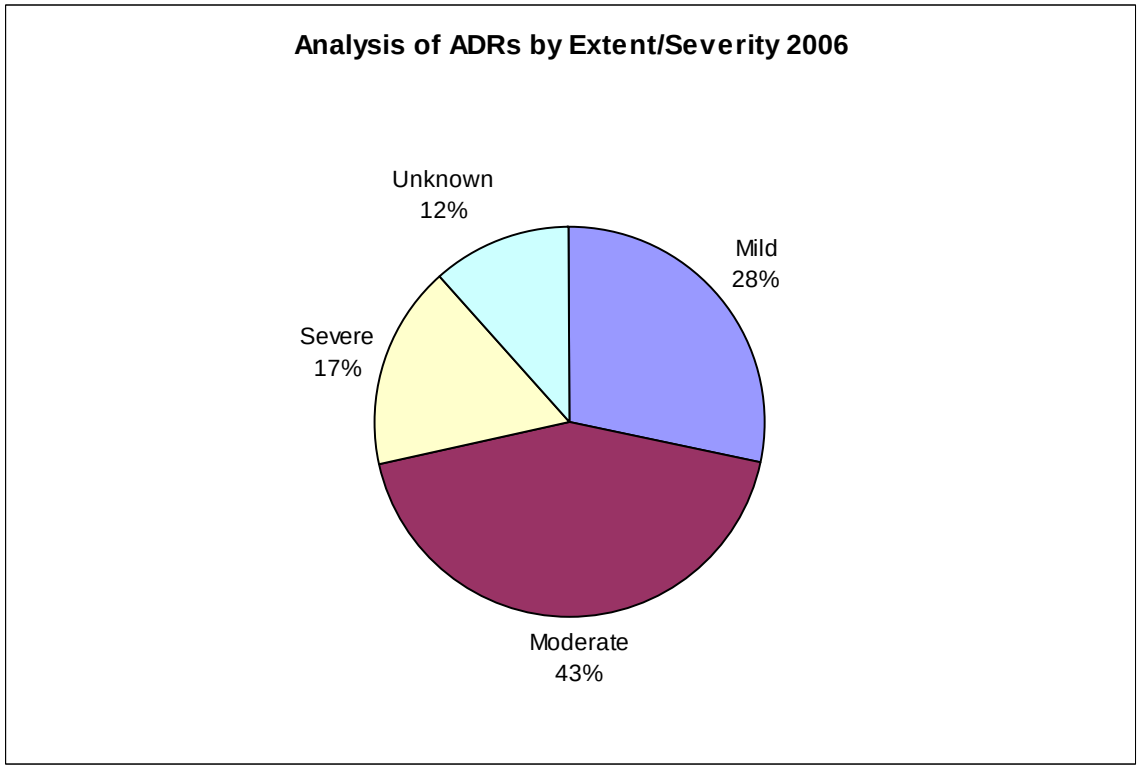
NAME OF INSTITUTION	NO. OF REPORTS
H Duchess of Kent	229
H Kuala Lumpur	182
H Selayang	112
H Pulau Pinang	107
H Tawau	100
H Seremban	94
H Melaka	81
H Hospital Sultanah Aminah	68
H Ipoh	67
Hospital Tengku Ampuan Afzan	52

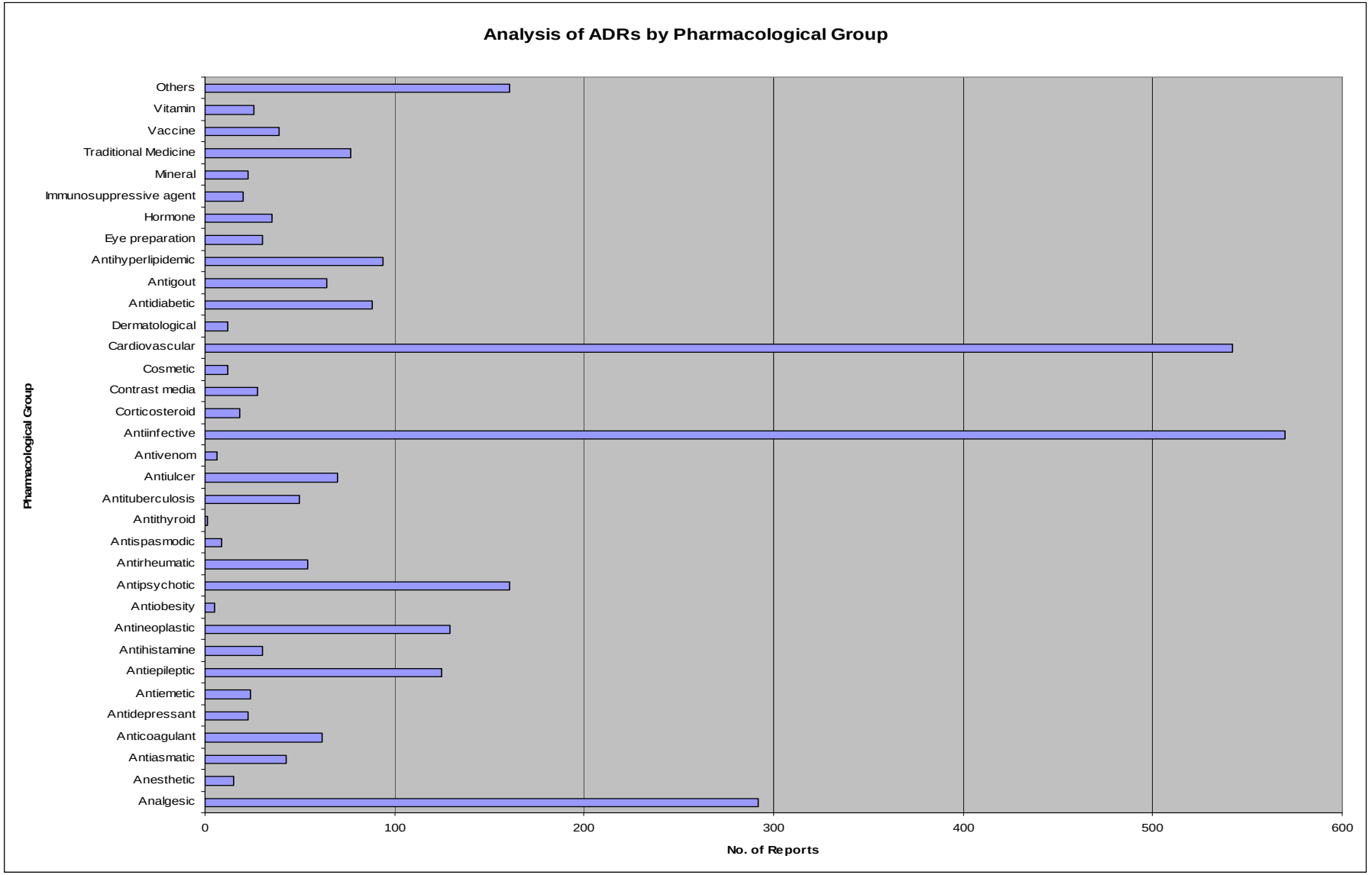


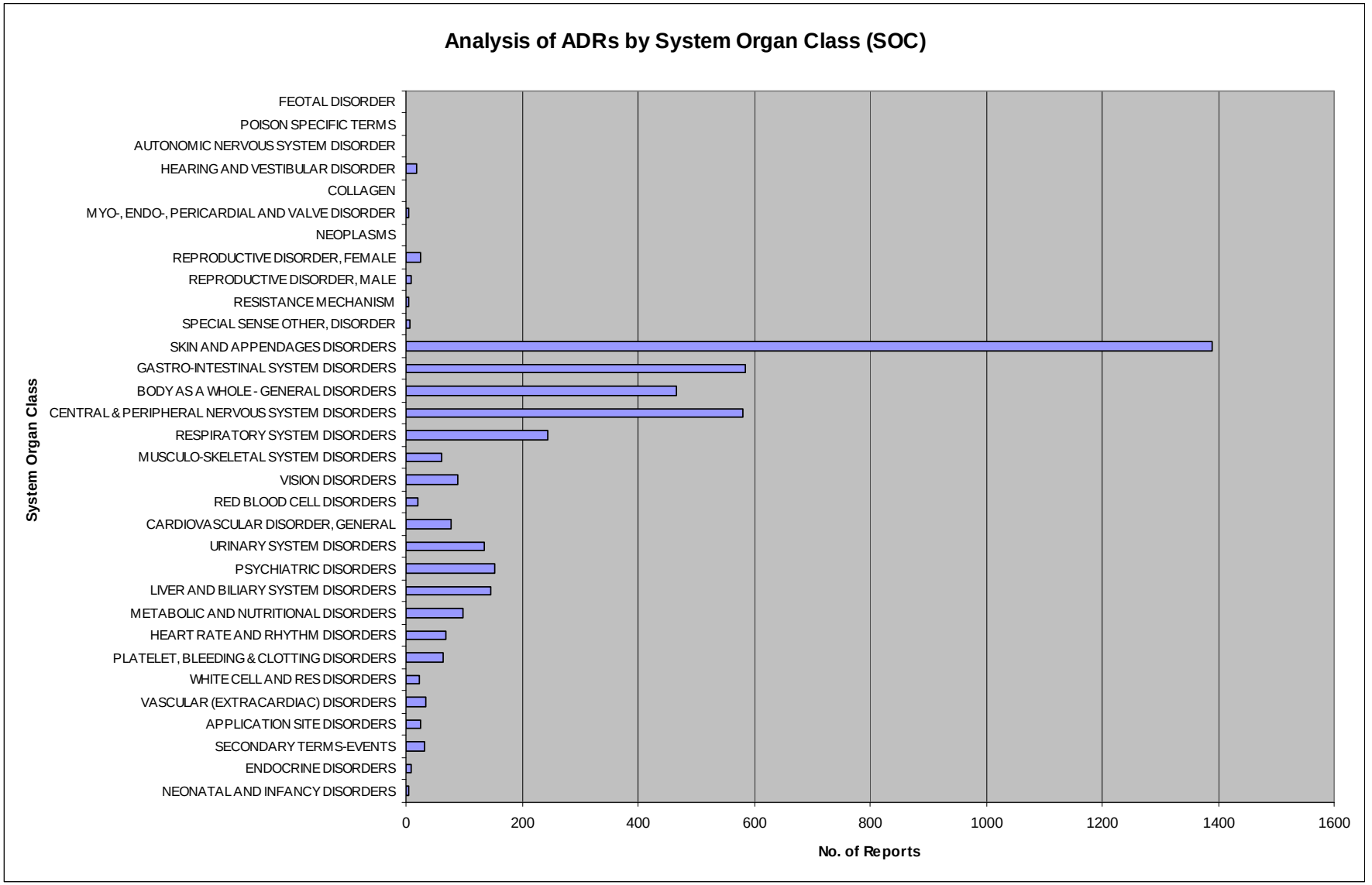

TOTAL ADRs REPORTS BY RACE
Unknown
13%
Others
10%
Indian
8%
Chinese
26%
Malay
43%
Malay
Chinese
Indian
Others
Unknown


Analysis of ADRs by Gender
Unknown, 84, 3%
Male, 1113, 44%
Female, 1346, 53%


TOTAL ADRs REPORT BY AGE
800
700
600
500
400
300
200
100
0
(< 1)
(1-6)
(7-12)
(13-21)
(22-45)
(46-60)
(>60)
Unknown
Number
48
74
59
168
734
710
608
142


Analysis of ADRs by Extent/Severity 2006
Unknown
12%
Mild
28%
Severe
17%
Moderate
43%


Analysis of ADRs by Pharmacological Group
Pharmacological Group
Others
Vitamin
Vaccine
Traditional Medicine
Mineral
Immunosuppressive agent
Hormone
Eye preparation
Antihyperlipidemic
Antigout
Antidiabetic
Dermatological
Cardiovascular
Cosmetic
Contrast media
Corticosteroid
Antiinfective
Antivenom
Antiulcer
Antituberculosis
Antithyroid
Antispasmodic
Antirheumatic
Antipsychotic
Antiobesity
Antineoplastic
Antihistamine
Antiepileptic
Antiemetic
Antidepressant
Anticoagulant
Antiasmatic
Anesthetic
Analgesic
0
100
200
300
400
500
600
No. of Reports


Analysis of ADRs by System Organ Class (SOC)
System Organ Class
FEOTAL DISORDER
POISON SPECIFIC TERMS
AUTONOMIC NERVOUS SYSTEM DISORDER
HEARING AND VESTIBULAR DISORDER
COLLAGEN
MYO-, ENDO-, PERICARDIAL AND VALVE DISORDER
NEOPLASMS
REPRODUCTIVE DISORDER, FEMALE
REPRODUCTIVE DISORDER, MALE
RESISTANCE MECHANISM
SPECIAL SENSE OTHER, DISORDER
SKIN AND APPENDAGES DISORDERS
GASTRO-INTESTINAL SYSTEM DISORDERS
BODY AS A WHOLE - GENERAL DISORDERS
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS
RESPIRATORY SYSTEM DISORDERS
MUSCULO-SKELETAL SYSTEM DISORDERS
VISION DISORDERS
RED BLOOD CELL DISORDERS
CARDIOVASCULAR DISORDER, GENERAL
URINARY SYSTEM DISORDERS
PSYCHIATRIC DISORDERS
LIVER AND BILIARY SYSTEM DISORDERS
METABOLIC AND NUTRITIONAL DISORDERS
HEART RATE AND RHYTHM DISORDERS
PLATELET, BLEEDING & CLOTTING DISORDERS
WHITE CELL AND RES DISORDERS
VASCULAR (EXTRACARDIAC) DISORDERS
APPLICATION SITE DISORDERS
SECONDARY TERMS-EVENTS
ENDOCRINE DISORDERS
NEONATAL AND INFANCY DISORDERS
0
200
400
600
800
1000
1200
1400
1600
No. of Reports

ANALYSIS OF ADR REPORTS RECEIVED WITH FATAL OUTCOME

DRUG	ADR	ASSESMENT
Ticlopidine	Gastrointestinal Tract Bleed NOS	Died – Due to Adverse Reaction
Perphenazine	Neuroleptic Malignant Syndrome	Died – Due to Adverse Reaction
Imatinib	Septicaemia Anaemia Disease Progression	Died – Due to Adverse Reaction
Ertapenem	Medicine ineffective (Diseases progression)	Drug maybe contributory
Celecoxib	Tachycardia ventricular Myocardial infarction	Drug maybe contributory
Sildenafil	Aneurysm Renal Artery	Drug maybe contributory
Carvedilol	Medicine Ineffective (Disease Progression)	Drug maybe contributory
Bi Ton Wan (Unregistered Product)	Jaundice	Drug maybe contributory
Mefenamic Acid	Vomiting Epigastric Pain	Drug maybe contributory
Chlorpromazine	Acute Coronary Syndrome	Drug maybe contributory
Lenogastrim	Sepsis Acute Megakaryoblastic Leukaemia	Drug maybe contributory
Parecoxib	Unconsciousness	Drug maybe contributory
Rofecoxib	Cerebellar Infarction Dizziness Myocardial Infarction	Drug maybe contributory
Imatinib	GI Haemorhage	Drug maybe contributory
Bortezomib	Renal Failure Acute Septicaemia Shock	Drug maybe contributory
Linezolid	Steven Johnson Syndrome	Drug maybe contributory
Varicella Zoster Inactivated Virus Vaccine	Milk aspiration	Died unrelated to drug
Indapamide	Lethargy Hypokalaemia Tinnitus Giddiness Hyponatraemia Breathing abnormal	Died unrelated to drug

**** This information is confidential

TEN DRUGS WITH THE MOST REPORTED ADRs

NO.	2000	2001	2002	2003	2004	2005	2006
1	CO-TRIMOXAZOLE (47)	CLOXACILLIN (34)	CO-TRIMOXAZOLE (36)	ALLOPURINOL (33)	ALLOPURINOL (37)	CAPTOPRIL (52)	TRADITIONAL MEDICINE (68)
2	DICLOFENAC (33)	CARBAMAZEPINE (33)	CARBAMAZEPINE (32)	CLOXACILLIN (30)	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC SODIUM (65)
3	AMOXYCILLIN (23)	CO-TRIMOXAZOLE (23)	CLOXACILLIN (31)	MEFENAMIC ACID (25)	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)
4	CARBAMAZEPINE (23)	ENALAPRIL (23)	AMOXYCILLIN (28)	DICLOFENAC (24)	NIFEDIPINE (28)	DICLOFENAC SODIUM (44)	NIFEDIPINE (58)
5	CLOXACILLIN (15)	DICLOFENAC (20)	ALLOPURINOL (22)	CHLOROTHIAZIDE (22)	CO-TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)
6	ALLOPURINOL (15)	PERINDOPRIL (19)	TRADITIONAL MEDICINES (22)	CARBAMAZEPINE (19)	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)
7	IBUPROFEN (14)	ALLOPURINOL (17)	ALENDRONATE SODIUM (19)	TRADITIONAL MEDICINES (18)	AMOXYCILLIN (23)	PARACETAMOL (38)	CO-TRIMOXAZOLE (55)
8	NIFEDIPINE (13)	AMOXYCILLIN (17)	DICLOFENAC (19)	AMOXYCILLIN (18)	MEFENAMIC ACID (21)	CO-TRIMOXAZOLE (37)	ASPIRIN (41)
9	ASPIRIN (12)	GENTAMICIN (13)	ISOSORBIDE DINITRATE (18)	PENICILLIN G SODIUM (15)	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)
10	PHENYTOIN (12)		LOVASTATIN (13)	VANCOMYCIN (15)	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)