ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (MADRAC) 2008

1. MADRAC MEMBERS

MADRAC Members	Alternate Members	Position
En. Selvaraja Seerangam		Chairman
Pn. Fuziah Abdul Rashid		Secretary
Pn. Sri Datuk Dr. Suraiya Hani Tun Hussein	Dr. Gangaram Hemandas	Committee Member
Prof. Dr. Rahmat b. Awang	Dr. Abdul Fatah Hj. Abdul Rahman	Committee Member
Prof. Dr. Nik Aziz b. Sulaiman	Prof. Dr. Ima Nirvana Soelaiman	Committee Member
Dr. G. R. Letchumanan a/l Ramanathan	Dr. Patmini Menon	Committee Member
Dr. Ganesananthan Shanmuganathan	Dr. Rosaida Hj. Mohd. Said	Committee Member
En. Mohd. Hatta b. Ahmad	Pn. Rosminah bt. Mohd. Din	Committee Member
Dr. Sarfraz b. Manzoor Hussain		Committee Member
Tan Sri Datuk Dr. R. P. Linggam		Committee Member
Prof. Jamiyah bt. Hassan		Committee Member
Dr. Norzila Mohamed Zainudin		Committee Member
Dr. Balachandran Satiamurti		Committee Member
Pn. Abida Haq bt. Syed M. Haq		Committee Member
Pn. Tan Lie Sie		Committee Member

2. MEETINGS

The committee met six times over the year and a total of 4487 adverse drug reactions reports were reviewed.

Meeting No.	101	102	103	104	105	106
Date	24/01/2008	22/05/2008	25/03/2008	24/07/2008	18/09/2008	13/11/2008
No. of Reports	760	506	638	1088	811	684

3. ANALYSIS OF ADVERSE DRUG REACTIONS REPORTS

A detailed review and analysis of the adverse drug reactions (ADR) reports received during the year 2008 was conducted (Appendix 1).

4. REGULATORY ACTIONS

a. 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.	103	Cardiamed Injection 1mg/1mL (4mL ampoule)	**Suspension of Registration Due to Seriousness of Adverse Drug Reactions** - MADRAC received seven ADR reports from two hospitals related to the usage of this product in February 2008. - Adverse reactions reported were gangrene and peripheral cyanosis. - According to the package insert, ñGangrene has been reported in a lower extremity when infusions of noradrenaline were given in an ankle veinò - Investigations were done and it was found that the product had been given to the patients in accordance to the administration method recommended in the product information. - It was also determined that 3 batches of the product were involved in these adverse reactions reports, which were voluntarily recalled from the market by the marketing authorization holder. - Other hospitals were contacted to get feedback on whether similar ADR reports had been observed. A further 10 ADR reports were received related to these 3 batches as well as other batches. - Due to the seriousness of the adverse reactions, the DCA has agreed to MADRACôs proposal to suspend the registration of this product and to monitor if such serious adverse reactions happen to the other noradrenaline product that is available in the market.	DCA 205 29/05/2008

2.	103	Oral tablets/capsules and injectable products containing salbutamol and terbutaline	**To Include Warning on Myocardial Ischaemia in Pregnant Women Receiving Oral Tablets/Capsules or Injectable Salbutamol or Terbutaline Products to Delay Premature Labour** - A review of safety data in published literature, spontaneous reports and clinical trials done by GlaxoSmithKline Canada found that worldwide, there were 17 incidences of myocardial ischaemia reported related to the use of salbutamol injection to delay premature labour. Eleven of the reports were classified as serious which included one death. However, 12 patients recovered without sequelae. - None reported for inhaled salbutamol. - Salbutamol and other beta agonist products used for this purpose are not indicated in Canada and Malaysia. - In Malaysia, salbutamol and terbutaline have been used for this purpose (off label use). - Hence, MADRAC has decided the following warning statements must be included in the product information leaflet:- - For injectable products:- ▪ As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 ï agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. ▪ Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patientôs cardiovascular status	DCA 205 29/05/2008

			should be made by a physi cian experienced in cardiology. ▪ Cautious use of salbutamol/terbutaline injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractibility. During IV infusion of salbutamol/terbutaline, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. - For oral products:- ▪ As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 ï agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. ▪ Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patientôs cardiovascular status should be made by a physi cian experienced in cardiology. - No warning statements need to be included in syrup, suspension and inhalation products because they are not used for such purpose.	
3.	105	Gamat Emulsion (MAL05061509TC) Gamatogen (MAL20041083TCE)	**Suspension of Registration Due to Seriousness of Adverse Drug Reactions** - Up to August 2008, MADRAC received 29 ADR reports from a few local hospitals related to oral ñGamat/sea cucumber (Stichopus horrens)ò products marketed under company Healwell	DCA 207 04/08/08

			Pharmaceuticals. - Sixteen of these ADR reports were renal related and four patients did not have any concomitant medications or disease. - Due to the serious nature of the reported ADRs received, the DCA decided to suspend all registered oral ñGamatò products of said company until further safety investigations have been completed. - The DCA also decided that market recall of the suspended products should be done.	
4.	106	Unihepa 5000IU/mL Injection (MAL20051411A) Unihepa 50IU/5mL Injection (MAL20012728A)	**Suspension of Registration Due to Contamination with Over-Sulphated Chondroitin Sulphate** - In February 2008 the USFDA reported receiving an increasing number of ADR reports related to a few batches of multi-dose heparin sodium products. - Adverse reactions reported were of allergic/anaphylactoid type symptoms including profound hypotension, bronchospasm and gastrointestinal symptoms. - Investigations were done and the heparin was found to be contaminated with over-sulphated chondroitin sulphate (OSCS). - These productsô crude heparin/active pharmaceutical ingredients were porcine-based from China and United States of America. - OSCS has the same structure as heparin and it does not occur naturally nor a byproduct of manufacturing. - Marketing authorization holders for all registered heparin products (unfractionated and fractionated) were instructed to screen for OSCS according to the methods suggested by the USFDA. - All local companies that manufactured heparin informed that screening results of their products were free from OSCS. - However, in September 2008 MADRAC was informed of a number of ADR reports related to Unihepa 5000IU. A total of 41 ADR	DCA 209 25/09/2008

			reports were received through Duopharma from 5 Dialysis Centres, with one Centre submitting 18 reports. - Screening was done and it was confirmed that two batches of Unihepa were contaminated with OSCS arising from one particular lot of Active Pharmaceutical Ingredient (raw material). - The registration of Unihepa 5000IU/mL Injection and Unihepa 50IU/5mL Injection was immediately suspended and a recall ordered for all batches of Unihepa manufactured using the batch of raw material that was contaminated with OCSC.	
5.	106	Systemic Fluoroquinolone Antimicrobials	**Additional Warning on Tendonitis and Tendon Rupture** - Based on analysis of ADR reports received, the USFDA found that tendonitis and tendon rupture were related to the usage of fluoroquinolone antimicrobials. - Despite having ñtendonitisòand ñtendon ruptureòstated in the product information leaflet, the USFDA continued to receive many ADR reports on this. - The USFDA has recommended all manufacturers of fluoroquinolone antimicrobials to include a boxed warning in addition to the already stated information on ñtendonitisòand ñtendon ruptureò - The DCA has agreed to MADRACôs proposal that all marketing authorization holders of fluoroquinolone antimicrobials include the following information in the product information leaflet:- ***<u>ëSpecial Warnings and Precaution for Use':</u>*** **Musculo – skeletal system:** **"The risk of developing fluoroquinolone-associated tendonitis**	DCA 210

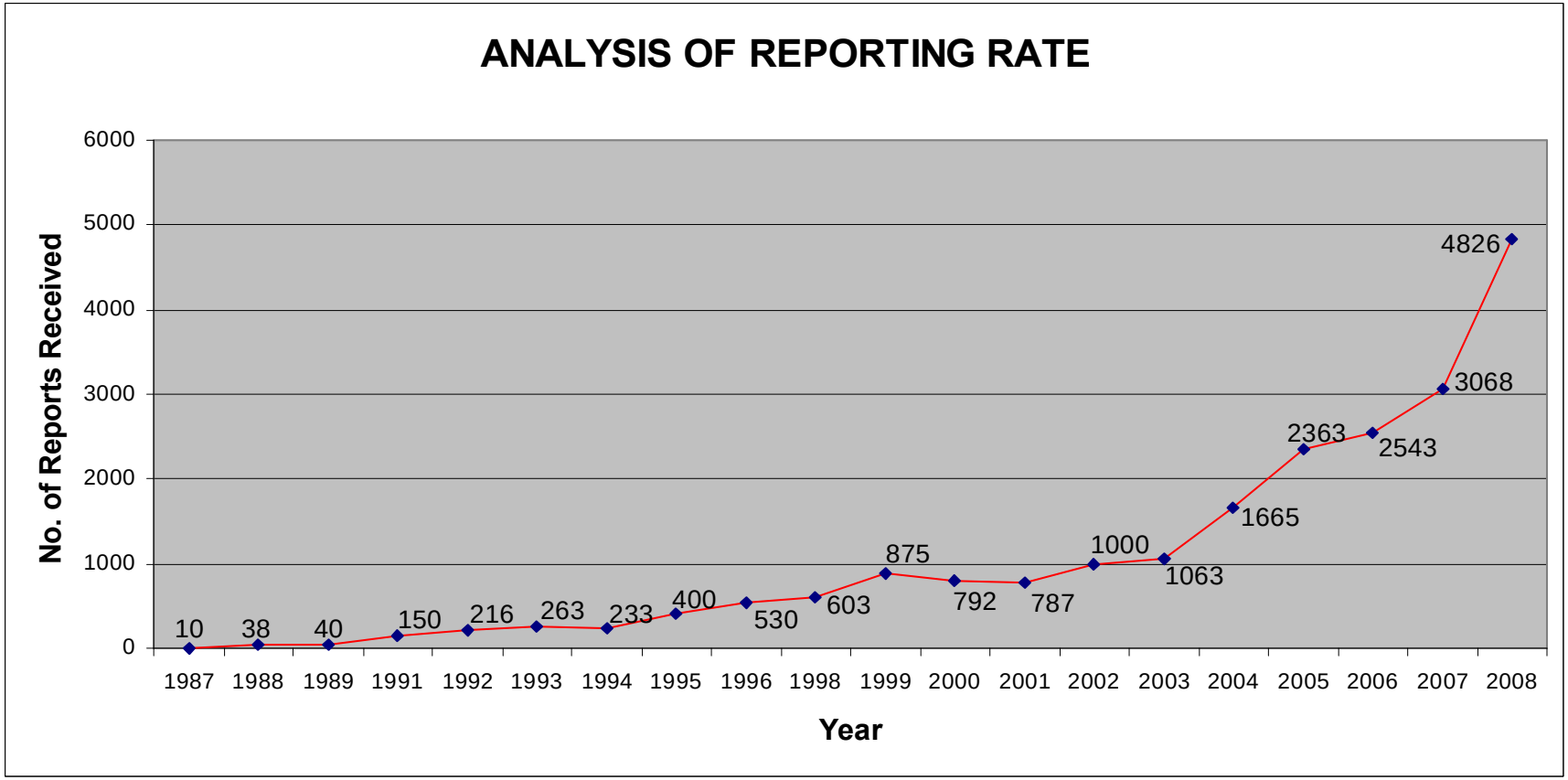
			and tendon rupture is further increased in people older than 60, in those taking corticosteroid drugs, and in kidney, heart, and lung transplant recipients. Patients experiencing pain, swelling, inflammation of a tendon or tendon rupture should be advised to stop taking their fluoroquinolone medication (to specify the active ingredient) and to contact their health care professional promptly about changing their antimicrobial therapy. Patients should also avoid exercise and using the affected area at the first sign of tendon pain, swelling, or inflammationò	

6. ACTIVITIES

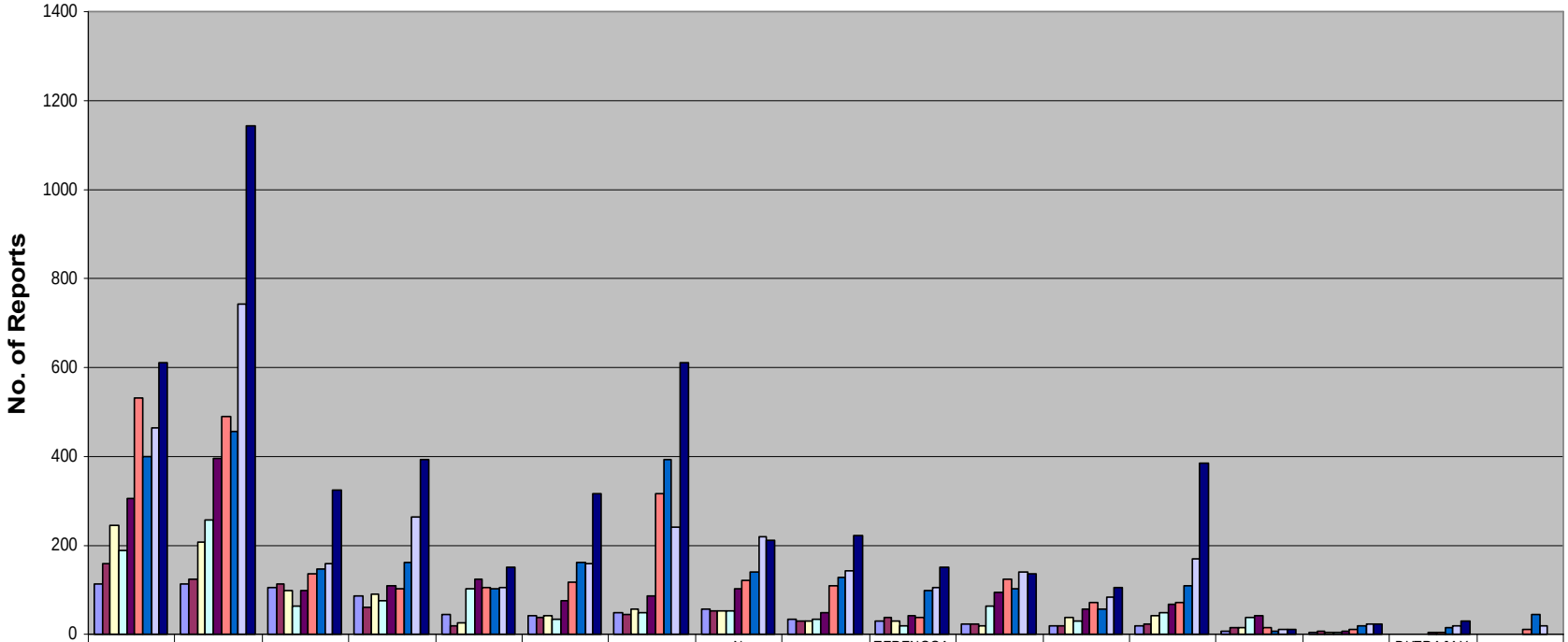
No.	FORUM	PLACE	TITLE OF PRESENTATION
1.	13th International Conference of Drug Regulatory Authorities	Bern, Switzerland	Involving Consumers in Medicines Surveillance: The Malaysian Experience
2.	5th IFPMA Asian Regulatory Conference	Kuala Lumpur Convention Centre	Evaluation of Safety Reports in Asia, Regulatorôs Perspective and Awareness
3.	Adverse Drug Reactions	Serdang Hospital	Adverse Drug Reactions
4.	Bengkel Dokumentasi Aktiviti Farmasi Klinikal	Concorde Inn, KLIA	Adverse Drug Reactions Revisited ï Adverse Drug Reactions Reporting History
5.	Bengkel Laporan Kesan Advers Ubat ï Ubatan dan Vaksin	1) Melaka Hospital 2) Slim River Hospital	Reporting, Recognizing and Reducing Adverse Drug Reactions
			Pharmacovigilance: Ensuring the Safe use of Medicines & Role of Pharmacists
			Current Reporting System for Adverse Drug Reactions
6.	Bengkel Laporan Kesan Advers Ubat ï Ubatan dan Vaksin	National Pharmaceutical Control Bureau	Background to Product Registration and Overview of Current System of Post-Market Surveillance
			Current Adverse Drug Reactions Reporting System and Causality Assessment

7.	Continuous Medical Education	Kuala Lumpur Hospital	Current Reporting System for Adverse Drug Reactions
8.	Continuous Medical Education	Sultanah Fatimah Specialist Hospital, Muar, Johor	Drug Safety Monitoring ï The Responsibility of Healthcare Professionals
9.	Drug Safety Issue ï Responsibility of All Healthcare Providers	Ipoh Hospital	Adverse Drug Reactions Due to Medication Error
10.	Induction Course for Pharmacists	Empress Hotel, Jabatan Kesihatan Negeri Sembilan	Adverse Drug Reactions Monitoring
11.	Kursus Teknikal Pegawai Farmasi Kesihatan Dalam Penjagaan Kesihatan Primer	Bayu Beach Resort, Port Dickson	Adverse Drug Reaction and Adverse Events Following Immunisation (AEFI)
12.	Medication Awareness Campaign	Ampang Hospital	Adverse Drug Reaction Reporting and Monitoring
13.	Senior Officers Meeting	Bayview Hotel, Langkawi	Adverse Events Following Immunisation (AEFI)
14.	Ward Pharmacy and Adverse Drug Reactions	Serdang Hospital	Adverse Drug Reactions Revisited ï Adverse Drug Reactions Reporting History

APPENDIX 1

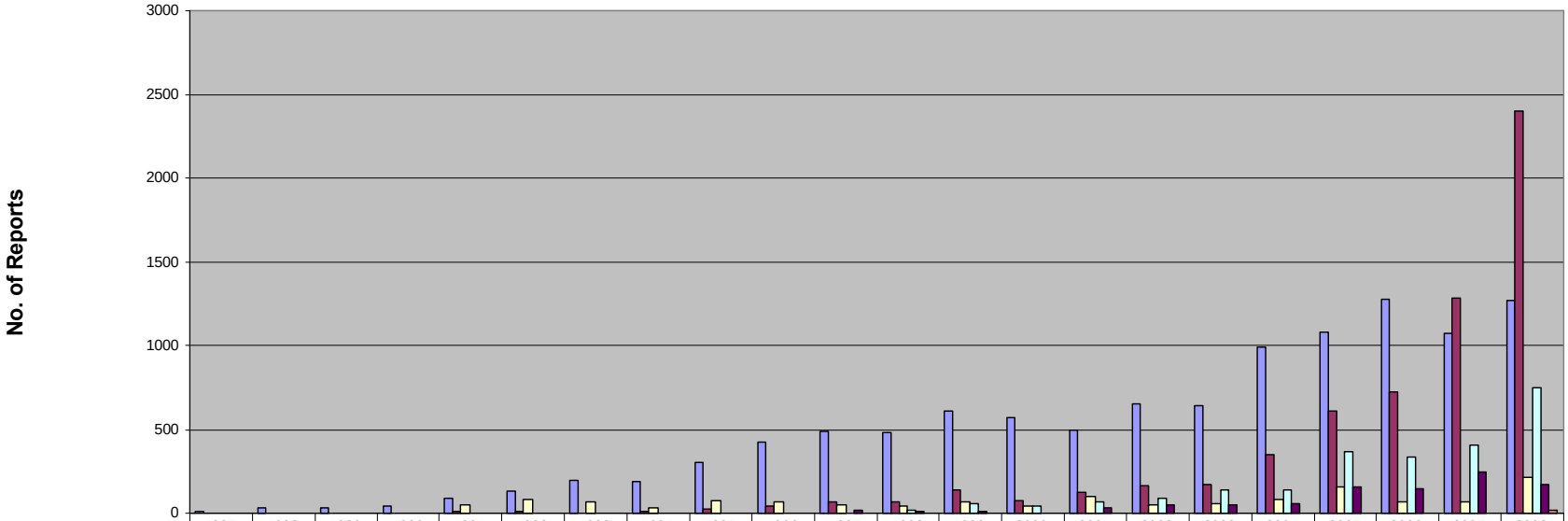

ANALYSIS OF REPORTING RATE
No. of Reports Received
6000
5000
4000
3000
2000
1000
0
10
38
40
150
216
263
233
400
530
603
875
792
787
1000
1063
1665
2363
2543
3068
4826
1987
1988
1989
1991
1992
1993
1994
1995
1996
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Year

ADR REPORTS BY STATE

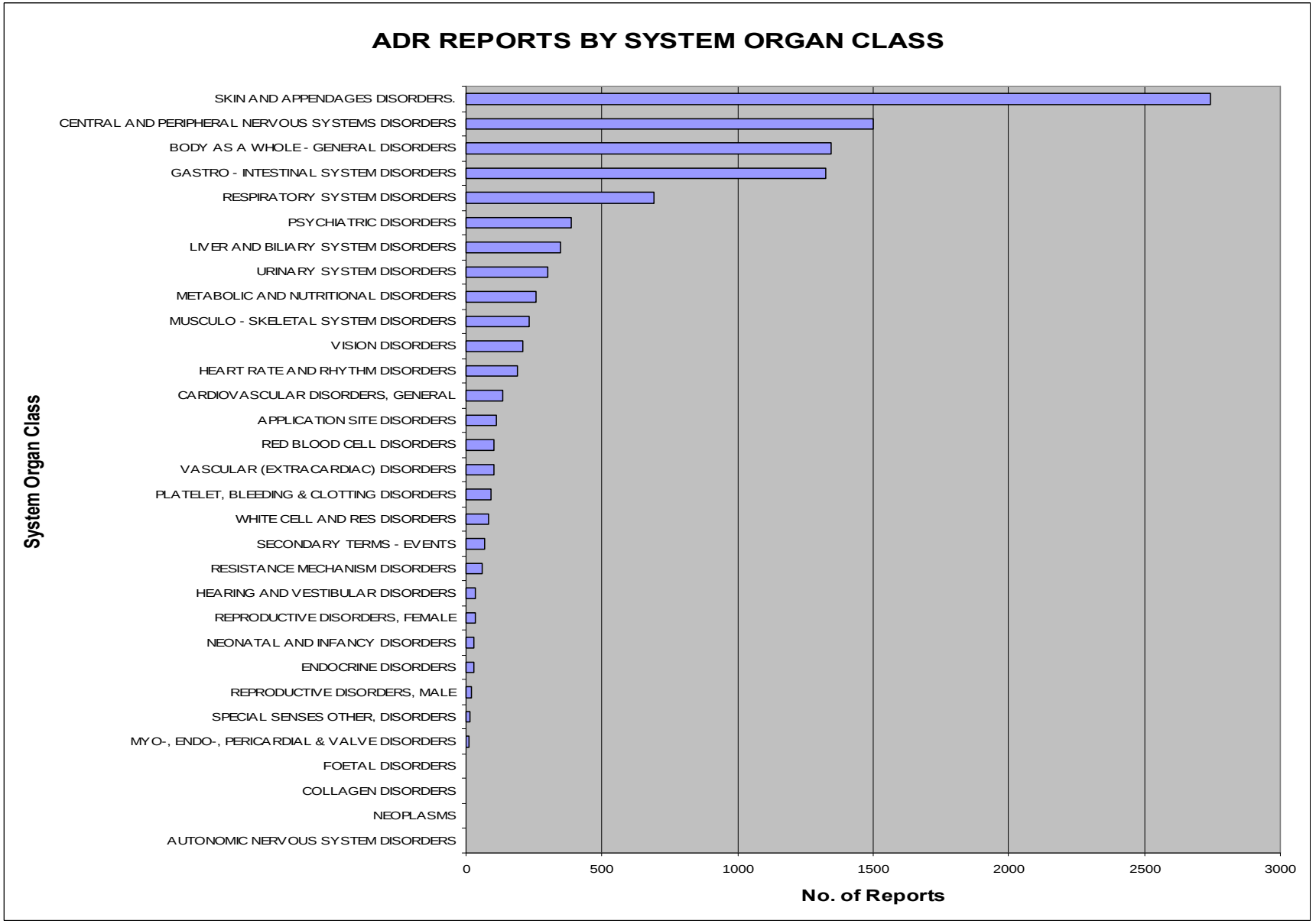


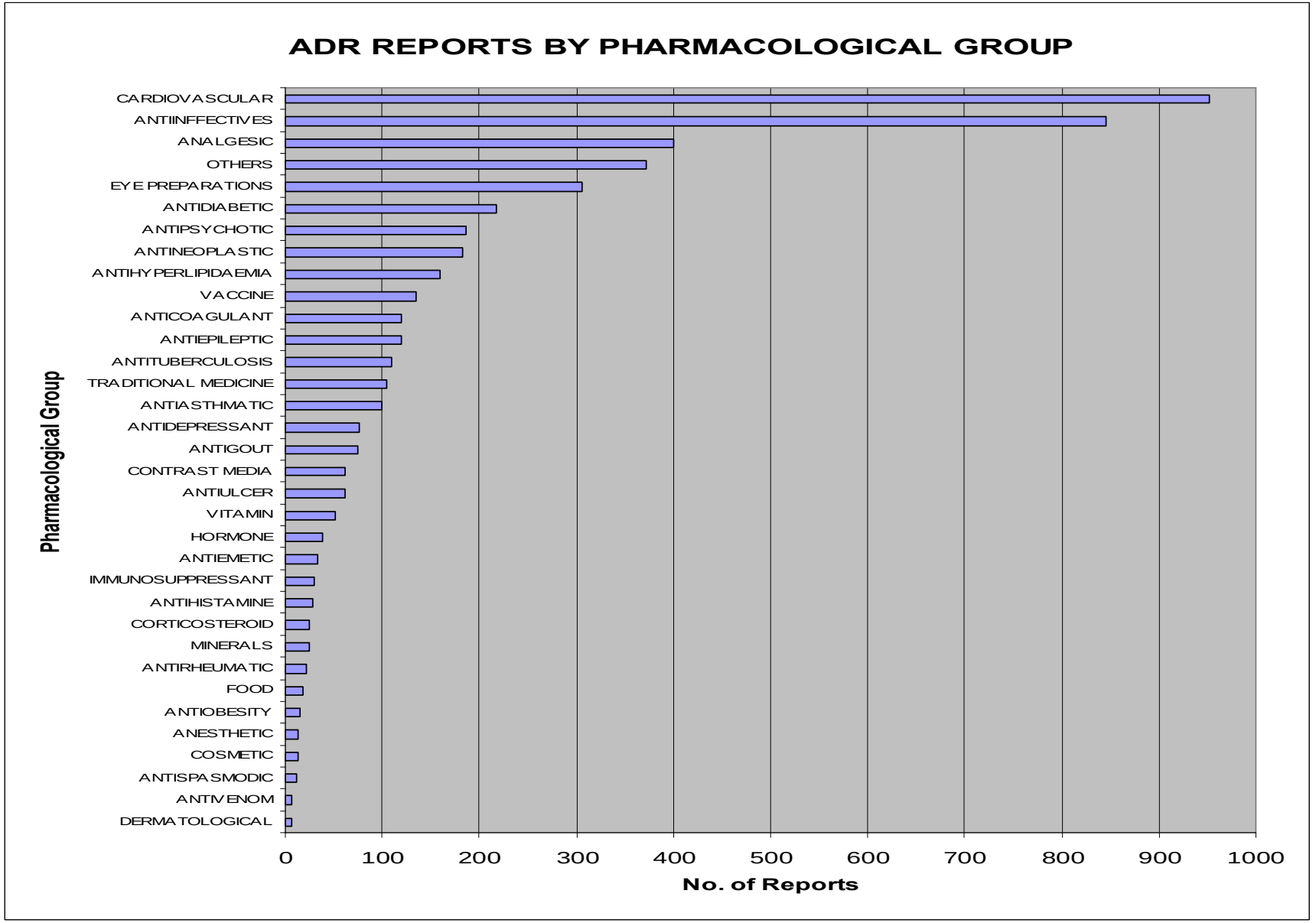
	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N SEMBILAN	P PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	39	46	53	32	38	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0
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
2005	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
2007	466	745	158	264	107	157	242	217	142	106	140	84	168	11	23	20	18
2008	612	1144	326	392	151	316	611	210	224	151	134	107	384	12	22	30	0

ADR REPORTS BY REPORTERS

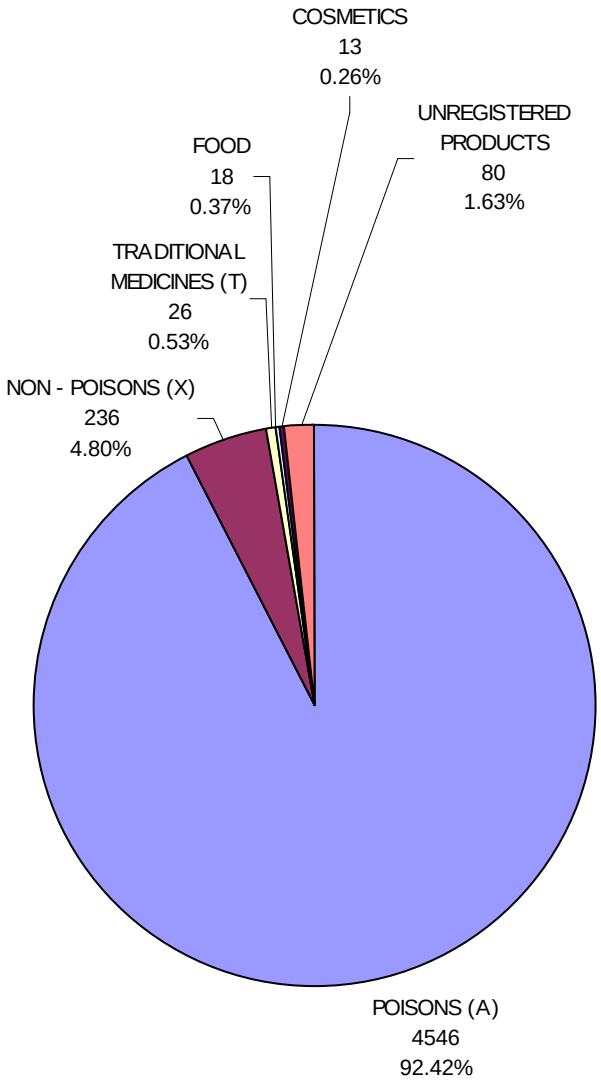


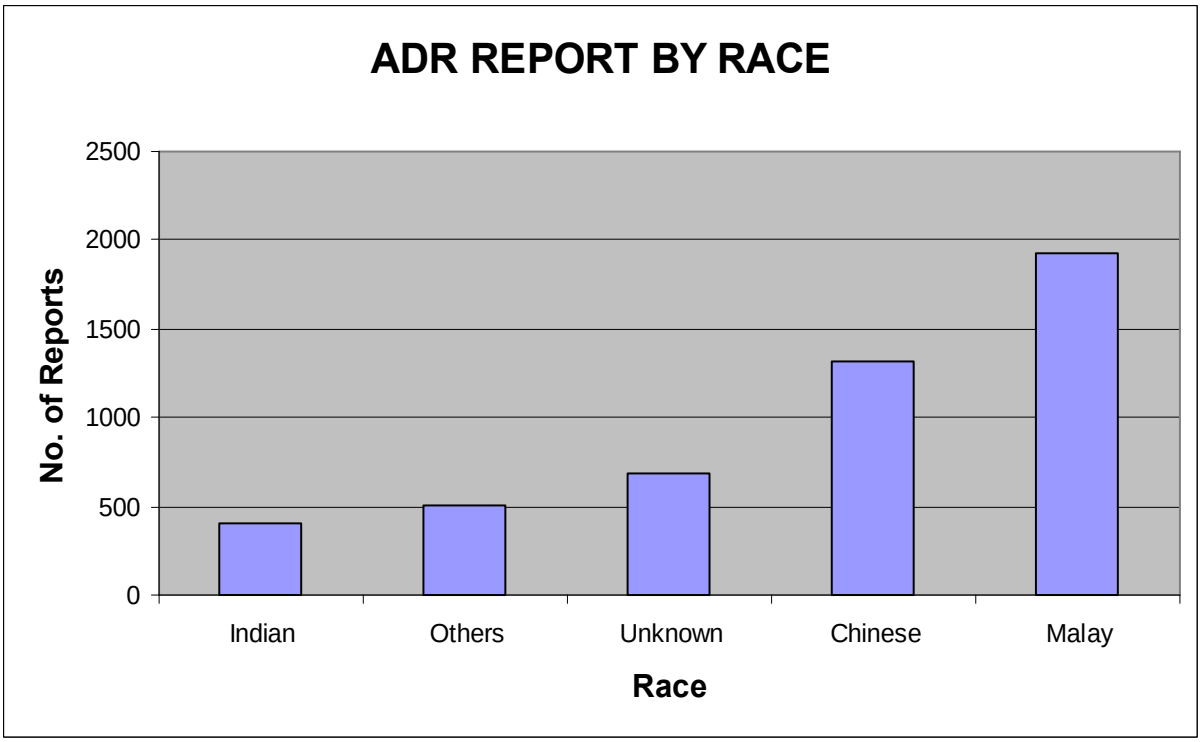
	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Government Doctor	10	32	36	39	87	129	193	191	303	419	489	480	608	573	496	651	646	988	1079	1273	1075	1272
Pharmacist	0	3	2	1	12	6	2	9	27	40	62	61	141	74	118	162	169	352	606	726	1283	2401
GP/Private Hospital	0	1	2	4	51	81	68	33	70	61	51	44	66	38	94	49	60	83	157	64	61	214
Registration Holder	0	0	0	0	0	0	0	0	0	0	1	18	54	43	67	90	141	141	368	330	409	751
University	0	0	0	0	0	0	0	0	0	0	16	11	7	0	36	47	47	54	153	150	240	173
Others																						15

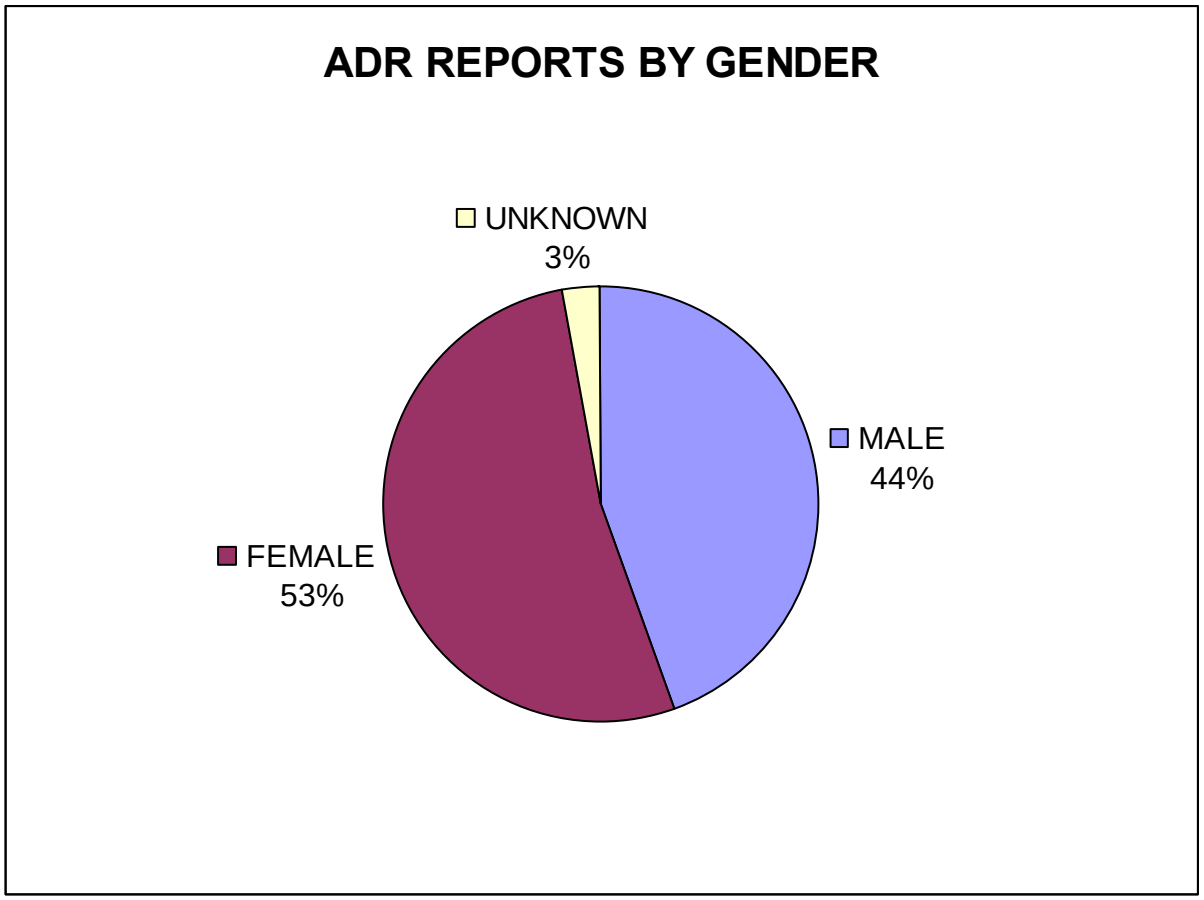

ADR REPORTS BY SYSTEM ORGAN CLASS
System Organ Class
SKIN AND APPENDAGES DISORDERS.
CENTRAL AND PERIPHERAL NERVOUS SYSTEMS DISORDERS
BODY AS A WHOLE - GENERAL DISORDERS
GASTRO - INTESTINAL SYSTEM DISORDERS
RESPIRATORY SYSTEM DISORDERS
PSYCHIATRIC DISORDERS
LIVER AND BILIARY SYSTEM DISORDERS
URINARY SYSTEM DISORDERS
METABOLIC AND NUTRITIONAL DISORDERS
MUSCULO - SKELETAL SYSTEM DISORDERS
VISION DISORDERS
HEART RATE AND RHYTHM DISORDERS
CARDIOVASCULAR DISORDERS, GENERAL
APPLICATION SITE DISORDERS
RED BLOOD CELL DISORDERS
VASCULAR (EXTRACARDIAC) DISORDERS
PLATELET, BLEEDING & CLOTTING DISORDERS
WHITE CELL AND RES DISORDERS
SECONDARY TERMS - EVENTS
RESISTANCE MECHANISM DISORDERS
HEARING AND VESTIBULAR DISORDERS
REPRODUCTIVE DISORDERS, FEMALE
NEONATAL AND INFANCY DISORDERS
ENDOCRINE DISORDERS
REPRODUCTIVE DISORDERS, MALE
SPECIAL SENSES OTHER, DISORDERS
MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS
FOETAL DISORDERS
COLLAGEN DISORDERS
NEOPLASMS
AUTONOMIC NERVOUS SYSTEM DISORDERS
0
500
1000
1500
2000
2500
3000
No. of Reports

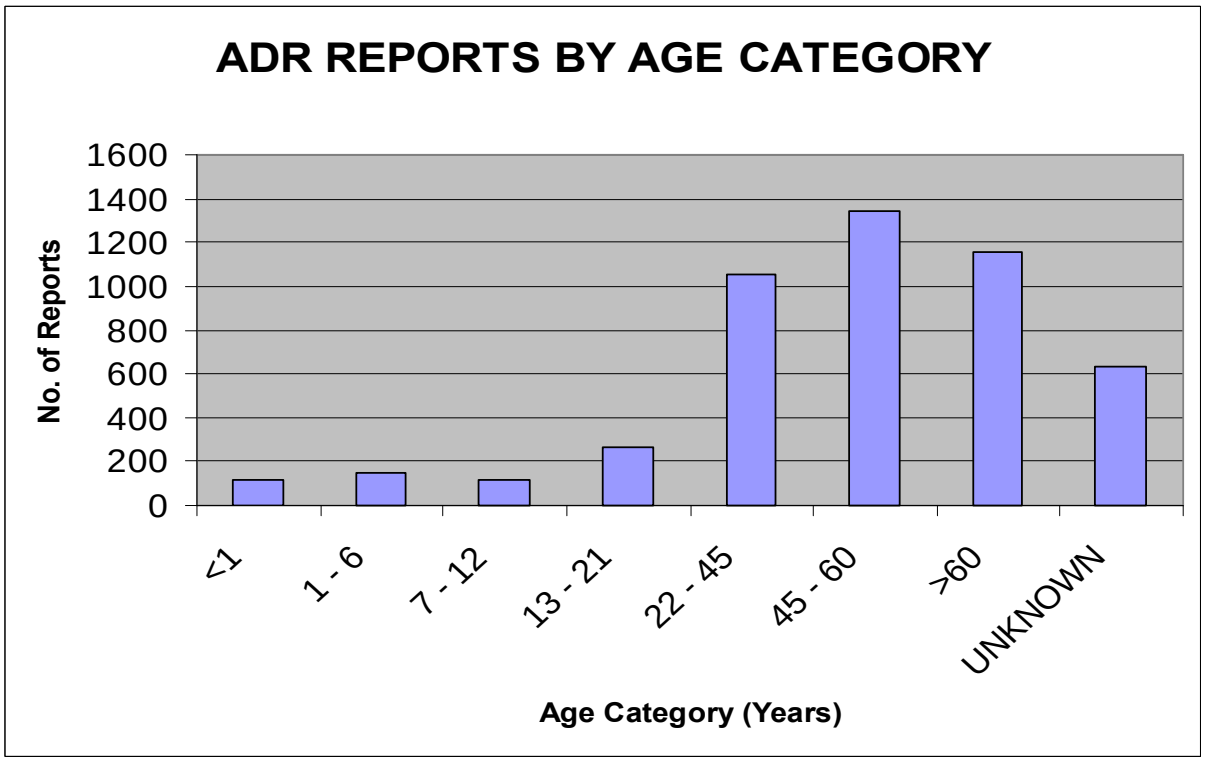

ADR REPORTS BY PHARMACOLOGICAL GROUP
Pharmacological Group
CARDIOVASCULAR
ANTIINFFECTIVES
ANALGESIC
OTHERS
EYE PREPARATIONS
ANTIDIABETIC
ANTIPSYCHOTIC
ANTINEOPLASTIC
ANTIHYPERLIPIDAEMIA
VACCINE
ANTICOAGULANT
ANTIEPILEPTIC
ANTITUBERCULOSIS
TRADITIONAL MEDICINE
ANTIASTHMATIC
ANTIDEPRESSANT
ANTIGOUT
CONTRAST MEDIA
ANTIULCER
VITAMIN
HORMONE
ANTIEMETIC
IMMUNOSUPPRESSANT
ANTIHISTAMINE
CORTICOSTEROID
MINERALS
ANTIRHEUMATIC
FOOD
ANTIOBESITY
ANESTHETIC
COSMETIC
ANTISPASMODIC
ANTIVENOM
DERMATOLOGICAL
0
100
200
300
400
500
600
700
800
900
1000
No. of Reports

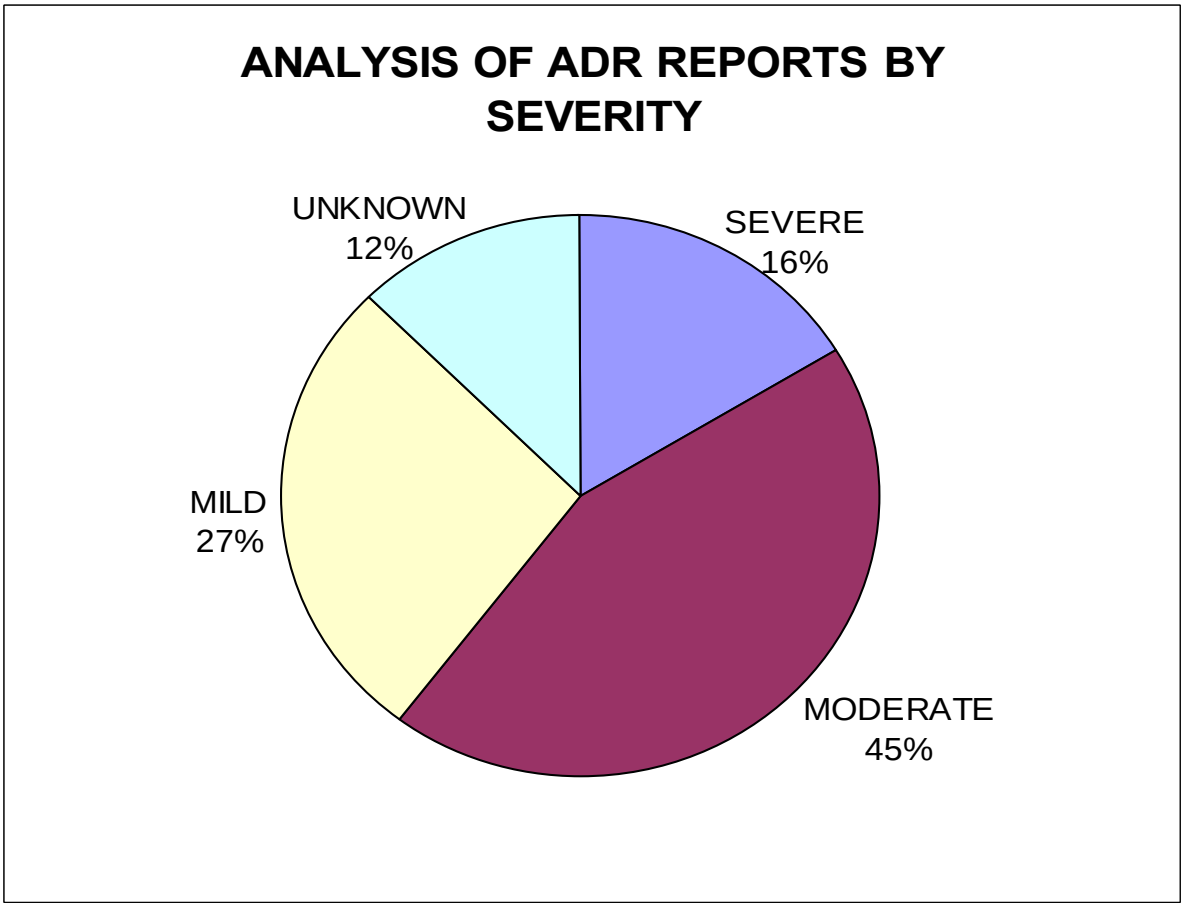
ADR REPORTS BY PRODUCT CATEGORY




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


ADR REPORTS BY GENDER
UNKNOWN
3%
MALE
44%
FEMALE
53%


ADR REPORTS BY AGE CATEGORY
No. of Reports
1600
1400
1200
1000
800
600
400
200
0
<1
1 - 6
7 - 12
13 - 21
22 - 45
45 - 60
>60
UNKNOWN
Age Category (Years)


ANALYSIS OF ADR REPORTS BY SEVERITY
UNKNOWN 12%
SEVERE 16%
MILD 27%
MODERATE 45%

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2002-2008)

NO	2002 (No. of Reports)	2003 (No. of Reports)	2004 (No. of Reports)	2005 (No. of Reports)	2006 (No. of Reports)	2007 (No. of Reports)	2008 (No. of Reports)
1	CO ï TRIMOXAZOLE (47)	ALLOPURINOL (33)	ALLOPURINOL (37)	CAPTOPRIL (52)	TRADITIONAL MEDICINE (68)	PERINDOPRIL (97)	PERINDOPRIL (217)
2	CARBAMAZEPINE (32)	CLOXACILLIN (30)	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC (65)	ALLOPURINOL (75)	ASPIRIN (134)
3	CLOXACILLIN (31)	MEFENAMIC ACID (25)	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)	CLOXACILLIN (71)	DICLOFENAC (111)
4	AMOXYCILLIN (28)	DICLOFENAC (24)	NIFEDIPINE (28)	DICLOFENAC (44)	NIFEDIPINE (58)	DICLOFENAC (71)	AMLODIPINE (92)
5	ALLOPURINOL (22)	CHLOROTHIAZIDE (22)	CO ï TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)	METFORMIN (69)	METFORMIN (91)
6	TRADITIONAL MEDICINE (22)	CARBAMAZEPINE (19)	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)	ASPIRIN (67)	TRADITIONAL MEDICINE (80)
7	ALENDRONATE (19)	TRADITIONAL MEDICINE (18)	AMOXYCILLIN (23)	PARACETAMOL (38)	CO ï TRIMOXAZOLE (55)	TICLOPIDINE (50)	ALLOPURINOL (80)
8	DICLOFENAC (19)	AMOXYCILLIN (18)	MEFENAMIC ACID (21)	CO ï TRIMOXAZOLE (37)	ASPIRIN (41)	RIFAMPICIN (46)	CO ï TRIMOXAZOLE (73)
9	ISOSORBIDE DINITRATE (18)	PENICILLIN G SODIUM (15)	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)	PHENYTOIN (44)	HEPARIN (70)
10	LOVASTATIN (13)	VANCOMYCIN (15)	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)	AMOXYCILLIN (43)	LOVASTATIN (66)

MAIN ADVERSE DRUG REACTIONS RELATED TO THE TEN DRUGS IN YEAR 2008 WITH THE MOST REPORTED ADVERSE DRUG REACTIONS

DRUG (No. of Reports)	MAIN ADR 1 (No. of Reports)	MAIN ADR 2 (No. of Reports)	MAIN ADR 3 (No. of Reports)
PERINDOPRIL (217)	COUGHING (72)	DRY COUGH (58)	DIZZINESS (15)
ASPIRIN (134)	OEDEMA PERIORBITAL (16)	ITCHING (14)	RASH (14)
DICLOFENAC (111)	OEDEMA PERIORBITAL (27)	ITCHING (23)	RASH (19)
AMLODIPINE (92)	HEADACHE (16)	DIZZINESS (13)	GIDDINESS (13)
METFORMIN (92)	DIARRHOEA (21)	NAUSEA (13)	VOMITING (12)
TRADITIONAL MEDICINE (80)	RENAL FAILURE (11)	JAUNDICE (9)	HEPATITIS ACUTE (7)
ALLOPURINOL (80)	RASH RELATED (MACULO-PAPULAR, ERYTHEMATOUS, MACULAR, PRURITIC) (46)	STEVENS JOHNSON SYNDROME (17)	ITCHING (12)
CO ï TRIMOXAZOLE (73)	RASH RELATED (MACULO-PAPULAR, ERYTHEMATOUS, MACULAR, PRURITIC, PETECHIAL, VESICULAR) (45)	ITCHING (17)	ERYTHEMA (MULTIFORME, PALMAR, PLANTAR) (6)
HEPARIN (70)	BREATH SHORTNESS (31)	HEARTBURN (18)	HEADACHE (12)
LOVASTATIN (66)	ITCHING (8)	HEADACHE (7)	RASH (7)

TEN BEST REPORTERS

NO.	NAME OF HOSPITAL	NO. OF REPORTS
1.	Hospital Duchess of Kent	302
2.	Hospital Kuala Lumpur	245
3.	Hospital Melaka	229
4.	Hospital Sultanah Aminah	180
5.	Hospital Pulau Pinang	128
6.	Hospital Umum Sarawak	119
7.	Hospital Pakar Sultanah Fatimah	109
7.	Hospital Raja Permaisuri Bainun (formerly Hospital Ipoh)	109
9.	Hospital Mesra Bukit Padang	99
10.	Hospital Selayang	93
10.	Hospital Queen Elizabeth	93