ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE
2007

1. MADRAC MEMBERS

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

MADRAC Members/*(Alternate members)*	
Pn Hasnah Ismail Director of National Pharmaceutical Control Bureau. En. Lim Siang Kwang Director of National Pharmaceutical Control Bureau	Chairman (September 2007 – December 2007) Chairman (January 2007 – September 2007)
Dr. Sarfraz Bin Manzoor Hussein Consultant Psychiatrist, Hospital Kuala Lumpur	Committee Member
Puan Sri Datuk Dr Suraiya H. Hussein/*(Dr. Gangaram Hemandas)* Consultant Dermatologist, Hospital Kuala Lumpur.	Committee Member
Tan Sri Datuk Dr R. P. Linggam Representative of the Malaysian Medical Association.	Committee Member
Prof Jamiyah Hassan Medical Faculty, University Malaya.	Committee Member
Prof Dr Rahmat b Awang/*(Prof Madya Abdul Fatah Hj. Abdul Rahman)* National Poisons Centre, Universiti Sains Malaysia.	Committee Member
Prof. Dr. Nik Aziz bin Sulaiman/*(Prof. Dr. Ima Nirvana Soelaiman)* Cyberjaya University College of Medicine/ *Universiti Kebangsaan Malaysia*	Committee Member
Dr G.R. Letchumanan s/o Ramanathan/*(Dr. Patmini Menon)* Consultant Physician, Hospital Taiping*/Hospital Ipoh*	Committee Member
Dr. S. Ganesananthan / (*Dr. Rosaida Hj. Mohd. Said)* Consultant Physician, Hospital Kuala Lumpur.	Committee Member
Dr. Mardziah Alias/*(Dr. Norzila Mohamed Zainudin)* Consultant Paediatrician, Hospital Kuala Lumpur	Committee Member
Mr. Selvaraja Seerangam Secretary, Drug Control Authority, Ministry of Health	Committee Member
En Mohd. Hatta Ismail / *(Pn. Rosminah Mohd. Din)* Deputy Director, Pharmacy Practice, Pharmaceutical Services Division, Ministry of Health.	Committee Member
Pn Tan Lie Sie Head, Centre for Post Registration, NPCB, Ministry of Health	Committee Member
Pn. Fuziah Abdul Rashid Principal Assistant Director, Centre for Post Registration, NPCB, Ministry of Health	Secretary

2. MEETINGS

The committee met six times over the year and a total of 2991 adverse drug reaction reports were reviewed.

Meeting	**95 01/07**	**96 03/07**	**97 05/07**	**98 07/07**	**99 09/07**	**100 11/07**
No Of Reports	**294**	**506**	**542**	**539**	**511**	**599**

3. ANALYSIS OF ADR REPORTS

A detailed review and analysis of the ADR reports received during the year 2007 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):

	Product	Regulatory Action Implemented	DCA Meeting
1.	Glucosamine	Due to the increasing number of adverse drug reactions reported locally, the DCA decided to update the information on side effects of all products containing glucosamine, by standardizing labeling of all glucosamine containing products to include the following statement under "Side Effects" :- *Cardiovascular :* Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. *Central nervous system:* Drowsiness, headache, insomnia have been observed rarely during therapy (less then 1%) *Gastrointestinal:* Nausea, vomiting, diarrhea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. *Skin :* Skin reaction such as erythema and pruritus has been reported with therapeutic administration of glucosamine.	DCA 193 (24.05.07)
2.	Tegaserod	Both the U.S. Food & Drug Administration (USFDA)–and Health Canada reported on 30 Mac 2007 that a new safety analysis on tegaserod found a higher chance of heart attack, stroke, and worsening heart chest pain that can become a	DCA 193 (24.05.07)

		heart attack in patients treated with it compared to those treated with placebo. A decision was taken on 2 April 2007 to suspend the importation, sale and distribution of the product Zelmac which contains tegaserod with immediate effect and a press release was made . In May 2007, the DCA at its 193rd meeting decided on the following actions: • To cancel the registration of product containing tegaserod (marketed as Zelmac 6mg tablet by Novartis Corporation) • Products containing tegaserod will no longer be registered in Malaysia • Novartis, the registration holder of Zelmac is given a grace period of 6 months to ensure this product is removed from the market • Novartis may import tegaserod upon request by prescribers on named patient basis when no suitable alternative drugs are available	
3.	Sedative – Hypnotic Products	Based on post-marketing adverse events reported, the USFDA directed that the labeling of several sleep disorder products be strengthened The DCA at its 193rd meeting decided that the following warning statements should be added to products containing *zolpidem, flurazepam, triazolam and midazolam* After reviewing the range of products approved as sedative-hypnotics in the local market and sourcing the WHO databank for reported ADRs related to the products, another 7 ingredients were added to the list of products that need to carry the warnings at its 195th meeting , namely *nitrazepam, alprazolam, zopiclone, diazepam, bromazepam, clobazam and lorazepam*: • *Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken.* • *Complex sleep related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep.*	DCA 193 (24.05.07) DCA 195 (07.08.07)
4.	Pergolide	Based on the studies which showed that patients with Parkinson's disease who were treated with pergolide had an increased chance of serious damage to their heart valves, the USFDA requested all manufacturers to voluntarily remove their products from the market. Due to this safety concern, the DCA has decided on the following: • To cancel the registration of all products containing pergolide	DCA 195 (07.08.07)

		• Not to register any product containing pergolide in the future.	
5.	Gadolinium – Based Contrast Agent	In view of the findings of the review of gadolinium-based contrast agents, the USFDA has directed to add a boxed warning and new warnings about risk of nephrogenic systemic fibrosis (NSF) to the full prescribing information of these products. Based on this information, the DCA has made the decision to strengthen the warnings of all gadolinium-based contrast agents. The following warnings must be included in their package inserts: <u>*Boxed warning*</u> • *Exposure to gadolinium – based contrast agents (CBCAs) increases the risks for nephrogenic systemic fibrosis (NSF) in patient with :* • *Acute chronic severe renal insufficiency (glomerular filtration <30mL/min/1.73m2), or* • *Acute renal insufficiency of any severity due to the hepato – renal syndrome or in the preoperative liver transplantation period.* • *NSF is a debilitating and sometimes fatal disease affecting the skin, muscle and internal organs.* • *Avoid use of GBCAs unless the diagnostic information is essential and not available with non – contrast enhanced magnetic resonance imaging (MRI)* • *Screen all patients for renal dysfunction by obtaining a history and /or laboratory tests.* • *When administering GBCAs, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any administration.* <u>*Additional new warnings*</u> • *Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of GBCA.* • *For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent elimination. However, it is unknown if haemodialysis prevents NSF.* • *Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA.* • *The risk, if any, for developing NSF among patients with mild to moderate renal*	DCA 195 (07.08.07)

		insufficiency or normal renal function is unknown. • *Post marketing reports have identified the development of NSF following single and multiple administrations of GBCAs.*	
6.	Nimesulide	The Irish Medicine Board (IMB) suspended the sales of nimesulide-containing products and recalled them from the market due to concerns over a number of serious adverse events (fulminant hepatic failure) reported associated with nimesulide. The risk-benefit profile of nimesulide is deemed unfavorable as the potential of an increased risk of serious hepatic reactions is not predictable Based on this safety concern, the DCA suspended the sales of all products containing nimesulide in Malaysia until further reviews from other regulatory agencies and feedback from local experts were received. In September 2007, the European Medicines Agency (EMEA) concluded the benefits of these medicines outweigh their risks. The Committee for Medicinal Products for Human Use (CHMP) therefore recommended that treatment with nimesulide should be limited to a maximum of 15 days and all packs containing more than 30 doses should be removed from the market. However, after reviewing the safety profile of nimesulide, availability of other alternatives and expert's opinion, the DCA decided to cancel the registration of all products containing nimesulide and not to register this ingredient in the future. All registration holders have been given a grace period of 3 months to recall their products from the market.	DCA 195 (07.08.07) DCA 199 (04.12.07)
7.	Ceftriaxone	New safety information was alerted by the USFDA on the interaction of ceftriaxone with calcium-containing products based on reports of fatal cases in neonates. Although there are no reported cases of ceftriaxone-calcium precipitates in patients other than neonates, the potential for this interaction exists in patients of any age. Hence, the DCA at its 196th meeting has decided the following precautionary statement should be included in the package inserts of all products containing ceftriaxone: <u>*Warning*</u> *Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions or products, even via different infusion lines.* *Calcium containing solutions or products must not*	DCA 196 (30.08.07)

		be administered within 48 hours of last administration of ceftriaxone. *Cases of fatal reactions with calcium – ceftriaxone precipitates in lungs and kidneys in both term and premature neonates have been described. In some cases the infusion lines and times of administration and calcium – containing solutions differed.* *<u>Dosage and Administration : Direction for Use</u>* *Do not use diluents containing calcium, such as Ringer's Solution or Hartmann's Solution, to reconstitute ceftriaxone. Particulate formation can result.*	
8.	Piroxicam	The EMEA has alerted all healthcare professionals on the restrictions of systemic piroxicam-containing products due to the risk of gastrointestinal side effects and serious skin reactions. Based on these issues the CMHP concluded that piroxicam should no longer be used for treatment of short term painful and inflammatory conditions. However, it can be used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The DCA has agreed to MADRAC's proposal to restrict the indications of all systemic piroxicam as follows: *For symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.* *However it should not be the first choice of non-steroidal anti-inflammatory drug (NSAID) treatment in these conditions.* The following warnings, precautions and contraindications must be included in their package inserts: *<u>Warning and Precautions</u>* • *Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases.* • *Use the lowest dose (No more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days.* • *Always considered prescribing a gastroprotective agent.* *<u>Contraindication</u>* • *Piroxicam should not be prescribed to patients who are more likely to develop side effects, such as those with a history of gastro – intestinal disorders associated with bleeding, or those who had skin*	DCA 199 (04.12.07)

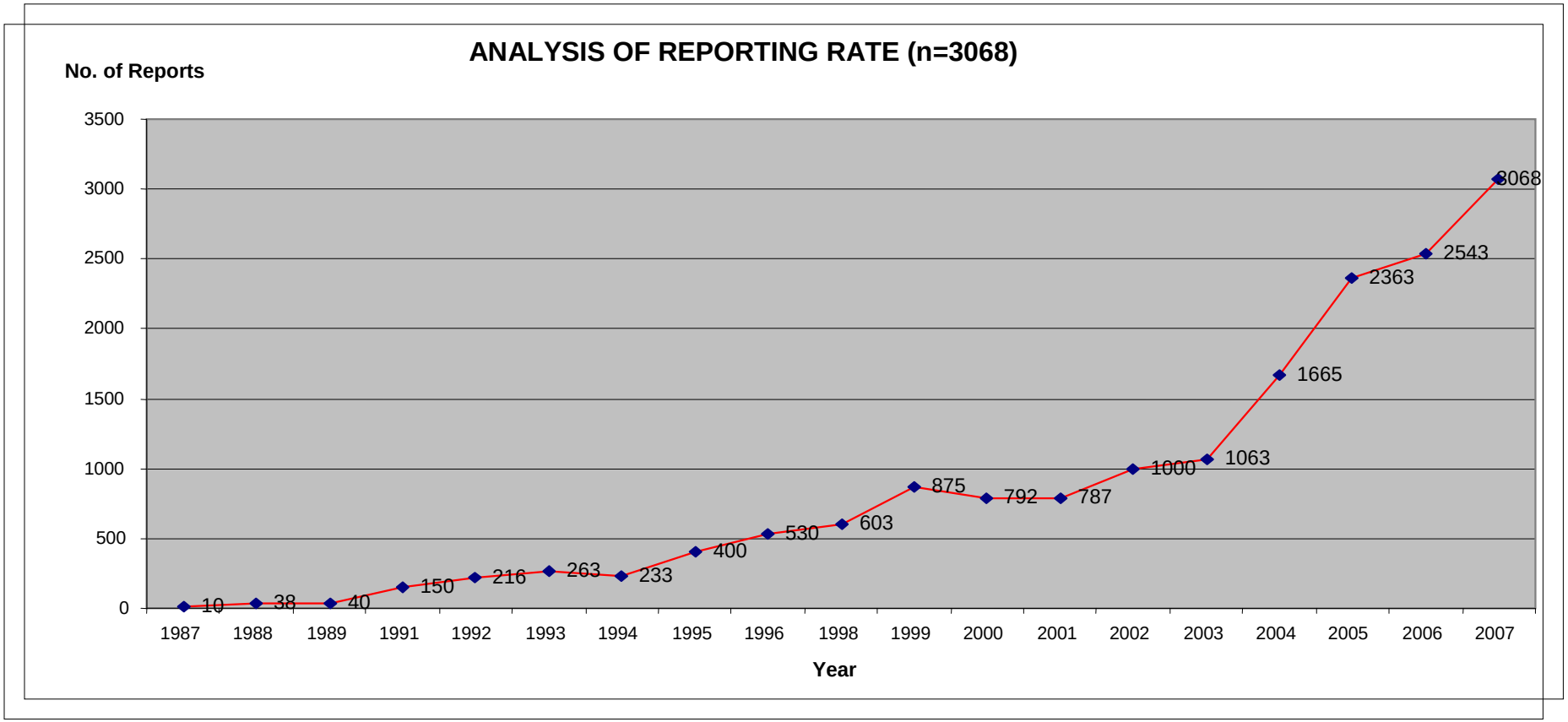
		reactions to other medicines. • *Piroxicam should not be prescribed in association with any other NSAIDs or an anticoagulant.*	
9.	Red 2G Colouring Agent	In October 2007, the Ministry of Health Malaysia has announced to ban the use of Red 2G with immediate effect. This is based on the issuance of a European Commission Directive in July 2007 which directed a ban on the use of Red 2G in food due to safety concerns that this colorant could be genotoxic and carcinogenic. Therefore, the DCA has decided to ban the usage of Red 2G in oral preparation products and also in all products that come in contact with mucous membrane. All product registration holders are advised to reformulate their formulations with other colorants.	DCA 199 (04.12.07)
10.	"Diluluskan oleh KKM (Approved by the MOH)"	In 2006, traditional medicines as a group were identified as one of the top among ten drugs with the most reported adverse drug reactions. Traditional medicines are easily available in the market and can be purchased without prescription. Most of the reports received are serious and some of the products taken from the market / submitted with the ADR reports were found to be adulterated with scheduled poisons. MADRAC has expressed concerns about this trend and suggested that the statement "Diluluskan oleh KKM (Approved by the MOH)" may mislead the consumers into thinking that such products are without safety concerns since these are "natural" products and have the KKM endorsement. Consumers can always identify the registered products based on the registration number and hologram labels which are mandatory to be stated on their labels. Based on this concern, MADRAC proposed to the DCA to delete this statement from the label of all categories of products already in the market and not to allow the same statement to be included in labels for new registration of products. A period of 6 months has been given to registration holders to comply with this requirement.	DCA 199 (04.12.07)

5. ACTIVITIES

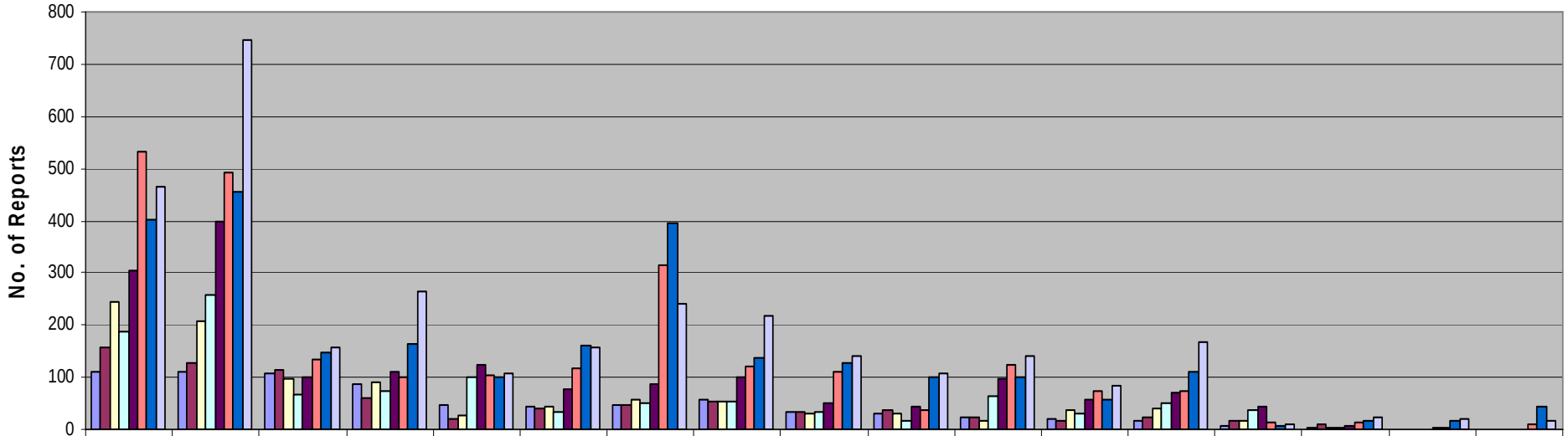
MADRAC members conducted several talks over the year in an effort to promote ADR reporting as well as to update health professionals on issues related to drug safety.

NO	TITLE OF PRESENTATION	FORUM	PLACE
1	Current Reporting System for Adverse Drug Reactions and Product Complaint.	Consumer Medicines Surveilance Seminar 2007	Petaling Jaya, Selangor
2	Involving Consumer in Medicine Surveillance	Consumer Medicines Surveilance Seminar 2007	Petaling Jaya, Selangor
3	Product Safety Monitoring – Traditional Medicines	Workshop on Regulatory Procedure for Traditional Medicines and New Chemical Entities	Kuala Lumpur
4	Adverse Drug Reactions - Psychopharmacology Drugs	Psychopharmacology Conference 2007	Johor Bahru, Johor
5	Drug Safety Monitoring	National Conference on Clinical Reasearch 2007	Kuala Lumpur
6	ADR Monitoring and Reporting	Continuous Professional Development Programme	Hospital Putrajaya
7	Management of Drug Related Problem and Safety Usage		Pahang
8	Pharmacovigilance in Malaysia	Continuous Professional Development Programme	Hospital Sg Buloh, Selangor
9	Involving Consumers In Medicines Surveillance: The Malaysian Experience	WHO Regional Workshop On Improving Medicines Surveillance And Regulatory Functions	Manila, Philippines

APPENDIX 1

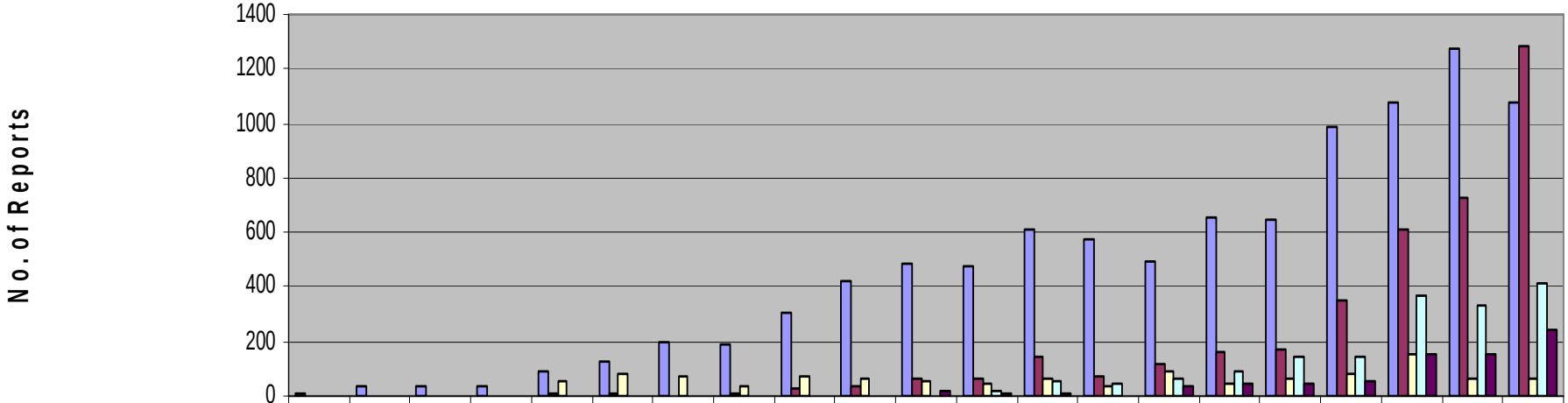

ANALYSIS OF REPORTING RATE (n=3068)
No. of Reports
3500
3000
2500
2000
1500
1000
500
0
10
38
40
150
216
263
233
400
530
603
875
792
787
1000
1063
1665
2363
2543
3068
1987
1988
1989
1991
1992
1993
1994
1995
1996
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
Year

TOTAL ADRs REPORT BY STATE (n=3068)

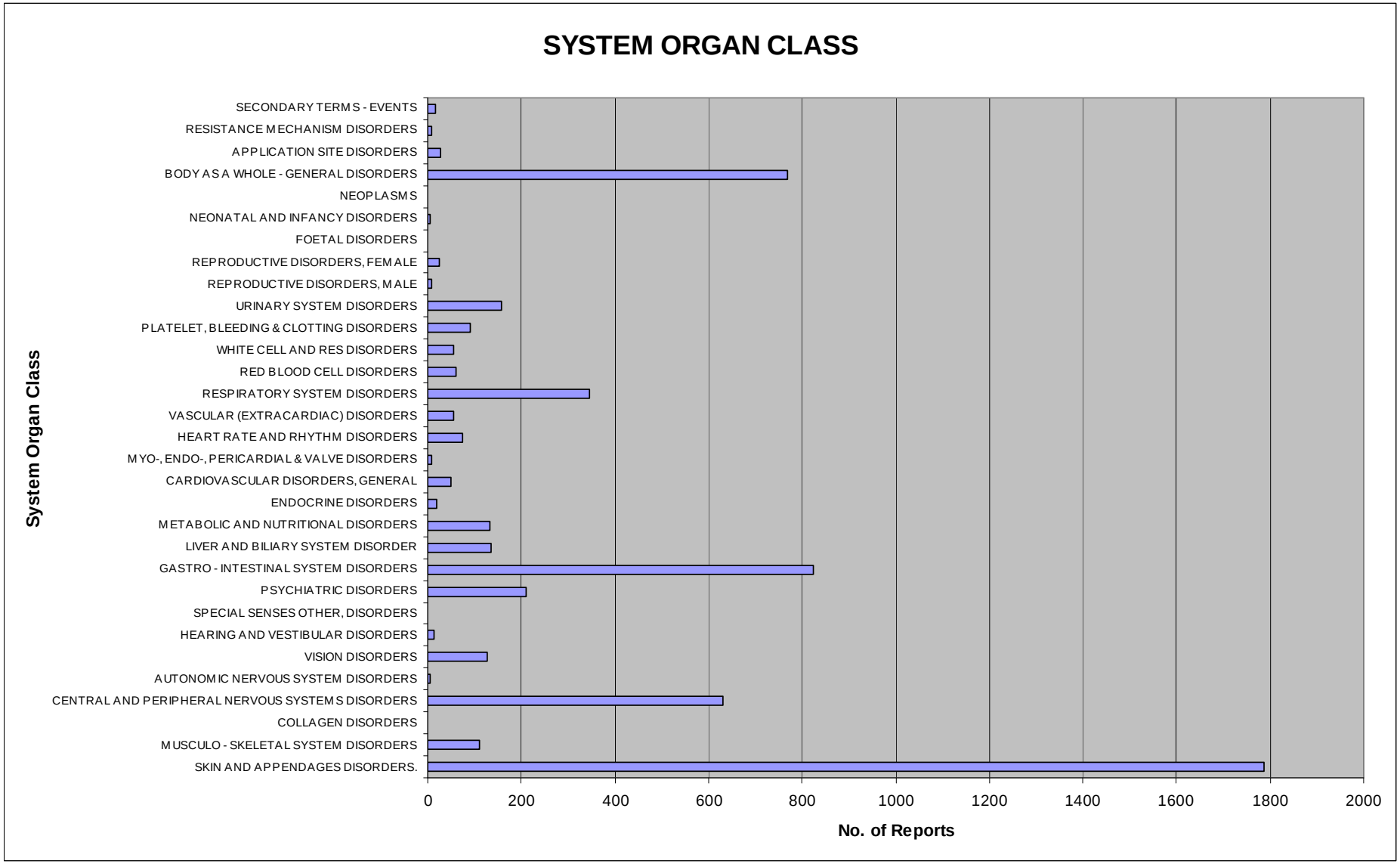


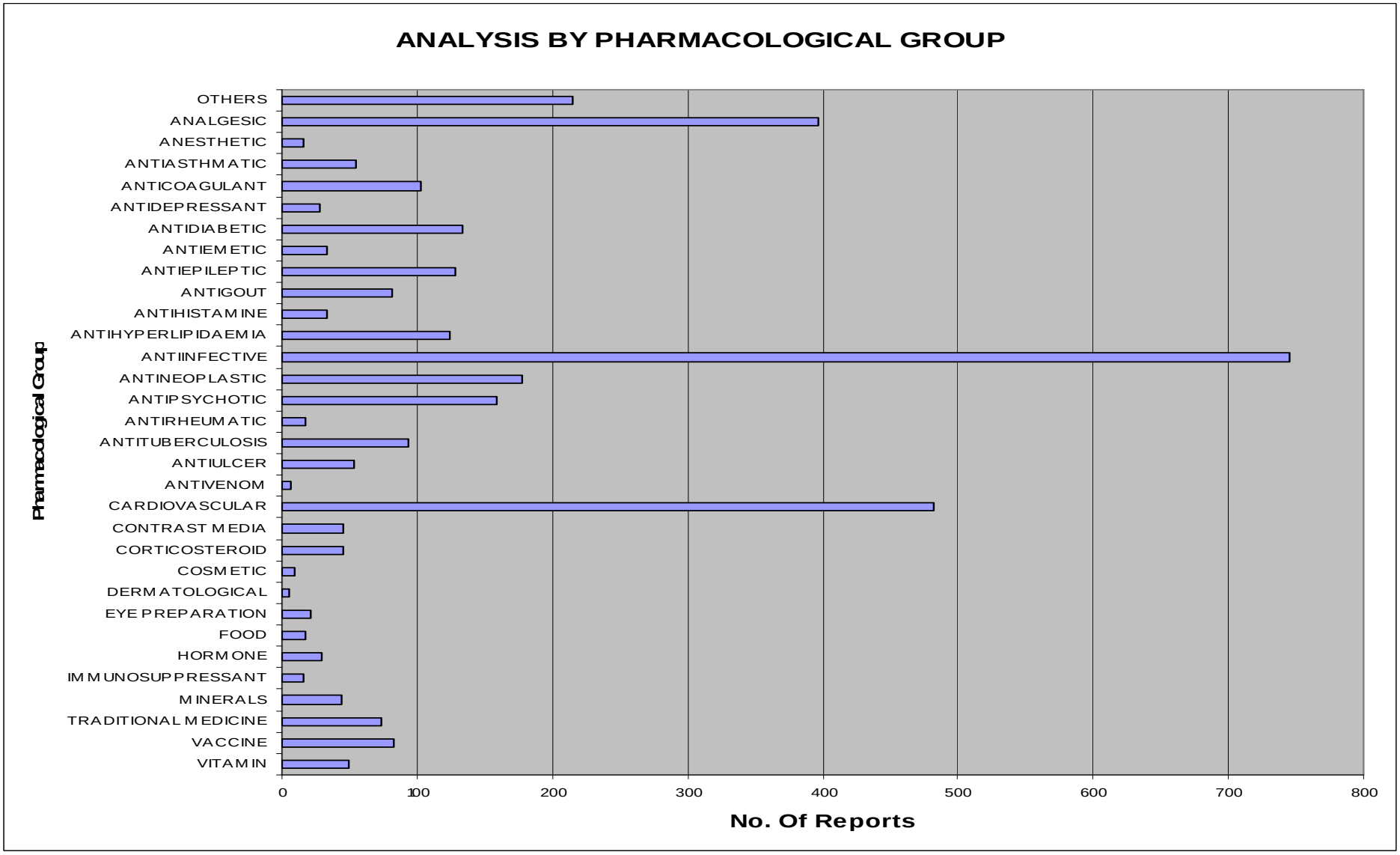
	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N SEMBILAN	P PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	39	46	53	32	38	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0
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

ADR REPORTS BY REPORTERS (n=3068)

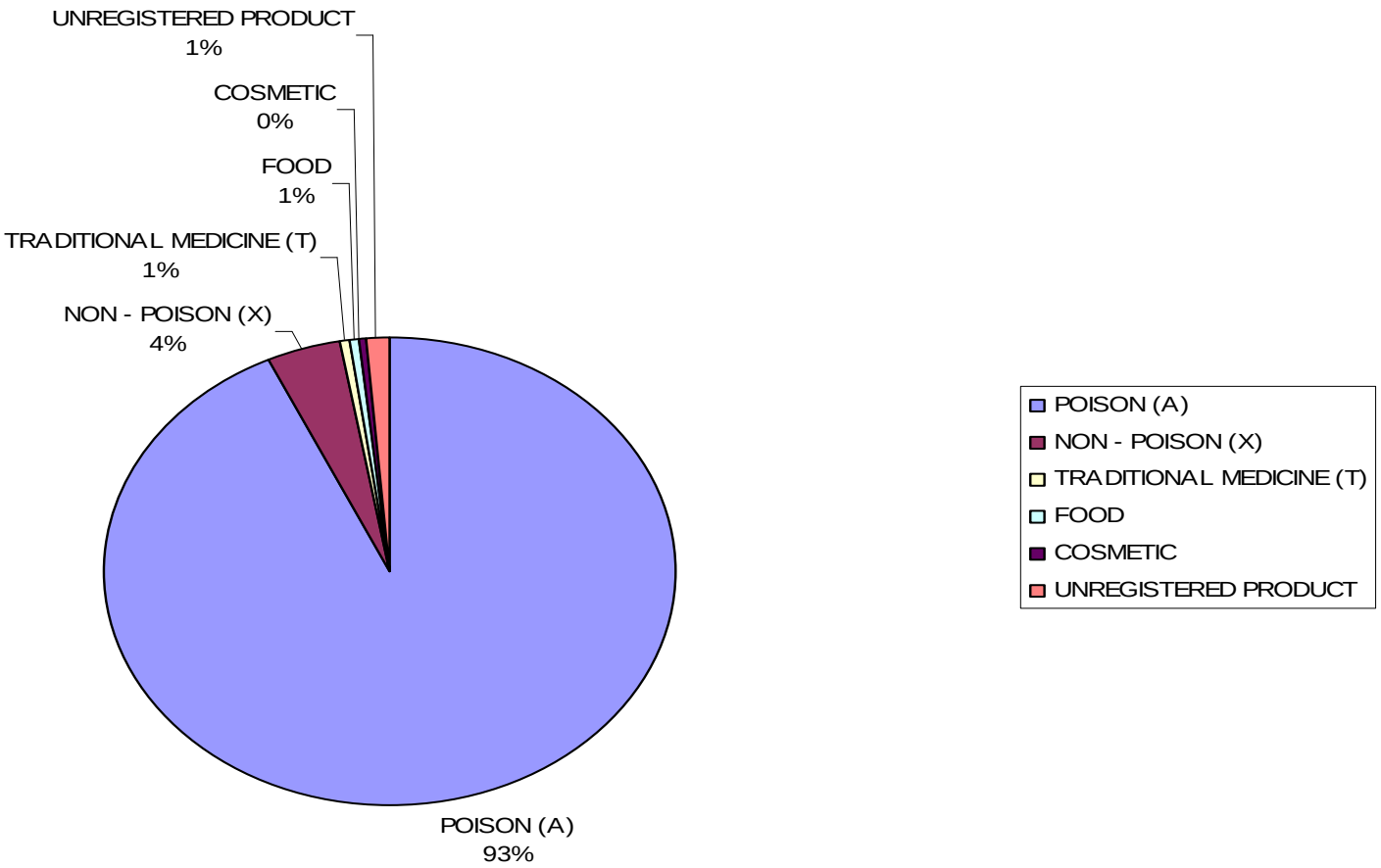


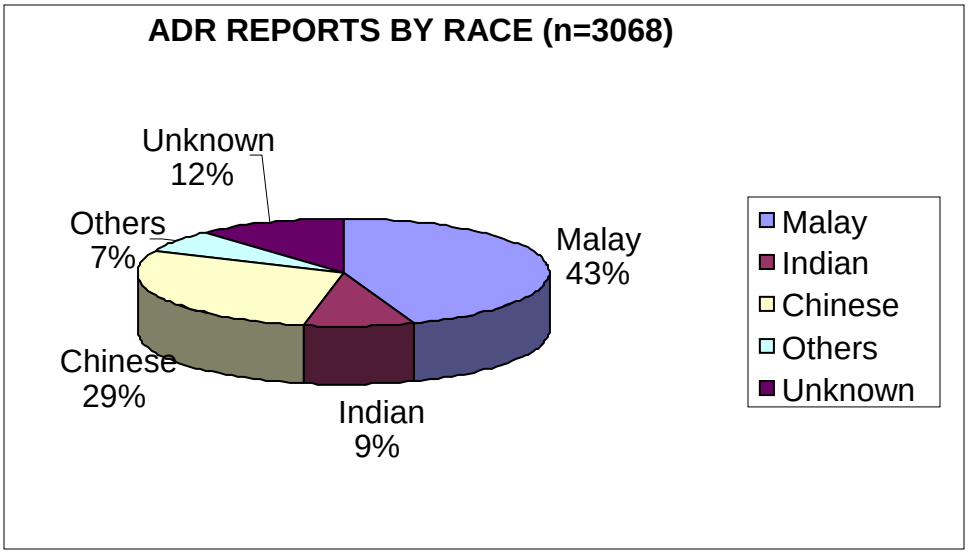
	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Government Doctors	10	32	36	39	87	129	193	191	303	419	489	480	608	573	496	651	646	988	1079	1273	1075
Others (Pharmacist, Dentist)	0	3	2	1	12	6	2	9	27	40	62	61	141	74	118	162	169	352	606	726	1283
GP/Private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

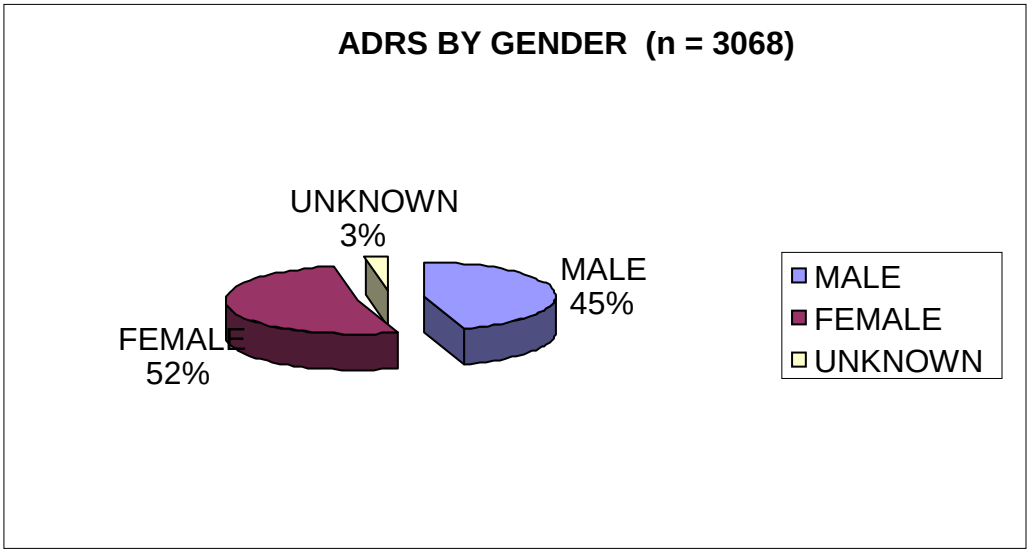

SYSTEM ORGAN CLASS
System Organ Class
SECONDARY TERMS - EVENTS
RESISTANCE MECHANISM DISORDERS
APPLICATION SITE DISORDERS
BODY AS A WHOLE - GENERAL DISORDERS
NEOPLASMS
NEONATAL AND INFANCY DISORDERS
FOETAL DISORDERS
REPRODUCTIVE DISORDERS, FEMALE
REPRODUCTIVE DISORDERS, MALE
URINARY SYSTEM DISORDERS
PLATELET, BLEEDING & CLOTTING DISORDERS
WHITE CELL AND RES DISORDERS
RED BLOOD CELL DISORDERS
RESPIRATORY SYSTEM DISORDERS
VASCULAR (EXTRACARDIAC) DISORDERS
HEART RATE AND RHYTHM DISORDERS
MYO-, ENDO-, PERICARDIAL & VALVE DISORDERS
CARDIOVASCULAR DISORDERS, GENERAL
ENDOCRINE DISORDERS
METABOLIC AND NUTRITIONAL DISORDERS
LIVER AND BILIARY SYSTEM DISORDER
GASTRO - INTESTINAL SYSTEM DISORDERS
PSYCHIATRIC DISORDERS
SPECIAL SENSES OTHER, DISORDERS
HEARING AND VESTIBULAR DISORDERS
VISION DISORDERS
AUTONOMIC NERVOUS SYSTEM DISORDERS
CENTRAL AND PERIPHERAL NERVOUS SYSTEMS DISORDERS
COLLAGEN DISORDERS
MUSCULO - SKELETAL SYSTEM DISORDERS
SKIN AND APPENDAGES DISORDERS.
0
200
400
600
800
1000
1200
1400
1600
1800
2000
No. of Reports


ANALYSIS BY PHARMACOLOGICAL GROUP
Pharmacological Group
OTHERS
ANALGESIC
ANESTHETIC
ANTIASTHMATIC
ANTICOAGULANT
ANTIDEPRESSANT
ANTIDIABETIC
ANTIEMETIC
ANTIEPILEPTIC
ANTIGOUT
ANTIHISTAMINE
ANTIHYPERLIPIDAEMIA
ANTIINFECTIVE
ANTINEOPLASTIC
ANTIPSYCHOTIC
ANTIRHEUMATIC
ANTITUBERCULOSIS
ANTIULCER
ANTIVENOM
CARDIOVASCULAR
CONTRAST MEDIA
CORTICOSTEROID
COSMETIC
DERMATOLOGICAL
EYE PREPARATION
FOOD
HORMONE
IMMUNOSUPPRESSANT
MINERALS
TRADITIONAL MEDICINE
VACCINE
VITAMIN
0
100
200
300
400
500
600
700
800
No. Of Reports

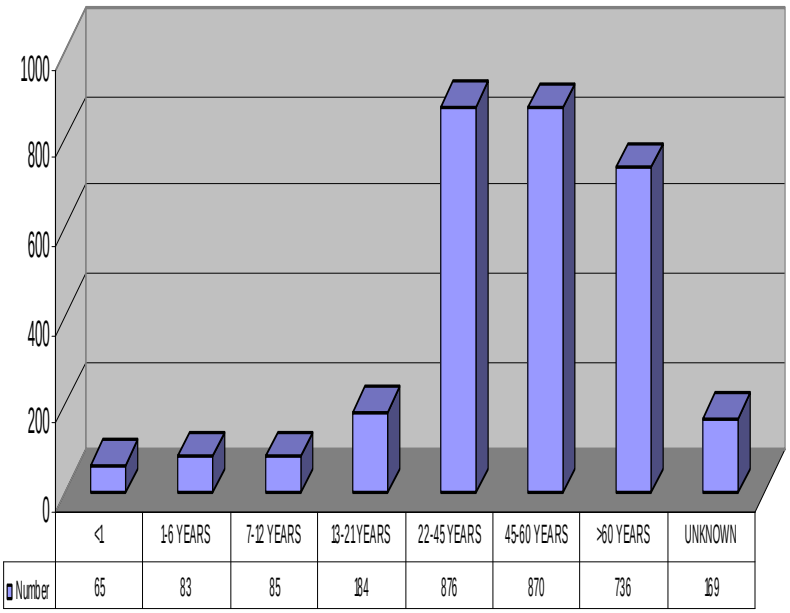
ADR BY PRODUCT CATEGORY




ADR REPORTS BY RACE (n=3068)
Unknown 12%
Others 7%
Malay 43%
Chinese 29%
Indian 9%
Malay
Indian
Chinese
Others
Unknown

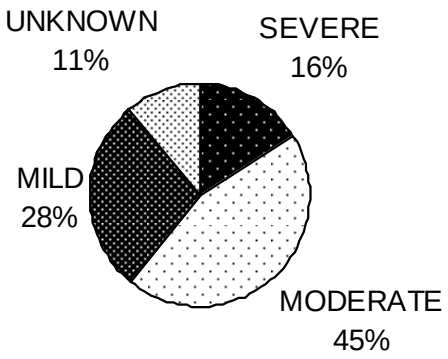

ADRS BY GENDER (n = 3068)
UNKNOWN 3%
MALE 45%
FEMALE 52%
MALE
FEMALE
UNKNOWN

ADR REPORTS BY AGE CATEGORY



No. of Reports

ANALYSIS OF ADR BY SEVERITY



TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS (YEAR 2002-2007)

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

TEN BEST REPORTERS

NO.	HOSPITAL NAME	NO. OF REPORTS
1.	HOSP. SELAYANG	197
2.	HOSP. KUALA LUMPUR	170
3.	UNIVERSITY MALAYA MEDICAL CENTRE	156
4.	HOSP. DUCHESS OF KENT	140
5.	HOSP. TUANKU JAAFAR	137
6.	HOSP. PULAU PINANG	126
7.	HOSP. SULTANAH AMINAH	122
8.	HOSP. MELAKA	121
9.	HOSP. UMUM SARAWAK	97
10.	HOSP. PAKAR SULTANAH FATIMAH	95