ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE 2005

1. MADRAC MEMBERS

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

MADRAC Members/*(Alternate members)*	
Puan 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 C.T. Chua Chin Teong 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. Patmini 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 2112 adverse drug reaction reports were reviewed.

Meeting	**83 02/05**	**84 03/05**	**85 05/05**	**86 07/05**	**87 09/05**	**88 11/05**
No Of Reports	**265**	**287**	**355**	**392**	**391**	**422**

3. ANALYSIS OF ADR REPORTS

A detailed review and analysis of the ADR reports received during the year 2005 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**
1.	Nevirapine	In view of the findings of the review of nevirapine by the US Food & Drugs Administration, it was recommended that: ***Indications and Usage section of the Viramune label now recommends <u>against</u> starting nevirapine treatment in women with CD4+cell counts greater than 250 cells/mm3 unless benefits clearly outweigh risks.*** In Malaysia, the indication that have been registered with DCA is : *VIRAMUNE is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on the analyses of changes in surrogate endpoints. At present, there are no results from controlled clinical trials evaluating the effect of VIRAMUNE in combination with other antiretroviral agents on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections or survival.* *Resistant virus emerges rapidly and uniformly when VIRAMUNE is administered as monotherapy. Therefore, VIRAMUNE should always be administered in combination with at least two additional antiretroviral agents.* The new recommended indication and usage should be included in the section of Indication and the usage of product containing Nevirapine and the product holder should notify the prescribers about this addition.	166

2.	COX-2 Inhibitors	Products containing Valdecoxib and Parecoxib had been suspended by DCA, in view of the findings of the review by US FDA: a) Valdecoxib ▪ The lack of adequate data on the cardiovascular safety of long – term use of Bextra, along with the increased risk of adverse CV events in short –term coronary artery bypass surgery (CABG) trials that FDA believes may be relevant to chronic use. b) Celecoxib ▪ Revised the Celebrex label to : Include a box warning containing the class of warnings and contraindication about CV and GI risk. ▪ Encourage practitioner to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. ▪ Include the medication guide as part of the labeling to inform patients of the potential for CV and GI risk associated with NSAIDs. ▪ Commit by Pfizer to conduct a long – term study to address the safety of Celebrex compared to naproxen and other appropriate drugs. In Malaysia, the inclusion of the following statement in the product inserts: ▪ COX-2 inhibitors be used as second line therapy • Contraindication in patients with the risk of ischemic heart disease and stroke • Prescribed with care in patients predisposed to the risk of hypertension, hyperlipidaemia, heart disease, peripheral arterial disease and in smokers • The lowest effective dose for the shortest possible duration should be used	DCA 169
3.	Thioridazine	Following the voluntary cancellation of registration for Melleril^{R} by Novartis (M) due to adverse cardiovascular events and poor benefit risk profile, a risk-benefit analysis of other generic products containing thioridazine was conducted. Based on this review, the DCA took the decision to disallow the continued use of thioridazine in Malaysia and the registration of these products be cancelled.	DCA 169

		However, a grace period will be given for patients to be switched to other safer antipsychotic agents before the product is fully withdrawn from the market.	
4.	Products containing Ginseng	For traditional products containing ginseng the current labeling requirement in Malaysia should contain: • *Safe use of ginseng in pregnant women and children has not been established.* • *Do not exceed the stated dose.* • *Continous use exceeding three months is not advisable.* But, there's no prove evidence that ginseng cannot be use more then 3 months. In the view review from Switzerland: *"The SPC is not consistent among the products: most carry a warning against use in pregnancy, some do not. Among does who do, most point out there is no teratogenicity has been seen in animal studies on ginseng but that there are no controlled studies in humans and therefore medical advice should be sought before taking the product during pregnancy or if breastfeeding.. As some products are alcoholic solutions, their SPCs focus on the focus on the alcohol content as a reason for not administering it during pregnancy. The same applies for combinations with a relevant content of vitamin A.* *As far as long term use goes, there are no limitations formulated as contraindications. Most combination products do advice against long term use but give no information on specific duration."* Because of that, labeling requirement for traditional medicines containing ginseng has been changed from *"Continuous use exceeding 3 months not advisable"* to ***"Safety on long term use has not been established"***	DCA 169
5.	Propolis and Royal Jelly	**Royal Jelly** For traditional medicines containing Royal Jelly, the product label must carry the following statements: • Royal jelly may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals • Asthma and allergy sufferers may be at a greater risk **Propolis** This is due to the fact that royal jelly has been identified as a possible cause of contact dermatitis, bronchospasm, anaphylaxis, asthma, urticaria and rhinitis. For traditional medicines, for topical use containing	DCA 170

		Propolis, the product label must carry the following statement: • Propolis may cause allergic skin reactions	
6.	Parecoxib	**REINSTATEMENT OF REGISTRATION** When the product registration for Bextra was suspended, it included both the oral and injectable form i.e valdecoxib and parecoxib. Following a review of the appeal submitted by Pfizer (M), the DCA decided to reinstate the registration for IV Parecoxib (Inj Dynastat) but with the following conditions: • Indication : Restricted to the management of post operative pain in the immediate postoperative setting only • Use limited to 2 days only with a maximum dose of 80mg • Boxed warning on the contraindication for use in patients undergoing CABG and those with cardiovascular risk.	DCA 171
7.	Product containing Glucosamine	DCA have registered a few products containing glucosamine and chitin which is derived from seafood but none of these products stated it on the label. Due to the literature, there's a few of anecdotal reports stated that for people who are allergic to seafood which can cause the reaction such as rash, will have the same allergy reaction when they use a product containing glucosamine derived from seafood. In Australia, if the source of the products is derived from seafood, the product label should state "derived from seafood". This can prevent people who are allergic to seafood to use this kind of products. To reduce the potential of adverse event, for product containing glucosamine and chitin which are derived from seafood, the label of the products should state **"Derived from seafood"**. But, this statement is not applicable to products which is the source is clearly from seafood.	DCA 175

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

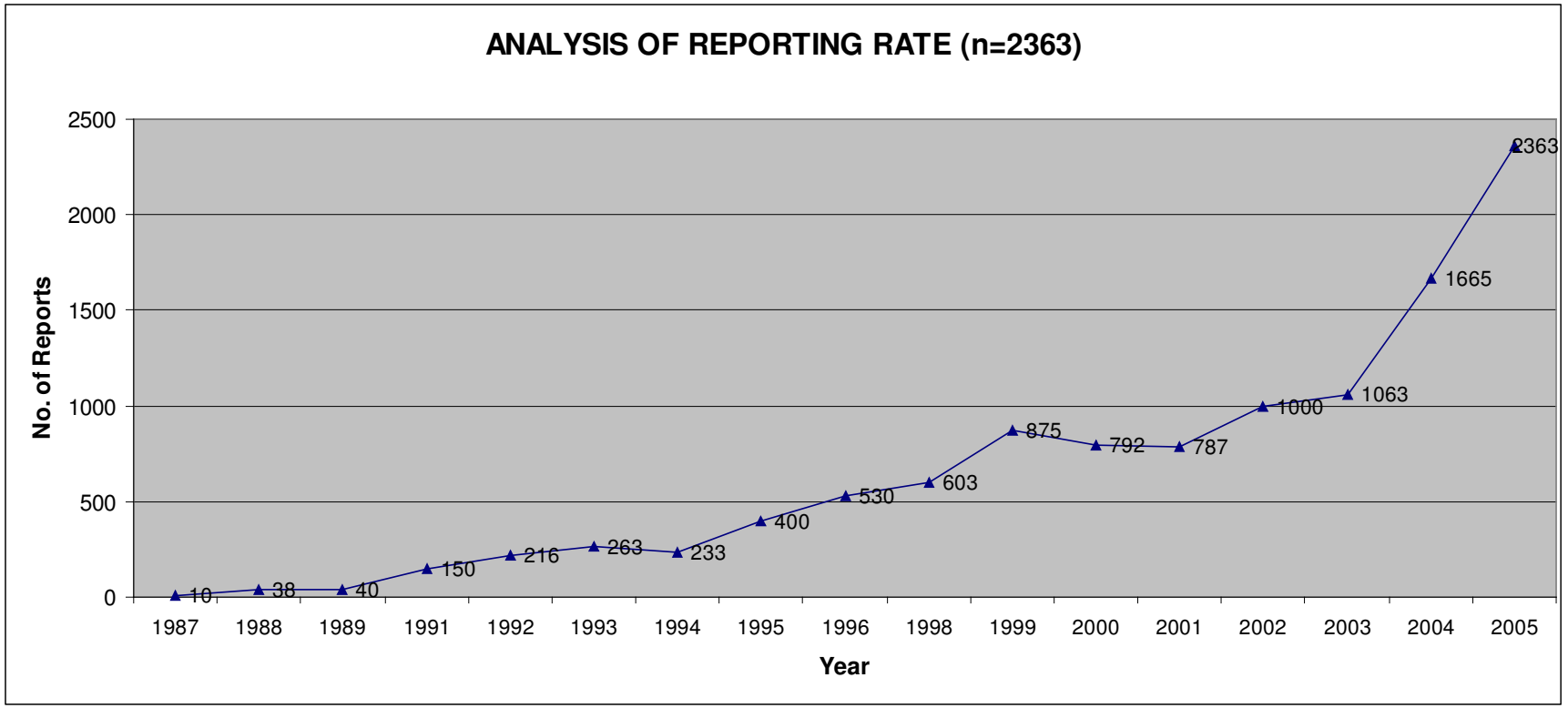
MADRAC members conducted several talks over the year in an effort to promote ADR reporting as well as to update health professionals on issues related to drug safety

NO.	TITLE OF PRESENTATION	FORUM	PLACE	DATE
1	Adverse Dermatological Manifestations of Drugs	Persidangan Farmasi negeri Melaka	Melaka	21 Jun 2005
2	ADR Reporting & Product Complaints	Bengkel Farmasi Klinikal	P. Pinang	1 April 2005
3	Adverse Drug Reactions, Aduan & Panggilbalik Produk	Kursus PTK4	Shah Alam	15 April 2005
4	Aduan & Panggilbalik Produk	Sessi Bimbingan Kompetensi Pegawai Farmasi U48	BPF, P. Jaya	13 Julai 2005
5	ADR Reporting: The Malaysian Experience (Plenary lecture)	Persidangan Kesihatan Negeri Kelantan	Kota Bharu, Kelantan	7 Julai 2005
6	ADR Reporting	Kursus PTK4	Seremban, N. Sembilan	26 Julai 2005
7	ADR Reporting	CME Hospital Kota Bharu	Kota Bharu, Kelantan	4 Ogos 2005
8	ADR Reporting	Kursus PTK4	Shah Alam	16 Sept 2005

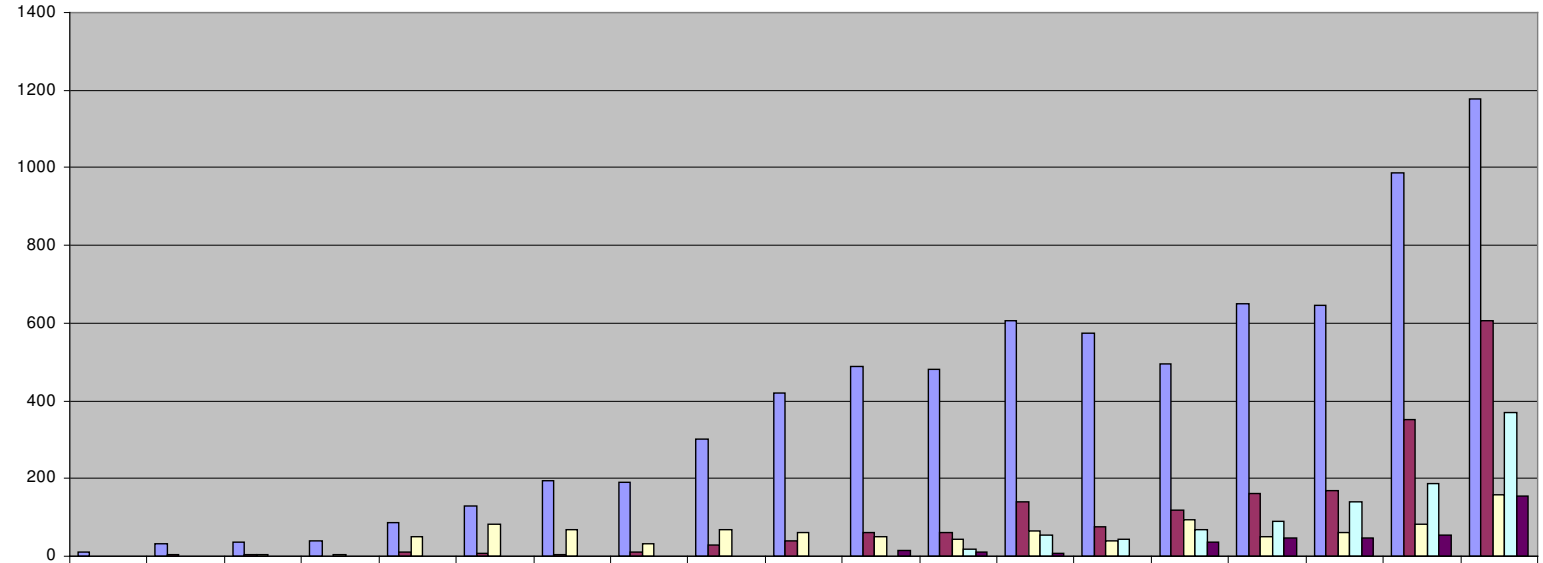
6. WORLD HEALTH ORGANISATION

2009 ADR reports reviewed by MADRAC were submitted to the International Centre for DRUG Monitoring (WHO) in Upssala, Sweden.

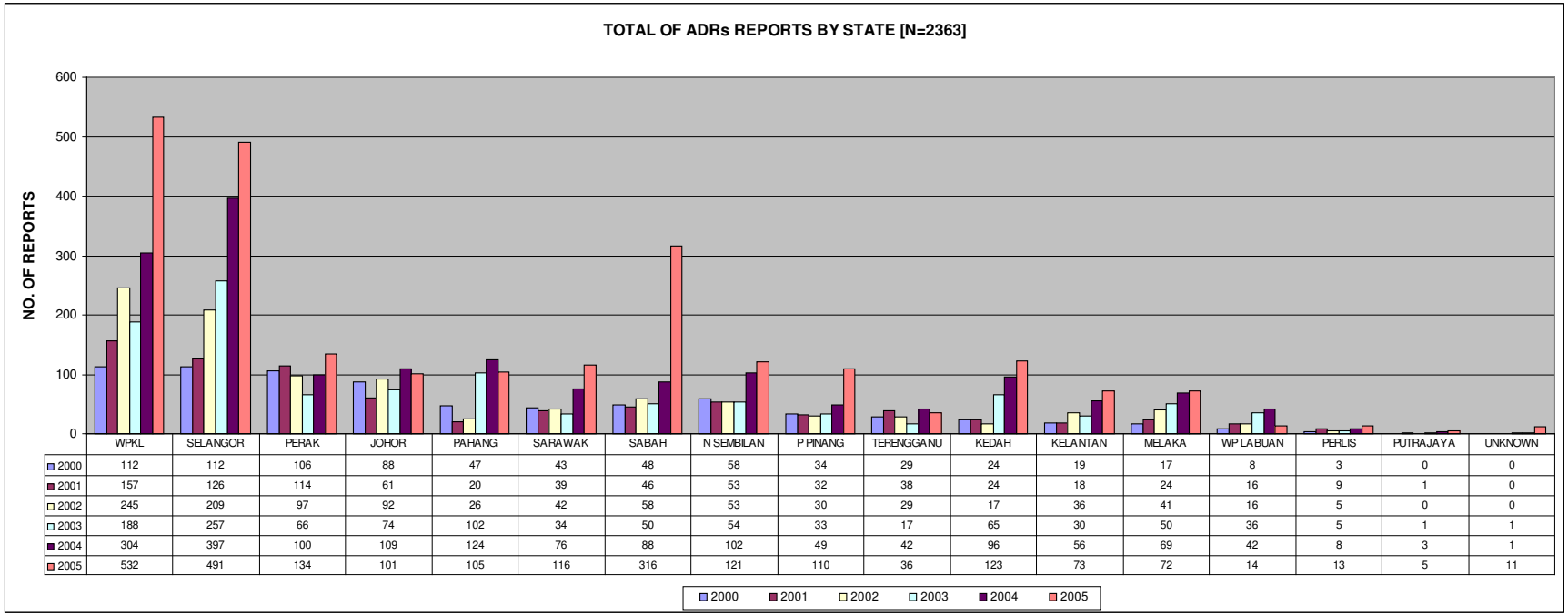
APPENDIX 1


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

ANALYSIS OF ADRs BY REPORTERS [N=2363]



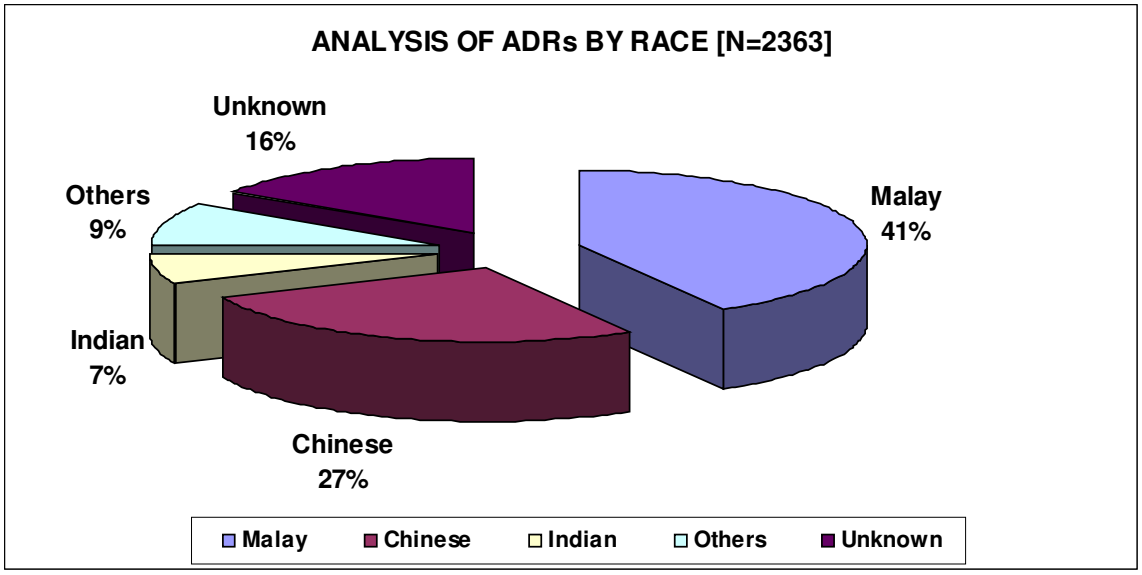
	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Government Doctors	10	32	36	39	87	129	193	191	303	419	489	480	608	573	496	651	646	988	1179
Others (Pharmacist, Dentist)	0	3	2	1	12	6	2	9	27	40	62	61	141	74	118	162	169	352	606
GP/Private Specialist	0	1	2	4	51	81	68	33	70	61	51	44	66	38	94	49	60	83	157
Company	0	0	0	0	0	0	0	0	0	0	1	18	54	43	67	90	141	188	368
University	0	0	0	0	0	0	0	0	0	0	16	11	7	0	36	47	47	54	153

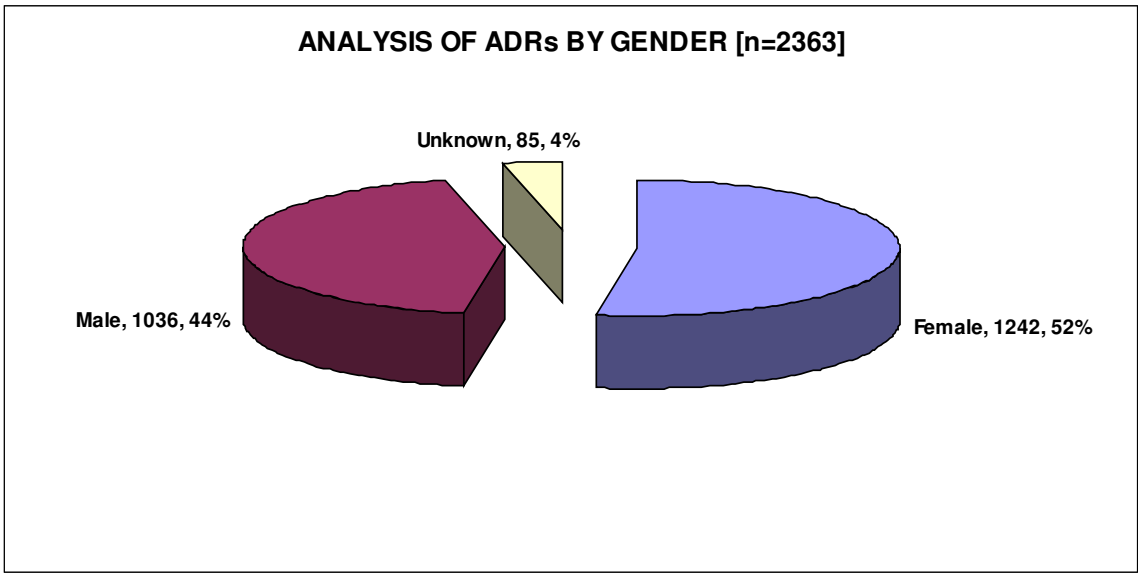


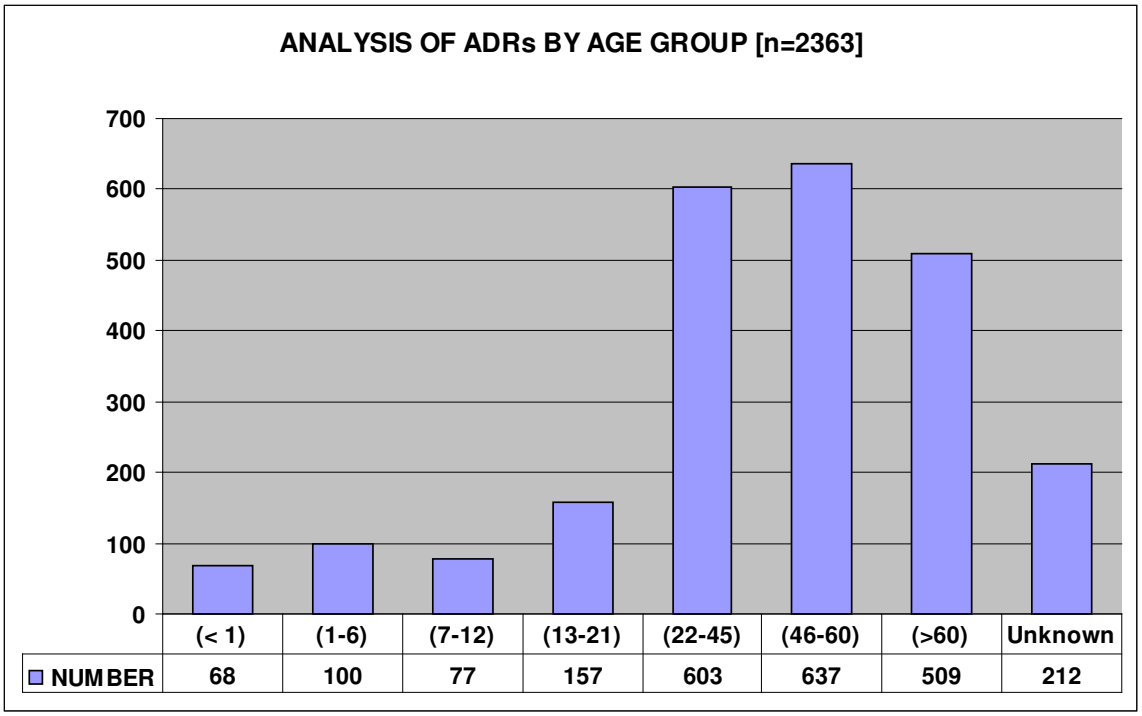
	WPKL	SELANGOR	PERAK	JOHOR	PAHANG	SARAWAK	SABAH	N SEMBILAN	P PINANG	TERENGGANU	KEDAH	KELANTAN	MELAKA	WP LABUAN	PERLIS	PUTRAJAYA	UNKNOWN
2000	112	112	106	88	47	43	48	58	34	29	24	19	17	8	3	0	0
2001	157	126	114	61	20	39	46	53	32	38	24	18	24	16	9	1	0
2002	245	209	97	92	26	42	58	53	30	29	17	36	41	16	5	0	0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

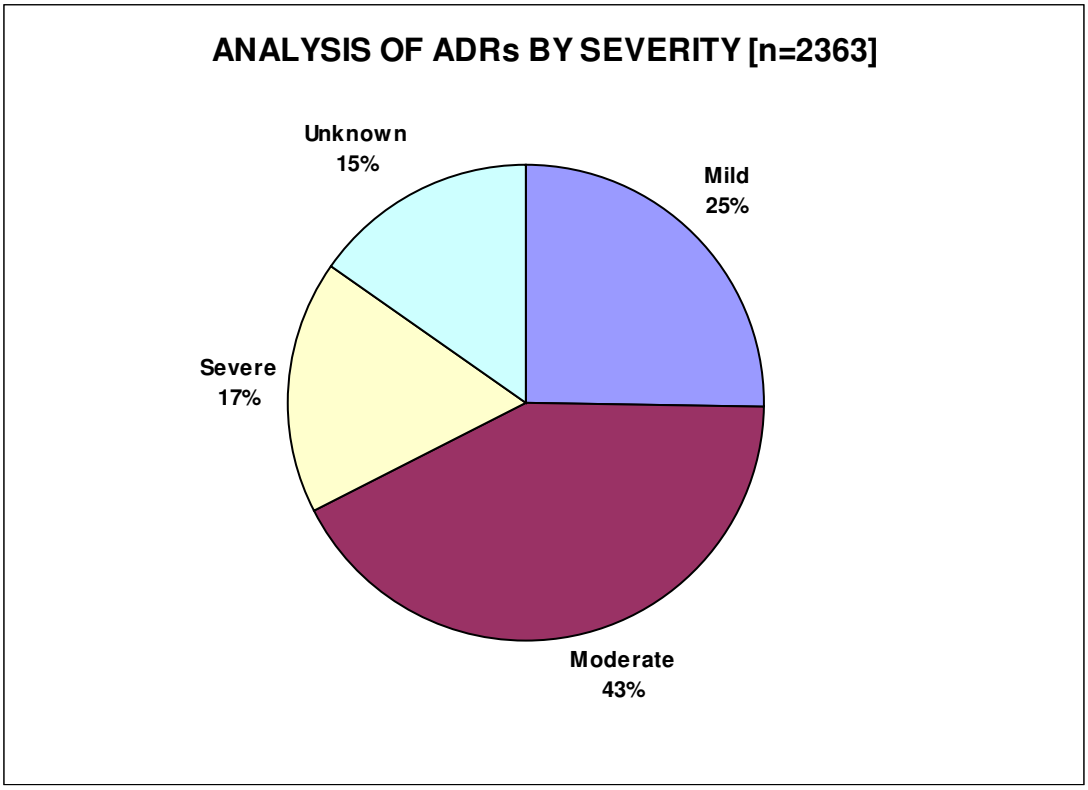
TOP TEN REPORTERS (INSTITUITION) – 2005

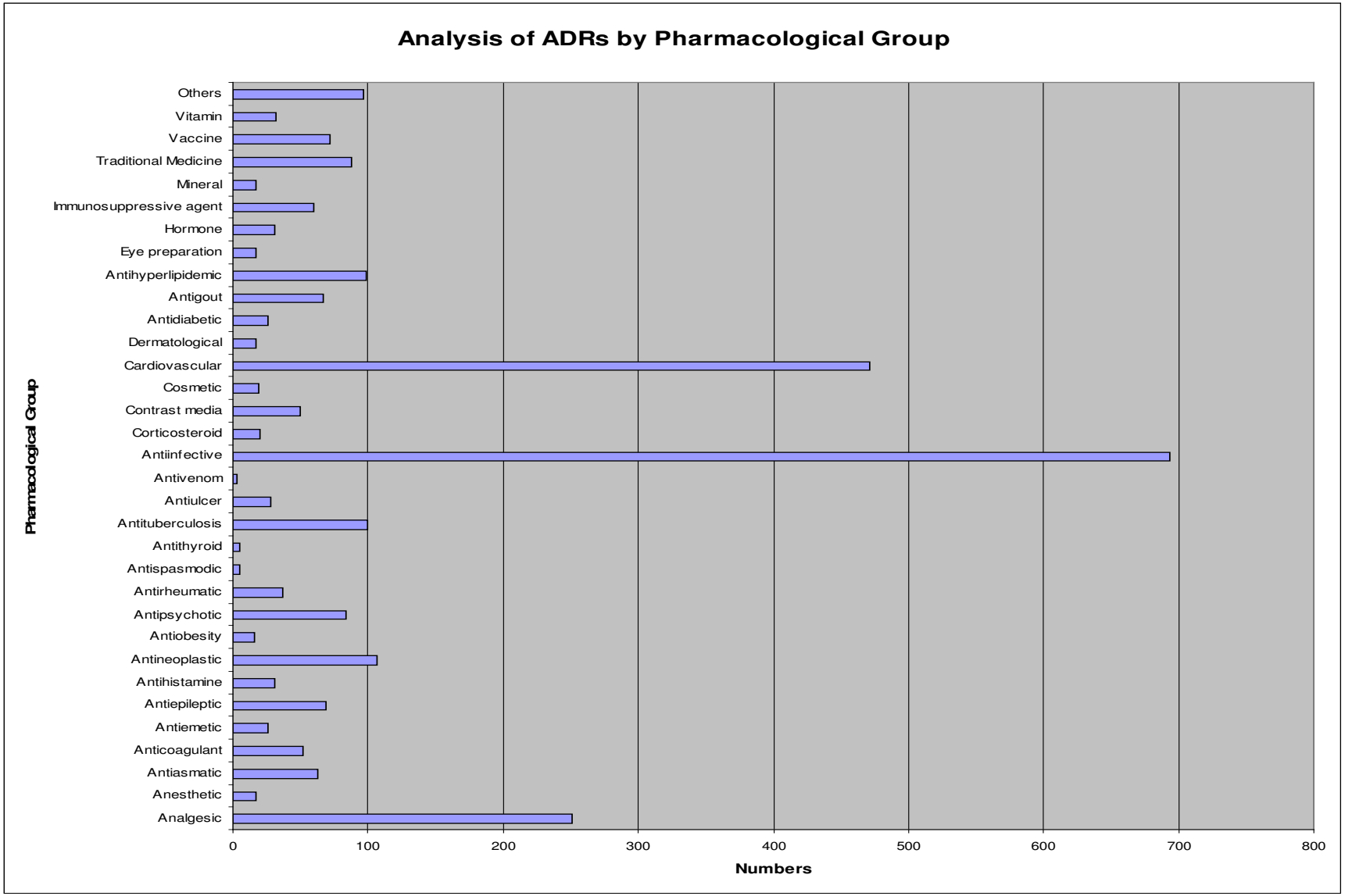
NAME OF INSTITUTION	NO. OF REPORTS
H Duchess of Kent	224
H Kuala Lumpur	192
H Selayang	172
H UKM	117
H Pulau Pinang	88
H Sultanah Aminah	68
H Seremban	68
H Melaka	64
H Umum Sarawak	52
H Ipoh	49

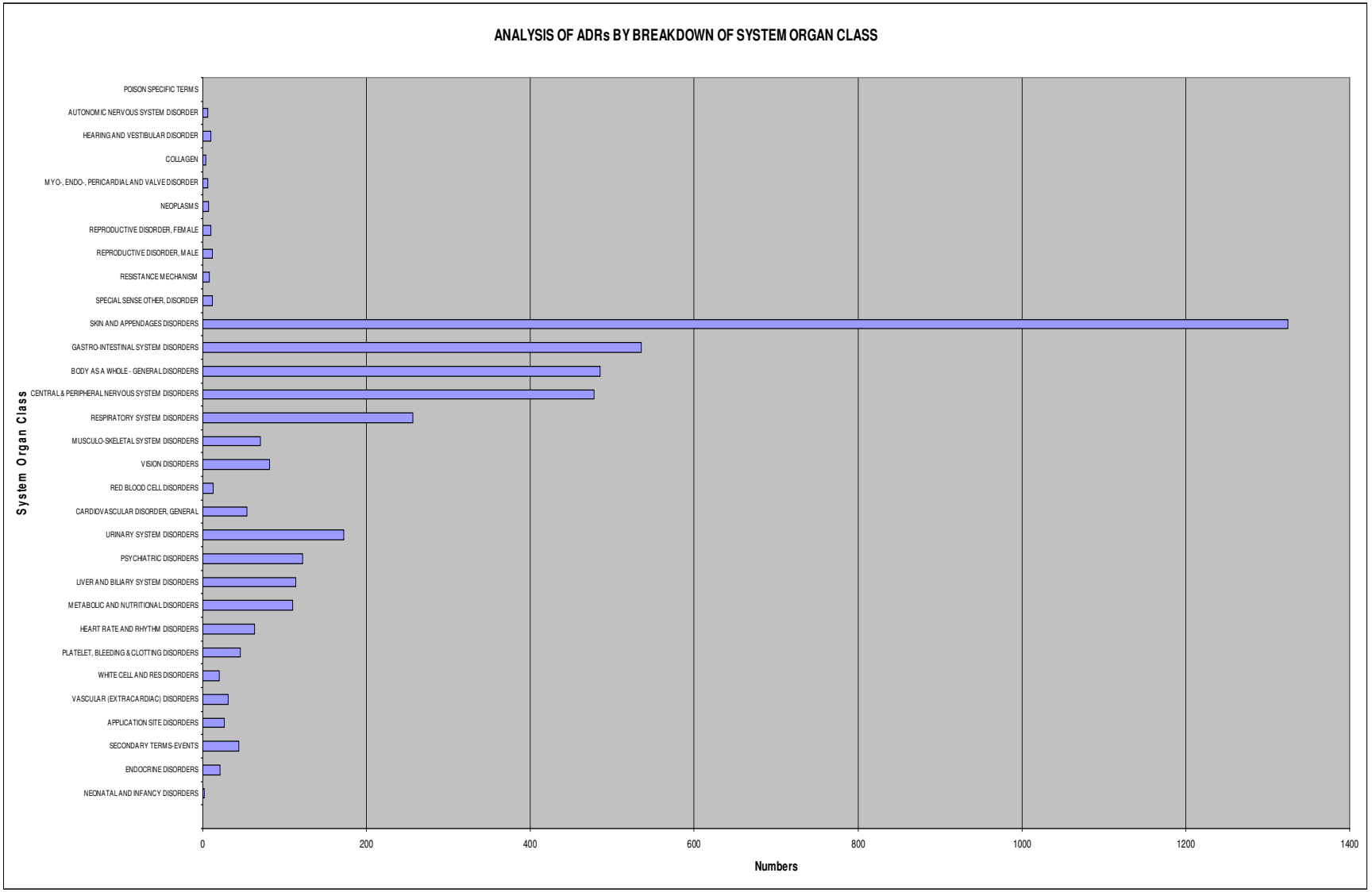

ANALYSIS OF ADRs BY RACE [N=2363]
Unknown
16%
Others
9%
Malay
41%
Indian
7%
Chinese
27%
Malay
Chinese
Indian
Others
Unknown


ANALYSIS OF ADRs BY GENDER [n=2363]
Unknown, 85, 4%
Male, 1036, 44%
Female, 1242, 52%


ANALYSIS OF ADRs BY AGE GROUP [n=2363]
700
600
500
400
300
200
100
0
(< 1)
(1-6)
(7-12)
(13-21)
(22-45)
(46-60)
(>60)
Unknown
NUMBER
68
100
77
157
603
637
509
212


ANALYSIS OF ADRs BY SEVERITY [n=2363]
Unknown
15%
Mild
25%
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
Anticoagulant
Antiasmatic
Anesthetic
Analgesic
0
100
200
300
400
500
600
700
800
Numbers


ANALYSIS OF ADRs BY BREAKDOWN OF SYSTEM ORGAN CLASS
System Organ Class
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
Numbers