MADRAC

Malaysian Adverse Drug Reactions Newsletter

National Pharmaceutical Control Bureau,
Ministry of Health Malaysia

This newsletter is also available on our website: **http://www.bpfk.gov.my**

To report an adverse drug reaction:
1. Visit http://www.bpfk.gov.my,
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:
National Centre for Adverse Drug Reactions Monitoring,
Centre for Post Registration
National Pharmaceutical Control Bureau
Ministry of Health
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ADVERSE DRUG REACTIONS (ADR) REPORTS FOR 2008 – AN OVERVIEW

For the year 2008, the National Centre for Adverse Drug Reactions Monitoring received a total of 4826 local spontaneous reports of suspected adverse drug reactions. This was an increase of 1758 reports (57.3%) over the 3068 reports received for 2007. Figure 1 below shows the reporting rate since 1987.

(*Please refer to* "**Figure 1 Analysis of Reporting Rate from Year 1987 to 2008**" *on Page 2*)

Since the year 2005, the Selangor state hospitals have topped all the other states' hospitals with the number of ADR reports submitted. This is followed by the hospitals in Wilayah Persekutuan (612) and Sabah (611). (Figure 2)

(*Please refer to* "**Figure 2 Total Number of ADR Reports Received Categorized by State**" *on Page 2*)

During the course of the year 2008, pharmacists submitted the most ADR reports, which was 49.75% of the total number of ADR reports received. It was an increase of 87.13% as compared to the year 2007. The number of government doctors reporting ADRs has also increased by 18.32% over the previous year. (Figure 3)

(*Please refer to* "**Figure 3 Total Number of ADR Reports Received Categorized by Reporters**" *on Page 2*)

Among the ADR reports received, the most number of suspected ADRs were attributed to the pharmacological group "cardiovascular". (Figure 4)

(*Please refer to* "**Figure 4 Analyses of Reports by Pharmacological Group**" *on Page 2*)

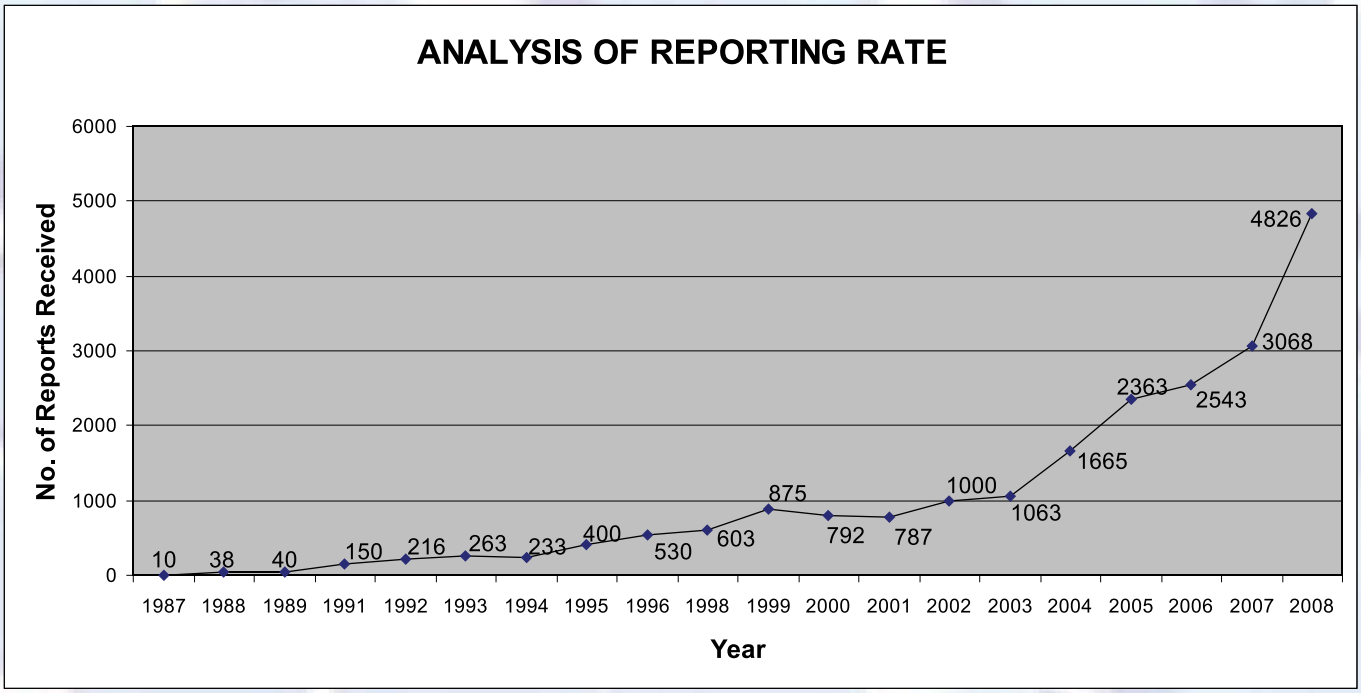
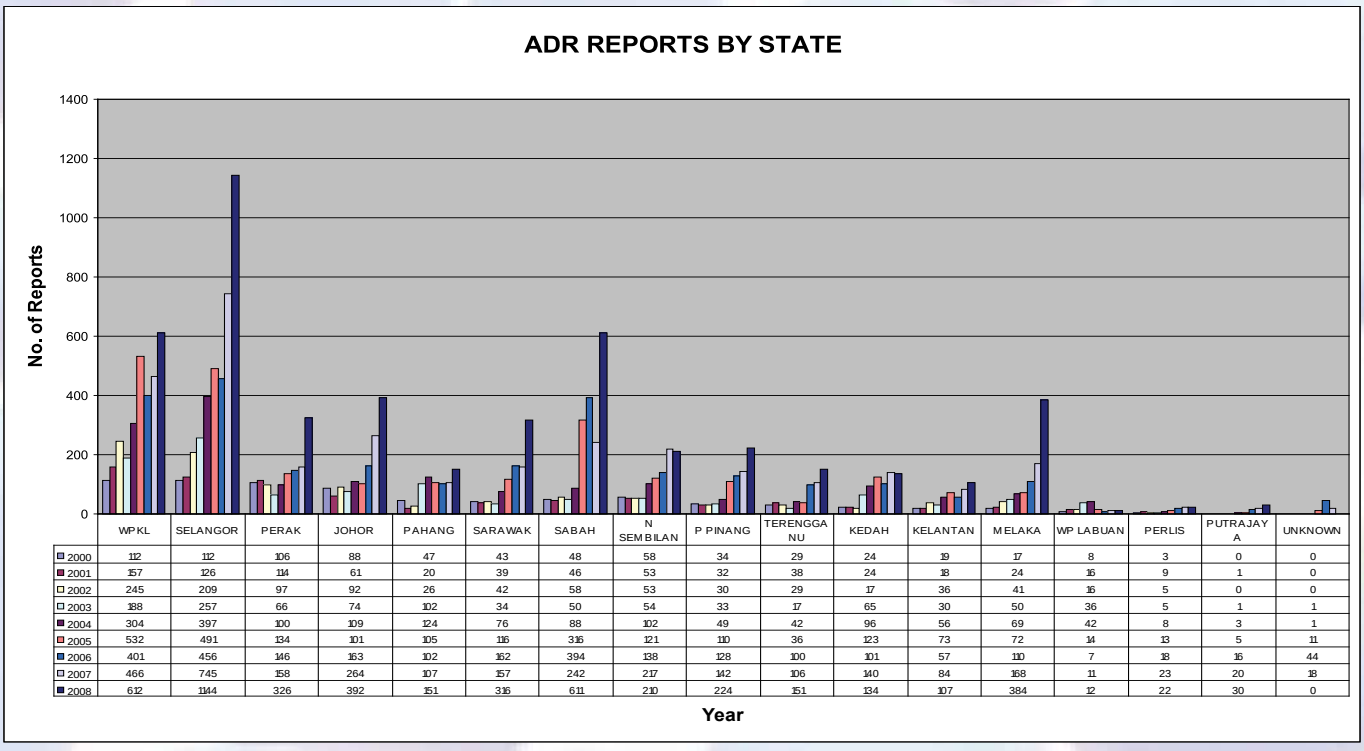
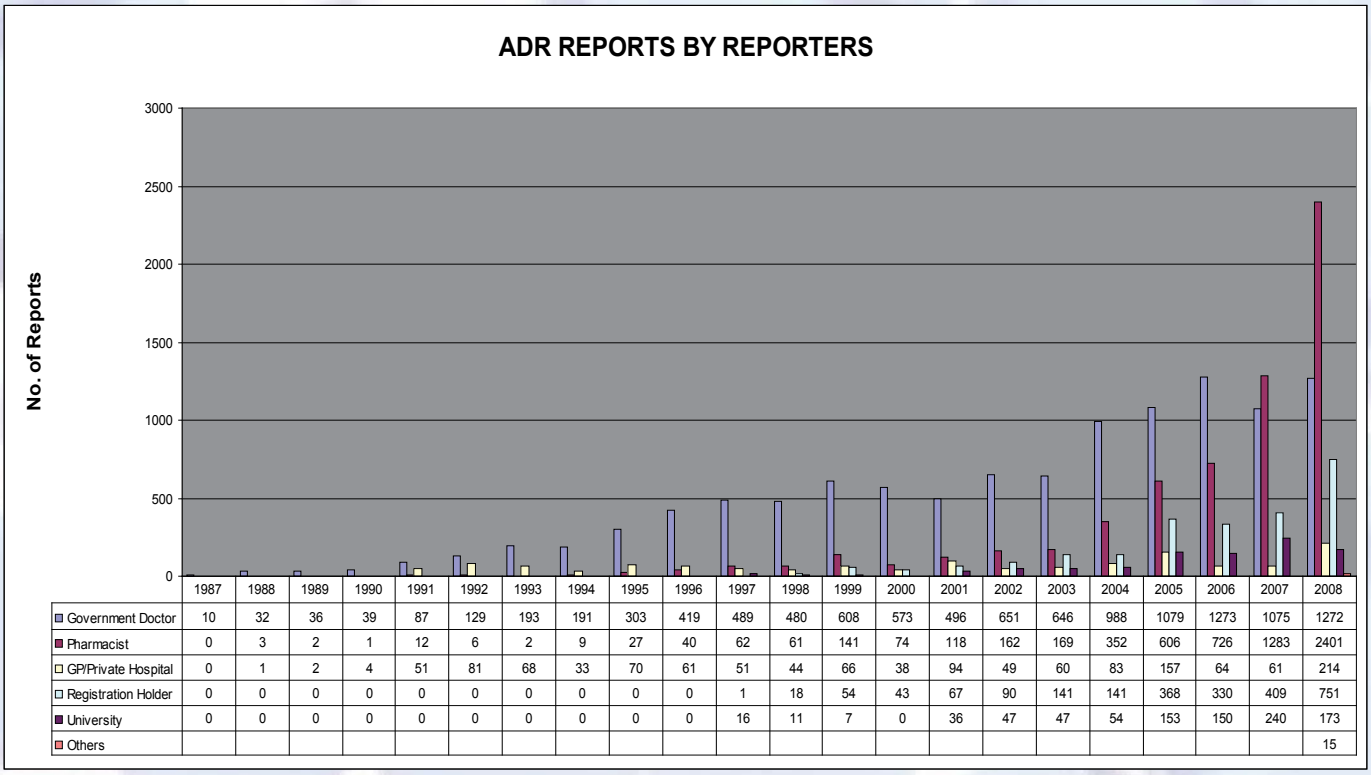


Figure 1 Analysis of Reporting Rate from Year 1987 to 2008



	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

Figure 2 Total Number of ADR Reports Received Categorized by State



	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

Figure 3 Total Number of ADR Reports Received Categorized by Reporters

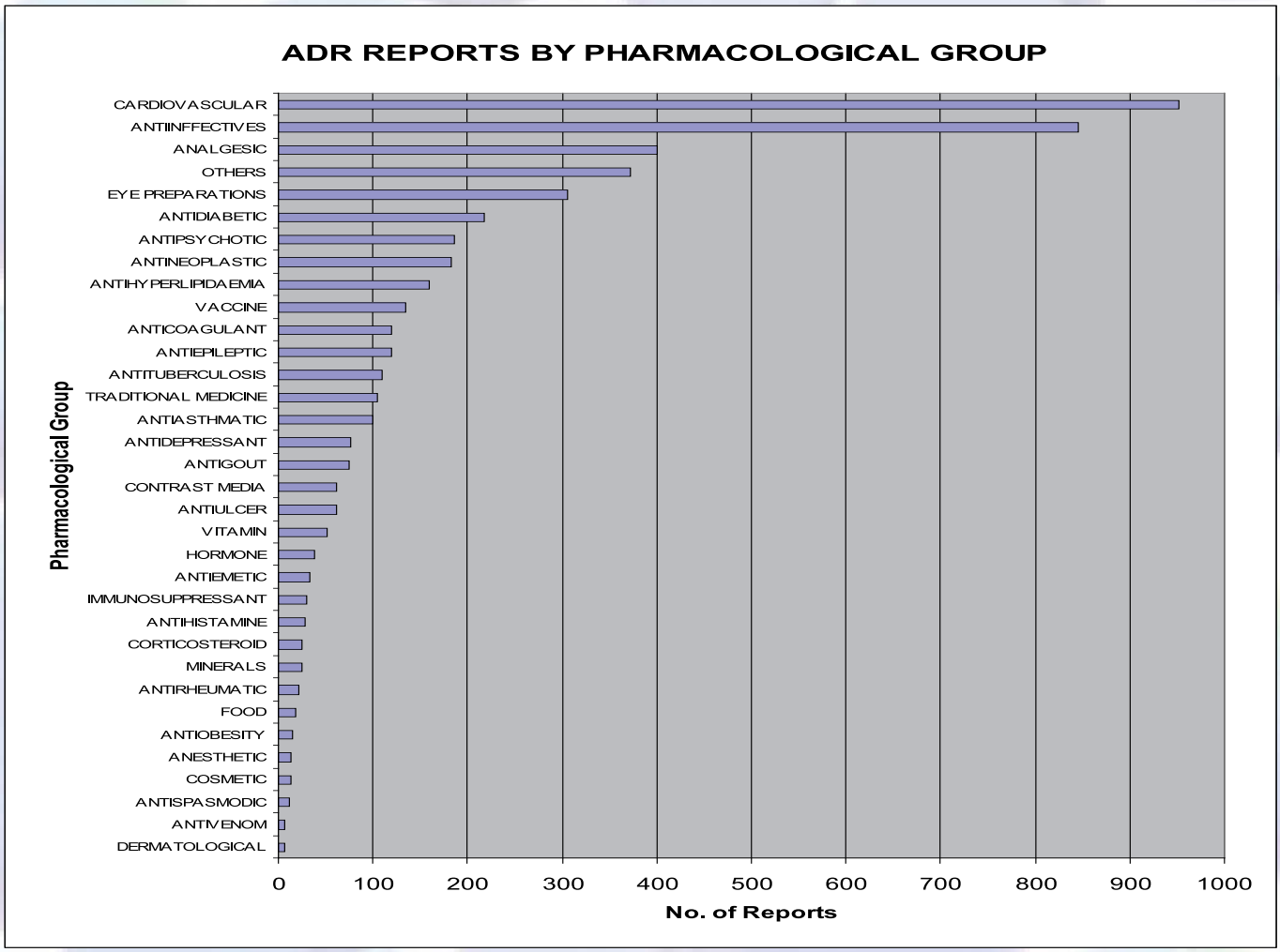


Figure 4 Analyses of Reports by Pharmacological Group

TEN DRUGS WITH THE MOST REPORTED ADVERSE DRUG REACTIONS

Figure 5 displays the ten drugs with the most ADR reports received from 2004 to 2008 whilst Figure 6 shows the main ADRs for the ten most reported drugs in year 2008. The figures are obtained from random reporting and are not absolute. Hence, the figures should not be interpreted to imply that these drugs are associated with or cause more ADRs than the other drugs of the same class.

In 2008, the suspected drug which contributed to the highest number of ADR reports was perindopril. This is no different if compared to year 2007. The ADR reports were mainly related to respiratory system disorders such as coughing/dry cough. The other suspected drugs among the top 10 which contributed to the most number of ADR reports were aspirin, diclofenac, amlodipine, metformin, allopurinol, co-trimoxazole, heparin and lovastatin. The ADR reports were mostly related to skin and appendages disorders.

NO	2004	2005	2006	2007	2008
1	(No. of Reports) ALLOPURINOL (37)	(No. of Reports) CAPTOPRIL (52)	(No. of Reports) TRADITIONAL MEDICINE (68)	(No. of Reports) PERINDOPRIL (97)	(No. of Reports) PERINDOPRIL (217)
2	PARACETAMOL (29)	ALLOPURINOL (51)	DICLOFENAC (65)	ALLOPURINOL (75)	ASPIRIN (134)
3	CARBAMAZEPINE (29)	CLOXACILLIN (50)	CARBAMAZEPINE (62)	CLOXACILLIN (71)	DICLOFENAC (111)
4	NIFEDIPINE (28)	DICLOFENAC (44)	NIFEDIPINE (58)	DICLOFENAC (71)	AMLODIPINE (92)
5	CO – TRIMOXAZOLE (28)	NIFEDIPINE (44)	ALLOPURINOL (57)	METFORMIN (69)	METFORMIN (91)
6	ERYTHROMYCIN (23)	METFORMIN (39)	PERINDOPRIL (57)	ASPIRIN (67)	TRADITIONAL MEDICINE (80)
7	AMOXYCILLIN (23)	PARACETAMOL (38)	CO – TRIMOXAZOLE (55)	TICLOPIDINE (50)	ALLOPURINOL (80)
8	MEFENAMIC ACID (21)	CO – TRIMOXAZOLE (37)	ASPIRIN (41)	RIFAMPICIN (46)	CO – TRIMOXAZOLE (73)
9	ASPIRIN (19)	ATENOLOL (37)	ERYTHROMYCIN (40)	PHENYTOIN (44)	HEPARIN (70)
10	CLOXACILLIN (18)	CEFUROXIME (36)	PHENYTOIN (39)	AMOXYCILLIN (43)	LOVASTATIN (66)

Figure 5 Ten Drugs with the Most ADR Reports

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)

DRUG (No. of Reports)	MAIN ADR 1 (No. of Reports)	MAIN ADR 2 (No. of Reports)	MAIN ADR 3 (No. of Reports)
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 – 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)

Figure 6 Main ADR Related to the Ten Drugs with the Most ADR Reports in Year 2008

*Due to contamination with over-sulphated chondroitin sulphate (OSCS). See Summary of regulatory actions taken in 2008 (page 8).

TEN BEST REPORTING HOSPITALS

In the year 2008, the National Pharmaceutical Control Bureau received the most adverse drug reactions reports from Hospital Duchess of Kent which contributed 6.26% of the total reports. This was followed by Hospital Kuala Lumpur (5.07%) and Hospital Melaka (4.75%). The other reporting hospitals that were among the top ten were Hospital Sultanah Aminah, Hospital Pulau Pinang, Hospital Umum Sarawak, Hospital Pakar Sultanah Fatimah, Hospital Raja Permaisuri Bainun, Hospital Mesra Bukit Padang, Hospital Selayang and Hospital Queen Elizabeth (Figure 7).

The National Pharmaceutical Control Bureau appreciates the contribution made by all reporters and would like to thank all hospitals and clinics which took the initiative to report suspected adverse events.

NO.	NAME OF HOSPITAL	TOTAL
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

* The ten best reporting hospitals were based purely on quantity of the reports sent in.

SUMMARY OF REGULATORY ACTIONS TAKEN IN 2008

During the course of the year MADRAC proposed a number of recommendations based on safety concerns for the consideration of the Drug Control Authority (DCA). As a result, the following regulatory actions were taken by the 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, "Gangrene has been reported in a lower extremity when infusions of noradrenaline were given in an ankle vein". - 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 MADRAC's 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	**DCA 205 29/05/2008**

			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-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 patient's cardiovascular status should be made by a physician 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-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 patient's cardiovascular status should be made by a physician 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 "Gamat/sea cucumber (Stichopus horrens)" products marketed under company Healwell 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 "Gamat" 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.	**DCA 207 04/08/2008**
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 products' 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 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.	**DCA 209 25/09/2008**

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 "tendonitis" and "tendon rupture" stated 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 "tendonitis" and "tendon rupture". - The DCA has agreed to MADRAC's proposal that all marketing authorization holders of fluoroquinolone antimicrobials include the following information in the product information leaflet:- ***'Special Warnings and Precaution for Use':*** Musculo – skeletal system: **"The risk of developing fluoroquinolone-associated tendonitis 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 inflammation".	**DCA 210 27/11/2008**

SAFETY ISSUES OF CURRENT INTEREST

ORAL SODIUM PHOSPHATE PRODUCTS FOR BOWEL CLEANSING

The United States Food and Drug Administration (USFDA) has alerted healthcare professionals and patients on the risk of acute phosphate nephropathy associated with the use of oral sodium phosphate (OSP) products for bowel cleansing prior to colonoscopy or other procedures. It has occurred in patients without identifiable risk factors. However, some of these patients were dehydrated prior to ingestion of OSPs or did not drink adequate fluids after ingesting OSPs.

Acute phosphate nephropathy is a rare, serious adverse event which is characterized by deposits of calcium-phosphate crystals in the renal tubules that may result in permanent renal function impairment. The risk of acute phosphate nephropathy increases in patients:-

- Age 55 years and above
- Who are hypovolemic or have decreased intravascular volume
- Having baseline kidney disease, bowel obstruction or active colitis
- Using medications that affect renal perfusion or function [diuretics, angiotension converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and possibly nonsteroidal anti-inflammatory drugs (NSAIDs)].

There are two OSP products registered in Malaysia; Fleet and Colclean. Both marketing authorization holders for these products have agreed to amend the package inserts of their products to include the following:-

- Use OSPs with caution in patients over 55 years of age.
- Use OSPs with caution in patients with dehydration, kidney disease, delayed bowel emptying, or acute colitis.
- Use OSPs with caution in patients taking medicines that affect kidney function or perfusion, such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and possibly non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients who may be at increased risk for acute phosphate nephropathy, including those with vomiting and/or signs of dehydration, obtain baseline and post-procedure laboratory data (electrolytes, calcium, phosphate, BUN and creatinine). For smaller, frail individuals, also monitor glomerular filtration rate.

The companies have also agreed to send a Dear Healthcare Professional (DHCP) Letter in regard to this issue and to hold constant discussion and education sessions with health care professionals as part of a risk evaluation and mitigation plan adopted to ensure patients are using these products according to indication and appropriate instructions.

Reference:

1. USFDA Medwatch, “Oral Sodium Phosphate (OSP) Products for Bowel Cleansing”, http://www.fda.gov/cder/drug/infopage/OSP_solution/default.htm, 12 November 2008.

ASSOCIATION OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY WITH EFALIZUMAB

On 19 February 2009, the European Medicines Agency (EMEA) recommended the suspension of marketing authorisation of Raptiva (efalizumab). Raptiva was authorized in the European Union (EU) in 2004 for the treatment of moderate to severe chronic plaque psoriasis in adults who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen ultraviolet-A (PUVA).

This EMEA decision was based on the conclusions drawn from a review of all available safety and efficacy data on this medicine. The EMEA’s Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Raptiva no longer outweigh its risks and safety concerns such as progressive multifocal leukoencephalopathy (PML) in patients taking the medicine. Three confirmed cases of PML were reported between September 2008 and January 2009 in patients who had been receiving Raptiva for more than three years and two of these cases resulted in the patients’ death.

In addition to PML, Raptiva was found to be associated with other serious side effects such as Guillain-Barré and

Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections. It was also found that there was not enough evidence to identify a group of patients in which the benefits of Raptiva outweigh its risks, in particular there was a lack of data on effectiveness and safety in patients who have no other treatment options and who may already have a weakened immune system as a result of previous treatments.

In Malaysia, Raptiva is indicated for the treatment of adult patients with moderate to severe plaque psoriasis. Upon EMEA's announcement, the Drug Control Authority (DCA) decided to suspend Raptiva's registration due to the serious adverse events reported. The DCA issued a public statement to announce the following:-

- The registration of Raptiva has been suspended with immediate effect.
- Merck Sdn. Bhd. has been instructed to stop the importation, sale and distribution of Raptiva with immediate effect.
- New patients should not be started on Raptiva.
- Patients being treated with Raptiva should not stop treatment abruptly but should contact their doctors to discuss the most appropriate replacement treatment needed for their condition.

Upon consultation with the DCA, Merck also issued a DHCP Letter to update healthcare professionals on this issue. The DCA will further assess the situation before taking a final position on Raptiva's product registration status.

References:

1. EMEA's website, "Press Release: European Medicines Agency recommends suspension of the marketing authorization of Raptiva (efalizumab)", http://www.emea.europa.eu, 19 February 2009

2. DCA's public statement, "New Safety Concerns Relating to Use of Raptiva (Efalizumab)", 25 February 2009.

3. Merck Sdn. Bhd. Direct Healthcare Professional Communication on the Suspension of Product Registration for Raptiva®, 10 March 2009.

LOCAL CASE REPORTS

GOJI GUARANA

A 69-year-old male patient of Malay ethnicity developed "headache", "on and off fever", "watery and itchy eyes", "choking" and "water retention, especially on face" in October 2008 after three months of consuming "Goji Guarana". The patient took it as a supplement for general health and well being. He felt energetic after consuming this product. This product is distributed by Health Builders (M) Sdn. Bhd located at 6-2 & 6-3, Block A, Jalan 2/114, Kuchai Business Centre, Jalan Kuchai Lama, 58200 Kuala Lumpur.

A sample was provided along with the adverse drug reaction report. The sample was tested by the Centre for Quality Control, NPCB and found to **contain sildenafil**. As this preparation is an unregistered product, the report was forwarded to the Pharmaceutical Enforcement Division for further action.

Reference:

1. MADRAC's Database

TADALAFIL AND SMELL LOSS

Since September 2008, MADRAC has received three ADR reports related to tadalafil causing smell loss. All three reports concerned patients who took one dose of tadalafil 20mg for erectile dysfunction. No onset time was given. No rechallenge was done and the outcome was unknown. All of the patients had no concomitant medications or disease and were aged 40 years for the first and third cases and 50 years old for the second reported case.

From the package insert and WHO database, smell loss is not a documented ADR. MADRAC will continue to monitor ADRs associated with this product and further regulatory action will be taken, if deemed necessary.

References:

2. MADRAC's Database
3. WHO's Database