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BERITA Ubat-ubatan

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NEWSLETTER OF THE DRUG CONTROL AUTHORITY MALAYSIA

PHARMACEUTICAL AND COSMETIC REGULATORY SEMINAR 1999

The above seminar, jointly organised by the National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia, Pharmaceutical Association of Malaysia (PhAMA), Malaysian Organization of Pharmaceutical Industries (MOPI), Cosmetic, Toiletry & Fragrance Association of Malaysia (CTFA), Federation of Malaysian Manufacturers (FMM) Malaysian Cosmetic and Toiletries Industry Group (MCTIG) was successfully held on 19th and 20th October 1999 in Subang Sheraton, Petaling Jaya, Malaysia. The main theme was "Achieving New Heights in the Next Millennium". In conjunction with this seminar was the launching of NPCB's website http://www.bpfk.gov.my.

The seminar was honoured by the presence of YB Dato' M. Mahalingam, Parliamentary Secretary to the Ministry of Health Malaysia, who officially opened the seminar and also launched the website.

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The objectives of this seminar were to enhance the co-operation between the National Pharmaceutical

Control Bureau and the Pharmaceutical and Cosmetic Industries, to provide the latest information on the implementation of registration and licensing for cosmetics and to provide on an update on current global issues, policies and trends in the regulatory control of pharmaceuticals.

The seminar was attended by 270 participants from the government and private sectors. Representatives from the drug regulatory agencies of Brunei Darussalam and the Philippines were also amongst the participants.

The keynote address entitled "The Malaysian Healthcare Sector – Achieving New Heights in The Next Millennium" was delivered by Tan Sri Dato' Dr. Abu Bakar bin Dato' Suleiman, the Director General of Health Malaysia. He gave an overview of the pertinent issues in the development of the Malaysian Healthcare sector, touching on the challenges of Vision 2020, the healthcare delivery system and commercialization of healthcare, health manpower, telemedicine and the global challenges of the 21st century.

Nineteen speakers presented their papers, which covered a very wide range of topics. "Regulatory Control in Malaysia – Directions Beyond 2000", was presented by Dr. Anis bin Ahmad, Director of Pharmaceutical Services, Ministry of Health who highlighted the future perspective of regulatory control in Malaysia. "Pharmaceutical Inspection Co-operation Scheme (PIC/S)" and "Toll Manufacturing and Packaging" were presented by Mr. Robert W Tribe, Chief GMP Inspector from the Therapeutic Goods Administration of Australia and Mr. Steve Williams, Director of Intertech Global Access, Australia respectively.

Research and development of pharmaceuticals, cosmetics and natural products were among the topics discussed in the seminar. These topics were presented by Dr. Tan Soo Bin from CCM Pharma, Ms Gordana Gacic-Vukovijak from Dow Corning, Australia and Dr. K.K. Bhutani from N.I.P.E.R India respectively. Mr. John Appleby from The Boots Co. (Far East) Pte Ltd. stressed on the need to have customer friendly information for OTC products while Dr. Lian Lu Ming, Deputy Director of Pharmaceutical Services presented an update on advertisements and claims for pharmaceuticals.

Other issues covered in the seminar included "Towards Effective Drug Safety Monitoring " by Dr. Man Fung of Eli Lilly, Taiwan, "Drug Surveillance Programme" by Mr. V. Subramaniam from the Food & Drug Administration USA and "Future Aspirations of Pharmacovigilance in Malaysia" by Ms. Abida Haq of NPCB.

Dr. Fidela Moreno, Director of International Clinical Research Group, Pfizer Central Research, USA gave a talk on "Good Clinical Practice in Drug Trials" while Dr. Ramli Abdul Ghani from NPCB presented a topic on "Conducting Clinical Trials in Malaysia". Dr. Wayne Hooper from the University of Queensland Australia and Ms. Fudziah Ariffin from NPCB presented topics relating to bioequivalence studies.

The seminar also covered a series of topics on cosmetics, which included global harmonisation of cosmetics and toiletries, implementation of cosmetic registration, Malaysian GMP requirements for cosmetics and also MATRADE's role in export promotion of Malaysian goods and services. Dr. Frank B Anastasia, Mr. Ramli Zainal, Mr. Sulaiman Hj. Ahmad and Mrs. Susila Devi presented these topics respectively.

The two-day seminar enlightened the participants on the regulatory requirements of the Drug Control Authority in the new millennium. This seminar also enabled the participants to exchange new ideas and approaches in research for pharmaceutical, natural and cosmetic products. Indeed, there is an increasing need for co-operation between the industry and regulators to facilitate the new challenges in the next millennium.

COSMETIC REGISTRATION IN MALAYSIA

Cosmetics and toiletries have become an integral part of our daily lives and since cosmetics are used repeatedly, maximum effort must be made to ensure that they are safe and of acceptable quality.

Realising the need to ensure the safety of cosmetic products, a concept paper on the regulatory process for cosmetics was proposed to the Drug Control Authority (DCA) in September 1998. The following are the guiding principles in the proposal:

- the industry must be responsible for the safety, quality, performance and overall value of their products.
- the consumer must be provided with adequate information to help them make an informed choice of the products that best suits them.
- the government is given the mandate and authority to actively monitor the products at the point of manufacture and in the market.

Based on the concept paper, a Technical Working Group (TWG) was formed to draft a guideline for the implementation of cosmetics registration in Malaysia. The TWG comprises of officers from NPCB, members of the Cosmetic, Toiletries and Fragrance Association of Malaysia (CTFA) and members of the Malaysian Cosmetic and Toiletries Industrial Group (FMM-MCTIG).

The formation of the TWG is a consequence of a change in approach and our effort to increase openness, access and transparency. Input from the industry is vital to bring about a better and simpler regulatory procedure for cosmetics, which take into account the need for a competitive economy. By combining the practical experience of the industry with the obligation of the regulators, the TWG have prepared the draft guidelines which was approved by the DCA in July 1999.

MALAYSIAN GMP REQUIREMENTS FOR COSMETICS

Efforts towards establishing the Malaysian GMP Guidelines for Cosmetics were initiated in 1995. The original draft was prepared by the National Pharmaceutical Control Bureau (NPCB) and comments sought from the cosmetic industry. The industry felt that the draft was too stringent, with much resemblance to requirements laid down for pharmaceuticals.

Subsequently, a joint drafting committee comprising of members of the cosmetic industry associations and NPCB was set up in 1997 to review and re-draft the original guidelines, focusing on current global trends. A comparative study of GMP requirements for cosmetics or related products adopted by various countries such as Australia, Thailand, Taiwan, United Kingdom and the European Cosmetic Toiletry and Perfumery Association (COLIPA) was carried out.

The primary objective of establishing these guidelines is to assist local manufacturers in ensuring that cosmetics are consistently produced and controlled to the quality standards appropriate to their intended use. A well-implemented system of Quality Assurance incorporating GMP and QC is of fundamental importance to the production and control of cosmetics. Attaining quality of cosmetic products is the responsibility of the management and requires the participation and commitment of many relevant parties.

The proposed Malaysian GMP Guidelines for Cosmetics, a blend of local and international experience, is the fruitful outcome of regulatory and industry commitment. The cosmetic manufacturer must adopt and tailor these recommended practices to its own specific conditions. However, these guidelines may not completely cover every aspect of manufacture, control and quality assurance. The ultimate responsibility for production and distribution indeed lies with the manufacturer.

With the forth-coming registration of cosmetics, licensing of manufacturing premises shall be implemented accordingly. Compliance to the proposed guidelines and achieving GMP status will be an important pre-requisite for licensing of local cosmetic manufacturers.

BIOEQUIVALENCE STUDIES – MALAYSIAN REQUIREMENTS

Bioavailability testing of drug products in humans provides the most reliable method available for determining bioequivalence. Registration requirements as in the *Guidelines for Application for Registration of Pharmaceutical Products* states that the applicant seeking approval for registration of New Chemical Entity products must submit data demonstrating the bioavailability and bioequivalence of the intended product.

The need to conduct bioequivalence studies on generic drug products has been made necessary with the increasing number of complaints on product ineffectiveness received by the National Pharmaceutical Control Bureau (NPCB). Thus the registration of generic products was reviewed to include Bioequivalence (BE) requirements for all immediate release products containing nifedipine, captopril and cyclosporine. This was made effective from 1st March 1999 for imported generic products, whilst the local products are given until 30th June 2000 to comply.

According to the WHO definition, '*bioavailability*' is the rate and extent of availability of an active ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine, while two pharmaceutical products are *bioequivalent* if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such degree that their effects can be expected to be essentially the same.

Acceptance of bioequivalence studies by NPCB is based on the WHO Guidelines on Registration Requirements to establish interchangeability which includes:-

- **Subjects :** healthy volunteers, age range 18-55 years, weight within normal range, preferably non-smokers, no history of alcohol or drug abuse problems, should be screened for medical history, physical examination, standard lab tests.

- **Study Design :** a cross-over design, a wash-out period - more than 5 times the drug half-life, as single dose study (multi-dose studies - controlled-release, non-linear kinetics), 12-24 subjects (ICH 18-36 subjects), administration of product with defined time of ingestion, volume of fluid (150 ml is usual) and in the fasting state.

- **Pharmacokinetic Parameters to be assessed :** AUC_{0-t}, AUC_{α}, AUC-ratio, C_{max}, T_{max}, others if appropriate.

- **Test Samples :** Should be identical to the commercial batches, ideally from batches of industrial batches. When this is not feasible, pilot or small-scale production batches (> 10% of a production batch) should be used.

  Contents of the active drug substances between the two products should not differ by more than +/- 5%.

- **Validation of Analytical test methods:** Must be well-characterized, fully validated and documented. They should meet requirements of specificity, accuracy, sensitivity and precision.

- **Data Analysis & Acceptance Criteria:** Model-independent pharmacokinetic methods are preferred
  - C_{max} - use log transformed data for ANOVA and 90% CI (accepted interval 0.7 - 1.43);
  - T_{max} : non-parametric test (e.g. Wilcoxon);
  - AUC - use log transformed data for ANOVA and 90% CI (accepted interval 0.8 - 1.25)

- **Reporting of Results:** Should give the complete documentation which includes :
  - declaration by investigators
  - full study protocol
  - ethical clearance
  - details of products studied
  - description of clinical studies with full clinical data, protocol deviations etc.
  - individual subject data
  - graphs on linear and log scale
  - full data analysis/statistical analysis
  - conclusion

At present there are only two centres i.e. USM and UM which are actively conducting BE studies for the local industry of which the demand for such services cannot be met if BE studies are made mandatory for all generic products. At the national level, a working group comprising of members from universities and NPCB has been formed to look into the shortcomings and the future of BE studies in Malaysia. Strategies for short term, mid-term and long term planning have been and will continue to be implemented with the objective of giving more attention to the therapeutic equivalence of local generic drugs.

BAN ON PRODUCTS CONTAINING ARISTOLOCHIA

At the 107th meeting of the Drug Control Authority of Malaysia held on 26 August 1999, a decision was made to cancel the registration of all products containing the herbal ingredient Aristolochia.

This decision was made in the light of reports received from Europe where the use of products containing Aristolochia has been associated with interstitial fibrosis, chronic interstitial nephropathy, and end-stage renal failure (ESRF). Aristolochia species contains aristolochic acid, which is suspected to cause interstitial nephropathy. They are normally found in Chinese traditional medicines and have been used as a diuretic. Aristolochia is also available in slimming preparations.

The DCA will not register any products containing Aristolochia species and subsequently will cancel all such products that have been registered. The products involved are as follows:

	Name of Product	Registration Number
1.	Long Dan Tablet 300 mg	MAL19973414T
2.	Longdan Jiedu Capsule	MAL19972595T
3.	Sea Gull Brand Longdan Xiegan Tablet	MAL19950871T
4.	Bai Ke Ling Pian	MAL19988775T
5.	Qikuan Yin Kechuan Pian Tablet	MAL19988702T
6.	Shou Wu Chuan Xi Ling Capsule	MAL19970144T
7.	Mistura Ba Wei Jiang Yao Tang	MAL19983916T
8.	Mistura Xiapzhihuare (Liquid)	MAL19961145T
9.	Pilecure No. 2 (Pill)	MAL19987563T
10.	Sea Gull Brand Longdan Xiegan Capsule	MAL19961074T
11.	Shi Wai Pai Zhu Tang	MAL19988141T
12.	Tsu Hsueh (Medicated Powder)	MAL19985298T
13.	Fang Chi Huang Chi Tang 'Sun T	MAL19990520T
14.	Feng Shi Re Bi Wan (0.25 gm pill)	MAL19984526T
15.	Qi Guan Yan Ke Sou Tan Chuan P	MAL19987165T
16.	Re Bi Wan (Capsule)	MAL19990884T
17.	Solaray Devil's Claw Plus Form	MAL19984149T

☞ *The registration holders have been given 3 months to withdraw all products from the market after they received notice from the DCA.*

☞ *New products, which are under evaluation, will be rejected.*

CASE REPORT: SUXAMETHONIUM INDUCED HYPERKALAEMIA

This case report involves a 14 year old boy with a history of bronchial asthma since childhood and multiple admissions to hospital but with no previous history of ventilation. His asthma was being managed by the use of salbutamol inhaler 200 μg prn and beclomethasone 50 μg tds.

The patient presented to a hospital with shortness of breath of two days duration associated with a productive cough and yellowish sputum but he was afebrile. On examination, he was midly tachynoiec but not cyanosed and was able to speak in full

sentences. His PEFR was 120L/min; BP was 120/80mmHG and PR was 96bpm. Air entry was fair and equal with bilateral ronchi on lung auscultation and there were no crepitations.

The patient was admitted and diagnosed as having an acute exacerbation of bronchial asthma precipitated by an upper respiratory tract infection. He was nebulised with ipratropium bromide and terbutaline and received prednisolone and erythromycin orally. Blood urea and serum electrolytes were all within the normal range.

After 3 days, the patient's condition deteriorated. He had decompensated respiratory acidosis with CO2 retention and was referred for assisted ventilation. Patient was then intubated and received IV Thiopentone, IV Suxamethonium and IV Atracurium as bolus doses and sedated with IV Pethidine and Midazolam.

Shortly after receiving the drugs prior to intubation, the cardiac monitor showed broad QRS complexes, absent P waves and tall tented T waves which were suggestive of hyperkalemia. Blood urea and serum electrolytes taken at this point in time confirmed that the serum potassium level was 9.2mmol/L. All resuscitative attempts were unsuccessful.

MADRAC's Comments:

Suxamethonium has been associated with cardiac arrest and some of these cases have been fatal. A literature search showed that suxamethonium can produce hyperkalemia (up to 0.5mEq/L) in healthy volunteers. A case report described a suxamethonium induced hyperkalemia in a patient with severe metabolic acidosis and exsanguinating haemorrhage. The patient developed hyperkalemia with subsequent arrhythmias and cardiac arrest following the administration of suxamethonium for laryngoscopy facilitation (Schartz et al, 1992).

Another case report describes cardiac arrest and death in a 23 year old female who was administrated suxamethonium to facilitate endotracheal intubation. The patient's serum potassium was 8.4mEq/L ten minutes after the cardiac arrest (Hansen, 1998). A risk factor which was identified in this case was the 5-day immobilization period prior to suxamethonium administration.

The use of suxamethonium in children should only be reserved for cases which require emergency intubation or in situations which require immediate stabilization of the airway. The risk for cardiac disturbances in children may be increased with skeletal myopathies, with repeated doses or in the presence of hypoxia. Caution should be exercised at all times when its use is unavoidable.

GINGKO BILOBA – ADVERSE DRUG REACTIONS

The use of products containing gingko biloba is gaining popularity worldwide and Malaysia is no exception. As such, health professionals should be aware of adverse reactions which have been reported in association with the use of these products.

Recently, MADRAC received a report whereby an interaction between warfarin and gingko biloba was suspected. A 67 year old male patient whose INR was in the therapeutic range while taking warfarin during a hospital admission was subsequently found to have an INR which had fallen to a value of 1 after discharge. On questioning, it was found that he had continued with all the medications which had been prescribed (i.e. warfarin, glipizide, metformin and frusemide) but, in addition, had started taking a product containing an extract of gingko biloba after discharge. The patient was advised to stop taking the latter product and to continue with all other medications and the INR then increased to 2.5 indicating a positive dechallenge.

The WHO database contains 11 case reports describing thrombocytopenia suspected to be connected to the use of products containing ingredients derived from gingko biloba. In four of the reports, gingko biloba was the sole suspected drug. In the remaining 7 cases, the patients had taken more than one drug. Thus, the evidence implicating gingko biloba in these cases is small[1].

A literature search showed that there have been case reports of haemorrhage attributed to the use of products containing extracts of gingko biloba presumably due to impaired platelet aggregation[2,3]. But there have not been any case reports on interactions involving gingko biloba such as the one received by MADRAC.

In order to establish the safety profile of products containing gingko biloba and its derivatives, health professionals are requested to report any adverse reactions encountered with the use of gingko biloba to MADRAC.

1. *Signal August 1999. Analyses of Adverse Reaction Reports New to the WHO System.*
2. *Extracts of Gingko biloba and bleeding or haemorrhage. Skogh M. Lancet 1998:352:1145, Oct 3*
3. *Subarachnoid haemorrhage associated with Gingko biloba. Vale S. Lancet 1998;352:36, 4 July.*

World Health Organization

Information Exchange System
Alert No. 84

γ-butyrolactone-related products promoted on the Internet – Warning : Severe adverse reactions including deaths

The US Food and Drug Administration has issued a warning to the public about a new group of products being marketed as sleep aids that have been associated with at least 3 deaths and several severe adverse reactions. These products are chemically related to γ-butyrolactone (gamma-butyrolactone, GBL) and γ-hydroxybutyric acid (gamma-hydroxybutyric acid, GHB), substances that have been determined to pose a significant health hazard. In particular, one of these products, 1,4-butanediol (BD) has been declared a Class I Health Hazard by the FDA – a potentially life-threatening risk.

1,4-butanediol is a chemical that can cause dangerously low respiratory rates, unconsciousness, vomiting, seizures and death. 1,4-butanediol may also increase the effects of alcohol and is even more dangerous when consumed with other depressant drugs. Products that contain 1,4-butanediol include: Revitalize Plus, Serenity, Enliven, GHRE, SomatoPro, NRG3, Thunder Nectar and Weight Belt Cleaner.

Some of the suspect products may list "1,4-butanediol", "tetramethylene glycol", "γ-butyrolactone" or 2(3H)-furanone dihydro" on the label.

These products are listed as "party drugs" on the internet sites, advertised in muscle-building magazines and sold in food stores as dietary supplements to aid in sleep. The FDA considers these products to be unapproved new drugs and has conducted seizures of the product to prevent the sale to consumers and further illnesses or deaths.

This is not the first time that products of this nature have caused a serious health hazard. In February 1997 the FDA re-issued a warning on GHB for body building and "recreational" uses. GHB continues to be an unapproved and potentially dangerous drug and cannot be legally marketed in the United States. It has been implicated as a "date rape" drug.

(Reference: FDA Talk Paper T99-21, 11 May 1999)

Based on the above report, the DCA issued a letter dated August 1999 to all registration holders of products containing GBL to recall such products from the market.

FLUTAMIDE – LIVER TOXICITY

Flutamide is a drug indicated in the treatment of prostate cancer. Post-marketing reports of hospitalization and rarely death to liver failure in patients taking flutamide have been reported.

In the United States, Schering Corporation has made labelling changes to Eulexin (flutamide capsules) to include a boxed warning of liver toxicity in patients taking this product as well as monitoring requirements for hepatic injury.

In Malaysia, Schering-Plough Sdn Bhd, the product registration holder for the market leader, has been instructed to make the necessary labelling changes to Fugeral Tablets 250mg and Eulexin Tablets 250mg as both these products contain flutamide. They have also been advised to bring this matter to the notice of physicians by sending out "Dear Doctor" letters.

All generic products containing flutamide registered in Malaysia will also be instructed to change their product inserts to carry warnings on this potentially serious adverse reaction.

CONTROL OF VETERINARY MEDICINES

In July 1999, the Minister of Health announced that under a proposed amendment to the Sale of Drugs Act 1952 (Revised 1989), veterinary medicines must be registered with the Drug Control Authority to prevent the use of unsafe drugs in animals.

Subsequently, the Sale of Drugs (Amendment) Bill 1999 was tabled in Parliament on 18/10/99 and 19/10/99 by the Minister of Health. This amendment is to extend the scope of the Sale of Drugs Act 1952 to any substance intended or capable of being used in animals in order to guarantee that such medicines are of quality and to ensure that Malaysia does not become a dumping ground for poor quality drugs. Veterinary drugs will have to be evaluated before registration and these drugs must be manufactured according to the requirements of Good Manufacturing Practice.

This Bill also seeks to impose a maximum fine of RM25,000 or up to three years' jail, or both, for the first offence. For subsequent offences, a maximum fine of RM50,000 or up to five years' jail, or both, would be imposed. For a corporate body, the penalties would be doubled.

It was also proposed that the minister could impose a maximum fine of RM50,000 or five years' jail for the first offence, and not more than RM100,000 for subsequent offences committed under any regulation in this Act.

ACCESSION TO THE PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S)

On 1st September 1999, the Ministry of Health Malaysia submitted a formal application for accession to the PIC/S.

Based on the Guidelines For Application to the Pharmaceutical Inspection Co-operation Scheme (Document PIC/S 2/95, November 1995), the following documents were presented to the Secretariat of the PIC/S in Geneva, Switzerland to enable the authorities to understand and assess our inspection system and benchmark the level of GMP compliance of our local pharmaceutical manufacturers against international standards:

i) Malaysian Laws on Poisons and Sale of Drugs
ii) Guidelines on Good Manufacturing Practice for Pharmaceuticals in Malaysia, 3rd Edition 1996
iii) National Inspection Systems with regard to the control of the manufacture of medicinal products
iv) Structure, Organisation of the Inspectorate and Quality System
v) Other relevant information to assist PIC/S in understanding our whole regulatory system

Malaysia's accession to PIC/S will invariably foster mutual confidence, promote quality assurance of inspections and ultimately contribute towards global harmonisation of standards of GMP.

INTERNATIONAL VISITORS

Date	Visitors	Objective
11.1.1999 until 3.3.1999	Two WHO Fellows from **Bangladesh:** • **Mr. Haque Mozammel** • **Mr. Das Ranjit Kumar**	Attachment Training on Quality Control of Essential Drugs
25.1.1999	WHO Fellow from Ministry of Health & Welfare of **Japan:** • **Mr. Akira Hamada**	Temporary Advisor - South-East Asian Regions & Western Pacific
8.2.1999 until 1.3.1999	WHO Fellow from **Bangladesh:** • **Mr. Md. Ruhul Amin**	Training on Quality Management in Pharmaceutical
23.3.1999 until 22.4.1999	WHO Fellow from MCA: • **Dr. David Moore**	As a Consultant Good Laboratory Practice (GLP)
3.5.1999 until 29.5.1999	Three WHO Fellows: • **Mr. Sun Lei** (from **China**) • **Ms. Prey Yean** (from Ministry of Health of **Cambodia**) • **Ms. Vongsavanh Insixiengmay** (from Ministry of Health of **Laos**)	Training on Drug Quality Control
10.5.1999 until 25.5.1999	WHO Fellow from Ministry of Health and Social Welfare of **Mongolia:** • **Ms. Zulzaga Zuzaan**	Training on Drug Registration
24.5.1999 until 27.5.1999	Three WHO Fellows from **Vietnam:** • **Mrs. Le Thi Nga** • **Ms. Chu Thi Tuyet** • **Mr. Luu Minh Triet**	Training on National Drug Policy Programme
1.6.1999 until 30.6.1999	Three WHO Fellows from **Mongolia:** • **Mrs. Gunjar Dolgormaa** • **Mr. Terbish Bayaraa** • **Dr/Mrs. Gendenjamts**	Training on Local Production and Methodology
7.6.1999 until 2.7.1999	WHO Fellows from **Vietnam:** • **Mr. Pham Hong Chau** • **Mr. Nguyen Trong Thuy**	Training on Drug Registration
13.7.1999 until 23.7.1999	Three WHO Fellows from **Vietnam:** • **Mr. Nguyen Duc Bon** • **Mr. Tran Cuc** • **Dr/Miss Hoang Thanh Mai**	Training on Methods to Organize and Run Drug Information Centres

Date	Visitors	Objective
19.7.1999 until 30.7.1999	Two Officers from **Pharmacy Board, Tanzania** • **Mr. Henry Irunde** • **Mr. N. A Msuye**	In House Training on Adverse Drug Reactions Monitoring & Drug Information Services
2.8.1999 until 27.8.1999	WHO Fellows from **Vietnam:** • **Ms. Hoang Thai Phuong Cac** • **Mrs. Thai Phan Quynh Nhu**	Study Tour on Drug Quality Control by Non-Pharmacopoeial Methods
2.8.1999 until 30.8.1999	Two WHO Fellows: • **Mr. Trinh Van Lau** (from **Vietnam**) • **Ms. Budjav Tavanjin (from Mongolia)**	Training on Quality Control of Pharmaceuticals in Malaysia
5.10.1999 until 8.10.1999	**Dra Rahmaniar Brahim** from **Indonesia** (SEAMIC Travel Research Fellowship)	Comparative Study on the Drug Information System
8.10.1999 until 12.10.1999	**Miss Charunee Krisanaphan** from **Thailand** (SEAMIC Travel Research Fellowship)	Study Tour on Drug Control System

NEW DRUGS APPROVED FOR MARKETING IN MALAYSIA

(July – September 1999)

No.	Product (Active Ingredient)	Therapeutic Class / Indication	Product Registration Holder
1.	Detrusitol 1mg & 2 mg tablets (Tolterodine L-tartrate)	Anticholinergic (muscarinic), peripherally acting muscle relaxant / Treatment of unstable bladder	Zuelling Pharma Sdn. Bhd.
2.	Syscor 5mg Tablets & Syscor 10 mg tablets (immediate release) (Nisoldipine)	Antihypertensive drug / Treatment of hypertension	Bayer (M) Sdn. Bhd.
3.	Omnicef 100 mg capsule (Cefdinir 100 mg)	Broad spectrum antibiotic (3rd generation cephalosporins) / Infections caused by susceptible organism – *Staphylococcus sp., Streptococcus sp., Streptococcus pneumonieae, Peptostreptococcus sp., Propionibacterium sp., Neisseria gonorrhoeae, Branhammela catarrhalis, Escherichia coli, Klebsiella sp., Proteus mirabilis, Providencia sp. & Haemophilus influenzae*	Warner-Lambert (M) Sdn. Bhd.
4.	Naramig tablet 2.5 mg (Naratriptan HCl)	Vasoconstrictor ($5HT_1$ receptor agonist) / For the acute treatment of migraine attacks with or without aura	Allen & Hanburys Sdn. Bhd.
5.	Hyperdix tablet (Rilmenidine 1 mg)	Antihypertensive drugs ($_{\alpha}(Alpha)_2$ receptor agonist) / Hypertension	Zuellig Pharma Sdn. Bhd.
6.	Gliadel Wafer (Carmustine 7.7.mg)	Antineoplastics; others / As an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated.	Rhone-Poulene Rorer (M) Sdn. Bhd.
7.	Feldene Flash 20 mg (Piroxicam)	Analgesic-antipyretic-antiinflammatory (NSAID) / rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, ankylosing spondilitis, acute musculoscletal disorder, acute gout and pain after operative intervention following acute trauma. Treatment of primary dysmenorrhea (>12 years old)	Pfizer (M) Sdn. Bhd.
8.	Zeffix tablet (Lamivudine 100 mg)	For the treatment of patients > 16 years of age with chronic Hepatitis B and evidence of hepatitis B virus replication	Allen & Hanburys Sdn. Bhd.
9.	Stocrin Capsule (Efavirenz 50mg, 100mg & 200mg	Antiinfective (Non-nucleoside Reverse Transcriptase inhibitor) / Antiviral combination treatment of HIV-1 infected adults, adolescents and children	Merck Sharp & Dohme, Corp.
10.	Infanrix-Hep B (-Diphteria toxoid not less than 30IU -tetanus toxoid not less than 40 IU -Pertussis toxoid 25 mcg -Filamentous Haemagglutinin 25 mcg -Pertactin 8 mcg - Recombinant Hbs Ag protein 10 mcg)	Vaccine / For active immunization of all infants from the age of 2 months against diptheria, tetanus, pertussis and hepatitis B.	SmithKline Beecham Sdn. Bhd.

No.	Product (Active Ingredient)	Therapeutic Class / Indication	Product Registration Holder
11.	Propecia Tablet (Finasteride 1 mg)	Male hormone disorder (5_{α}) reductase inhibitor) / For the treatment of male patternhair loss (androgenetic alopecia) to increase hair growth and to prevent further loss.	Merck Sharp & Dohme, (I.A.) Corp.
12.	Unat 2.5 mg Tablet (Torasemide)	Diuretics (pyridine-sulfonylurea) / Essential hypertension	Roche (M) Sdn. Bhd.
13.	Unat 5 mg Tablet (Torasemide)	Diuretics (pyridine-sulfonylurea) / Essential hypertension, oedema due to CHF or cirrhosis of the liver with ascites & improvement of cardiac reserve in heart failure	Roche (M) Sdn. Bhd.
14.	Unat 10 mg Tablet (Torasemide)	Diuretics (pyridine-sulfonylurea) / Oedema due to CHF or cirrhosis of the liver with ascites, renal failure and nephrotic syndrome & improvement of cardiac reserve in heart failure	Roche (M) Sdn. Bhd.
15.	Unat 10 mg Ampoules (Torasemide)	Diuretics (pyridine-sulfonylurea) / Oedema due to CHF or cirrhosis of the liver with ascites, renal failure and nephrotic syndrome if an IV therapy is indicated & supportive measure in cerebral oedema	Roche (M) Sdn. Bhd.
16.	Pentaglobin 50 ml (Human Plasma 95% protein 50 mg/ml Immunoglobulin G 38 mg/ml Immunoglobulin M 6 mg/ml Immunoglobulin A 6 mg/ml)	Human immunoglobulin / Adjuvant therapy of severe bacterial infection additional to antibiotic therapy & Immunoglobulin substitution in immunocompromised patient with high risk of bacterial infection.	Lazuli Sdn. Bhd. P. Jaya
17.	Tablet Plavix (Clopidogrel 75 mg)	Antiplatelet agent / For the reduction of atherosclerotic events (myocardial infarction, stroke and vascular death) in patients with artherosclerosis or established peripheral arterial disease.	Sanofi Synthelabo (M) Sdn. Bhd.
18.	Xenetix 250 (Iobitridol)	Radiography Contrast Media (Non-ionic iodinated)/For adults and children undergoing phlebography, whole-body CT or intra-arterial digital substraction angiography.	Ken-Med Sdn. Bhd.
19.	Xenetix 300 (Iobitridol)	For adults and children undergoing intravenous urography, brain and whole-body computed tomography (CT), intravenous digital substration angiography, anteniography and angiocardiography.	Ken-Med Sdn. Bhd.
20.	Xenetix 350 (Iobitridol)	For adults and children undergoing intravenous urography, brain and whole-body computed tomography (CT), intravenous digital substration angiography, anteniography and angiocardiography.	Ken-Med Sdn. Bhd.
21.	Aggrastat Solution for Infusion (Tirofiban HCl)	Anticoagulant (Glycoprotein 11b / 111a inhibitors) / In combination with heparin, it is indicated for patients with unstable angina or non Q-wave myocardial infarction to prevent cardiac ischaemic events and for patients with coronary ischemic syndromes undergoing coronary angioplasty or atherectomy to prevent cardiac ischaemic complications related to abrupt closure of the treated coronary artery.	Merck Sharp & Dohme (I.A) Corp.

No.	Product (Active Ingredient)	Therapeutic Class / Indication	Product Registration Holder
22.	Tetramune vaccine [-Haemophilus influenza type B -Diphteria toxoid (adsorbed) -Tetanus toxoid (adsorbed) -Pertussis vaccine (adsorbed)]	Vaccine / Active immunization of children 2 months to 5 years of age for protection against diptheria, tetanus, pertussis and Haemophilus B disease when indication for immunization with DTP vaccine and Haemophius B conjugate co-incide.	Wyeth (M) Sdn. Bhd.
23.	Tevetan tablet – 300mg & 400 mg (Eprosartan mesylate 367.91mg & 490.55mg)	Antihypertensive drug (Angiotensin II receptor antagonist) / Treatment of essential hypertension	SmithKline Beecham Sdn. Bhd.
24.	Lipobay 0.1mg, 0.2 mg & 0.3 mg tablets (Cerivastatin)	Antilipaemic drugs (HMG-CoA reductase inhibitor) / Primary hypercholesterolaemia (Frederickson type IIa) & mixed hyperlipidaemia (Frederickson type IIb) in patients who have not responded adequately to an appropriate diet.	Bayer (M) Sdn.Bhd.

NEW INDICATIONS APPROVED FOR REGISTRATION

(July-September 1999)

No.	Product (Active Ingredient)	Additional Indication	Product Registration Holder
1.	Dilatrend 25 mg (carvediol)	• Treatment of angina pectoris	Roche (M) Sdn. Bhd.
2.	Emla Cream 5% (Lidocaine 25 mg/g & Prilocaine 25 mg/g)	• Surface anaesthesia of leg ulcer prior to cleansing	Astra Pharmaceuticals (M) Sdn Bhd.
3.	Gemzar 100 mg (Gemcitabine Hydrochloride)	• Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer	Eli Lilly (M) Sdn. Bhd. P. Jaya
4.	Hycamtin 4 mg Injection (Topotecan HCl)	• Treatment of patients with small cell lung carcinoma (after failure of first line chemotherapy)	SmithKline Beecham, Sdn. Bhd.
5.	(i) Pentasa Slow Release Tablet 250 mg (ii) Pentasa Slow Release Tablet 500 mg (Mesalazine)	• Maintenance therapy for patients with Crohn's Disease in remission induced by surgery or medication	United Italian Trading (M) Sdn. Bhd. Selangor
6.	(i) ReoPro Injection 10 mg/5 ml (ii) ReoPro Injection 40 mg/20 ml (Abciximab)	Percutaneous coronary intervention • The prevention of ischaemic cardiac complication in patients undergoing percutaneous coronary intervention (balloon angioplasty, atherectomy and bailout stent) Unstable Angina • The short term (1-month) reduction of risk of myocardial infarction, in patients with unstable angina, not responding to full convention therapy who have been scheduled for percutaneous coronary intervention	Eli Lilly (M) Sdn. Bhd.
7.	(i) Rytmonorm 150 tablet (ii) Rytmonorm 300 tablet (Propafenone HCl)	• Prophylaxis and treatment of supraventricular arrythmias	Diethelm (M) Sdn. Bhd.

No.	Product (Active Ingredient)	Additional Indication	Product Registration Holder
8.	Voltaren ampoule 75 mg/3ml (Diclofenac sodium 75mg/3ml)	• IV infusion – Treatment or prevention of postoperative pain in a hospital setting	Novartis Corp. (M) Sdn. Bhd.
9.	(i) Zoloft 50 mg (Australia) (ii) Zoloft 100 mg (Australia) (iii) Zoloft 50 mg (UK) (iv) Zoloft 100 mg (UK) (Setraline 50 mg)	• Antidepressant / Panic Disorder	Pfizer (M) Sdn. Bhd.

CLINICAL TRIALS

Clinical Trials Import License Permit Approved by DCA
(July-September 1999)

No.	Topic	Place of Trial	CTIL Holder
1.	An active comparator-controlled, parallel group, 6-week, double blind study, conducted under in-house binding conditions, to assess the safety and efficacy of Vioxx (MK-0966) vs Naproxen in patients with osteoarthritis of the knee and hip.	Hospital Universiti, Petaling Jaya.	Merck Sharp & Dohme Corp. (M) Sdn. Bhd.
2.	An open-labeled, multicentre, randomized, phase II study of 5-Day Oral Topotecan vs 21-Day Oral Topotecan vs CPT II (Irinotecan) for second line therapy in patients with colorectal carcinoma.	Radiotherapy Unit, Hospital UKM, Cheras.	SmithKline Beecham (M) Sdn. Bhd. & Rhone-Poulene Rorer (M) Sdn. Bhd.
3.	Efficacy of Tolterodine 2mg b.i.d. with or without a simplified pelvic floor exercise regimen. A phase IV, randomized, single-blind, parallel group trial in adult patients with overactive bladder with symptoms of urinary frequency, urgency and/ or urge incontinence.	Hospital KL, Kuala Lumpur; Hospital Universiti, Petaling Jaya; Hospital UKM, Cheras.	Zuellig Pharma Sdn. Bhd.
4.	To determine the efficacy of a new dose for a more bioavailable formulation of artemisinin.	Hospital Tawau, Sabah.	Prof. Madya Dr. Yuen Kah Hay
5.	A double-blind, placebo-controlled, safety, efficacy and dose response trial of three intravenous dose of BMS – 204352 in patients with acute stroke (Phase IIb and IIIa).	Hospital Universiti, Petaling Jaya.	Bristol-Myers Squibb (M) Sdn. Bhd.
6.	A phase II study of the safety and antiviral activity of Entecavir (BMS – 200475) vs Lamivudine in adults with chronic hepatitis B infection.	Hospital Universiti, Petaling Jaya; Hospital Kuala Lumpur.	Bristol-Myers Squibb (M) Sdn. Bhd.

No.	Topic	Place of Trial	CTIL Holder
7.	An open-label, multicentre, randomized, phase II study of Topotecan/Paclitaxel vs Etoposide /Cisplatin as first line therapy for patients with extensive Small Cell Lung Cancer Disease. (New Indication)	Hospital Universiti, Petaling Jaya.	SmithKline Beecham Sdn. Bhd.
8.	Topiramate open-label in paediatrics subjects with inadequately controlled epilepsy (Phase III). (New Indication)	Hospital Universiti, Petaling Jaya; Hospital KL, Kuala Lumpur; Hospital UKM, Cheras; Hospital Pulau Pinang, Pulau Pinang.	Johnson & Johnson Sdn. Bhd.
9.	A multicentre, randomized, controlled trial of intravesical BCG and Interferon α-2b in the treatment of superficial bladder cancer (Phase II). (New Indication)	Hospital Universiti, Petaling Jaya; Hospital KL, Kuala Lumpur.	Schering-Plough Sdn. Bhd.
10.	A 16-week, open –labeled, randomized, parallel-group, multicentre comparison of Repaglinide and Glibenclamide for the treatment of Type 2 diabetes in Muslim patients over the Ramadhan period (Phase IIIb).	Hospital USM, Kubang Krian, Kelantan; Hospital Universiti, Petaling Jaya; Hospital KL, Kuala Lumpur; Hospital Tengku Ampuan Rahimah, Klang.	Novo Nordisk Pharma (M) Sdn. Bhd.
11.	A multicentre, double-blind, randomized trial to compare the effects of Nandrolone decanoate and placebo on body composition and body weight in HIV-positive men with mild to moderate wasting, with Sustanon 250 as active reference treatment (Phase III). (New Indication)	Hospital KL, Kuala Lumpur.	Organon (M) Sdn. Bhd.
12.	A double-blind, randomized, placebo-controlled study of Adefovir dipivoxil for the treatment of patients with HbeAg chronic Hepatitis B virus infection (Phase II).	Hospital Universiti, Petaling Jaya; Hospital KL, Kuala Lumpur.	Dato' Dr. Mohd. Ismail Merican
13.	To assess the glomerular filtration rate in healthy volunteers and the effect of AT-I blockade on the renal effects of circulating noradrenaline in humans.	Pusat Perubatan, UM, Petaling Jaya.	Prof. Lang Chim Choy

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Drug Evaluation and Safety Division	Deputy Director	Che Mohd. Zin Che Awang	270
– Certificate of free sale – General information regarding registration	Secretariat Unit	Hasnah Ismail (Head)	242
Application for Registration of – Poisons – Non Poisons – Traditional Medicines – New Chemical Entity – Cosmetics	 – Poisons Unit – Non Poisons Unit – Traditional Medicines Unit – New Chemical Entity Unit – Cosmetic Unit	 Fudziah Ariffin (Head) Tan Lie Sie (Head) Napsah Mahmud (Head) Dr. Ramli Abd. Ghani (Head) Ramli b. Zainal (Head)	 233 245 238 239 241
– Manufacturer's Licence – Import Licence – Wholesaler's Licence	GMP and Licensing Division	Eishah Abd. Rahman (Head)	201
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– Report of Adverse Drug Reaction – Marketing Surveillance Programme – Product Complaints / Product Recalls	Pharmacovigilance Division	Abida Haq (Head)	258
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