HONG KONG PHARMACEUTICAL JOURNAL

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Pharmaceutical Care & Safe Medication Practice

Drugs for Summer

Hormone Replacement Therapy (2 CE Units)

Pharmacy Conference 2004 Welcome Message from the Chairperson

The Inaugural AASP Conference - Pharmacy Education, Research & Practice in Asia (Supplement)

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Editorial

Pharmacy Practice

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One year after the emergence of Severe Acute Respiratory Syndrome (SARS), the Centre for Health Protection (CHP) has been established. CHP is a governmental organization within the Department of Health to strengthen the Government's capacity to prevent and control infectious diseases. Six branches will be formed within CHP to deal with matters on disease surveillance, infection control, emergency response & information, laboratory services, public programs, and professional development. The Centre is targeted to commence operation in June 2004 according to the Department of Health. The set up the Centre results from recommendations given by the government's Expert Committee after reviewing the management and control of the SARS outbreak. The Expert Committee also recommended the development of a population-based framework to respond to any future infectious disease outbreaks that will fully utilize the skills of healthcare professionals in caring for the needs of vulnerable groups, provide sentinel surveillance, and engage the community in health promotion activities. Critics complained that such a functional organization came into play too late. It should have been in place well before hundreds of lives were lost during the SARS period. Nonetheless, may believe that is never too late to do the right thing to prevent such a tragedy from happening again. Now, the question is "who can be involved?"

In May 2004, the Controller and the working members of CHP met representatives from the three pharmacist associations in Hong Kong (i.e. the Pharmaceutical Society, the Society of Hospital Pharmacists and the Practising Pharmacists Association). In the meeting, preliminary discussions included the idea of inviting volunteer pharmacists to join the emergency response team. Two main roles of pharmacists in the team were identified - providing a public inquiry hotline & health education services, and dispensing prophylactic medications.

In the previous issue of HKPJ (Vol 13, No 1), we published reports about how we pharmacists demonstrated our spontaneous support to the community as a health care profession. We have no doubt as to our knowledge, skill or ability. However, most agree that pharmacists in Hong Kong have not been utilized as well as doctors or nurses, especially when facing social health crisis. The initiative of CHP signifies that pharmacy profession plans on being recognized as a key resource of health promotion in our society. The concern is that pharmacy might only become a "free-of-charge" profession. Pharmacists' voluntary participation to the CHP initiative should be seen as a part of professional development rather than a permanent solution. If pharmacy service is valuable to public health, the Government needs to think how to make this profession sustainable in the long run; perhaps through supporting the separation of dispensing & prescribing or considering pharmacists when developing any other major health care policies.

This issue of HKPJ begins with an article by Tsang and Fok on the concept of pharmaceutical care, highlighting the importance of eliminating drug-related problems and introducing means to promote safe medication practice. As a prologue to the Pharmacy Conference 2004, Miss Vivian Lee, the Chairperson of the Conference posts her welcome message in the Society Activities section.

You may recall that we published an article discussing Menstrual Disorder in the previous issue of the HKPJ (2004;13:11-14). For this issue, we continue to focus on women's health but shift to another age group. This is a Continuing Education (CE) article looking at the pros and cons of hormone replacement therapy for post-menopausal women.

Summer time is approaching. Our front-line colleagues will become busy in selling products and providing health care advice for holiday makers. In response, the Editorial Committee has included the article "Drugs for Summer" in the Over-the Counter & Health Section. It provides general advice on selection of several types of health care products including insect repellent, sunscreen oil and anti-perspirant that our HKPJ readers may find immediately useful.

The rest of the HKPJ pages are complemented by a special supplement. In the supplement, we publish the abstracts presented in the Inaugural Asian Association of Schools of Pharmacy (AASP). Every association has to have a leader. The president for the AASP is Professor Moses Chow. At the beginning of the supplement, Professor Chow introduces the contents of the Inaugural Conference as well as the establishment of the AASP. The series of abstracts covers a variety of topics ranging from evolution of schools of pharmacy to enhance pharmacists' competence, sharing of pharmacists' contribution in different practice settings, and tools / models developed in pharmacy practice, to basic pharmaceutical research. It provides opportunities for our local pharmacists to learn from the experiences and best practices of our colleagues in different Asian countries. As you read through the abstracts, we hope you enjoy the eye-opening journey.

Michael Leung
Managing Editor

The Promotion of Safe Medication Practice: A Major Focus of Pharmaceutical Care

Tsang, YWW; Fok, SMM

I INTRODUCTION

Pharmaceutical care is recently developed in the health care arena in most of the countries as in Hong Kong. The development of pharmaceutical care is in response to the needs of the community particularly aiming at eliminating the drug-related problems such as drug-drug interactions, poor drug compliance and polypharmacy. These drug-related problems are always the concerns of pharmacists and other health care professionals such as nurses and doctors. Not only patients who have received prescriptions would develop these problems but also would the community citizens who have practised over-the-counter (OTC) medications. This paper thus explores the relevant issues of pharmaceutical care with particular emphasis on the promotion of safe medication practice.

II PHARMACEUTICAL CARE

Pharmaceutical care is described as the process by which a pharmacist collaborates with a patient and other health care professionals in designing, implementing and monitoring a therapeutic plan that will produce a desirable outcome for the patient (Crealey *et al.*, 2003). This desirable outcome implies that the patients will be able to receive appropriate prescriptions, achieve better drug compliance, gain better knowledge about drugs and better manage their health with their use of drugs. Essential elements of pharmaceutical care include pharmaceutical counselling for in-patients (Al-Rashed *et al.*, 2002), pharmacotherapeutic evaluation by reviewing medical and medication record in hospital (Taylor *et al.*, 2003), measuring medication used to assess patient adherence to complex medical regimens (Todd *et al.*, 2002), and conducting pharmaceutical intervention program to improve clinical and economic outcomes (Haumschild *et al.*, 2003). These areas of pharmaceutical care are of greatest benefit to in-patients. However, providing primary care is also a major role of pharmacists, as it is of other health care professionals such as nurses. Unlike in-patients, people from the community do not necessarily have a medical history and/or medication records on which pharmacists and other health care professionals can rely for assessing, planning, implementing and evaluating pharmaceutical care. People in the community also take prescription and/or non-prescription drugs and may develop drug-related problems. For instance polypharmacy (Brummel-Smith, 1998; Bardel *et al.*, 2000), poor drug compliance (Burnier *et al.*, 2003) and drug-drug interactions (Haumschild *et al.*, 2003). Therefore they also deserve to receive quality pharmaceutical care. The subsequent sessions address the drug-related problems.

III DRUG-RELATED PROBLEMS

i) Polypharmacy

Polypharmacy refers to concurrent use of multiple medications in a single patient (NASMHPD, 2001). Polypharmacy is usually seen as a negative connotation and that implies an inappropriate or irrational use of multiple medications. Therefore the National Association of State Mental Health Program Directors (NASMHPD, 2001) suggests that when the term polypharmacy is used, it should be related to specific context of the situation. In this paper, polypharmacy is interpreted as a drug-related problem which particularly occurs in the older population which has practised multiple medications in an inappropriate and irrational approach. A Swedish study (Bardel *et al.*, 2000) was conducted on the use of prescription drugs for middle-aged women. It was reported that, in seven countries in central Sweden, 40% (n=1196) were currently using drugs and 12% (n=369) of the users were taking four or more drugs. Apparently polypharmacy increased according to age. Other factors such as body mass index and educational level were found to be related to drug use by these women. Brummel-Smith (1998) supported that older persons are more likely to have medical problems and polypharmacy is commonly found in this population. He further indicated that a relationship existed between the number of drugs taken and increased potential for adverse drug reactions. In order to eliminate this problem, safe medication practice should be promoted.

ii) Poor drug compliance

To achieve the therapeutic effects of the drugs, drug compliance is important. This problem is commonly found in patients with hypertension who lack of adequate blood pressure control because of poor adherence to antihypertensive treatment (JNC, 1997). However compliance is difficult to measure as poor compliance is often incorrectly interpreted as a lack of response to treatment (Buriner *et al.*, 2003). Therefore several ways are suggested to monitor compliance including self-reported compliance, counting pills or biological markers. These methods however have their limitations. For instance, manipulating pill count, blood obtaining or urine sampling for monitoring the effects of the drugs is time-consuming and resource-draining. Apparently promoting drug compliance is better than compliance monitoring for achieving the therapeutic effects of the drugs.

iii) Drug-drug interaction

Drug-drug interaction is another drug-related problem. Hypoglycaemia, digoxin toxicity or hyperkalemia were secondary diagnoses contributing to hospitalization and regarded to be the result of a drug-drug interaction (Juurlink *et al.*, 2003). It is unrealistic to expect the health care professionals including doctors, pharmacists or nurses to memorize a considerable amount of drug-drug interactions and their clinical significance. It may be possible to develop a pharmaceutical plan for individual patients in which knowledge of the drugs including effects and side effects, possible drug-drug interaction and a guidance of safe medication practice are contained. Of the most importance, this plan should be based on the medical history of the patients. In addition, food-drug interaction is another related

生髮有計[△]，脫髮男士唔駛傷腦筋。

[△]一項長達五年的臨床研究，顯示90%服用保康絲™5年的男士停止進一步脫髮*，而65%男士的頭髮數量更比參與研究前有增長[Ref1]。服用保康絲™後的第3至6個月有減少脫髮的現象，而在第6至12個月，脫髮的部位開始有頭髮增長[Ref2]。**想減少脫髮或想新髮再現，請打脫髮資料熱線：2126 3888 www.hair38.com**

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Ref1. K.D. Kaufman et al, Long term (5 year) multinational experience with finasteride 1mg in ther treatment of men with androgenetic alopecia, Eur J Dermatol 2002; 12:38-49
Ref2. Laufman K.D., et Al., Finsateride in the treatment of men with androgenetic alopecia, J Am Acad Dermatol 1998; 35:578-89

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problem (McCabe, 2004) and that may also lead to serious morbidity and mortality. Therefore relevant information of the possible food-drug interactions should also be provided in the pharmaceutical plan.

IV SELF-MEDICATION

As mentioned earlier, drug-related problems not only occur in patients who receive prescription drugs but also those people who practise self-medication. Self-medications means taking drugs which can be used without a physician's advice or supervision (Bergmann, 2003). In Hong Kong, the behaviour of self-medication adopted by the Chinese adults was studied (Lam *et al*., 1994). The practice of self-medication of 1,068 Hong Kong Chinese in the preceding two weeks was studied. Telephone interviews were employed in the study and it was found that 32.5% (n=347) adopted the practice of self-medication. Those who reported illness were significantly more likely to self-medicate than those who did not and the former had used one more type of medication than the latter. In Hong Kong, both Western and Chinese medications are used although the scientific use of Chinese medications is less often reported. A lack of knowledge among these people regarding the therapeutic effects and side effects of Western medications and, the therapeutic effects and precautionary measures on taking Chinese medications was also reported (Lam *et al*., 1994). Self-medication practice is also commonly practised in the European countries (Chen *et al*., 2001; Bardal *et al*., 2001) and America (Abebe, 2002). Apart from the lack of consumers' knowledge of the drugs, adverse risks such as drug interaction was also reported as a possible result of unsafe self-medication practice (Tallia & Cardone, 2002). As self-medication is a common practice in the community, community-based education on safe medication practice is necessary and is also an important element of pharmaceutical care.

i) Promotion of safe medication practice

To plan evidence-based pharmaceutical care to promote safe medication practice, a valid and reliable instrument is necessary to assess the drug utilization patterns of the community citizens. When the drug utilization patterns of the community citizens are identified, the responsible parties will be able to use the data to plan and develop education programme on safe medication practice that will include the use of both prescription and non-prescription drugs. In light of the characteristics of the Hong Kong Chinese, it is worth studying drug utilization patterns for both Western and Chinese medications. Although there are differences in the nature of the two types of medications, the principles of the safe use of drugs in these two major branches of medications are similar.

ii) The proposed instrument

In view of the relevant literature, demographic data such as gender, age, marital status, educational level, occupation, body mass index (BMI) and medical history were the variables studied in relation to patterns of drug use. Thus, these variables will be included in the proposed instrument. Items such as dose, frequency, time for taking medication, reason for taking medication, the preparation of medications and source of obtaining medications will also be included in order to further investigate what drug-knowledge the subjects may possess. It is documented (Lam *et al*., 1994) that Hong Kong Chinese who adopted the practice of self-medication know about some of the therapeutic effects but little about the side effects of Western medications. They have even less knowledge of Chinese medications. In other related studies (Bardel *et al*., 2000; Chen *et al*., 2001), insufficient knowledge of drugs can lead to polypharmacy and the inappropriate use of prescription and non-prescription drugs. Therefore, the therapeutic effects and side effects of the Western medications and the therapeutic effects and precautionary measures of the Chinese medications will be the major items to be included. With respect to the Western medications, it is proposed to use the British National Formulary (BMA, 2002) as a major reference to derive the categories, sub-categories, therapeutic effects and side effects of the Western medications. Different bodily systems will become the main categories of the medications. For instance, respiratory, cardiovascular, gastrointestinal, urinary, neurological systems will be used. Regarding Chinese medications, references will be taken from a Traditional Chinese Formulary (Duan, 1995). The 18 main categories of the Chinese formulary are listed out in Panel 1.

Traditional Chinese medical practitioners believe that there is no side-effect of Chinese medications. If the therapeutic effects of the medications are not achieved, this might relate to the clients' lack of knowledge of the precautionary measures such as taking food or drugs that counteract the therapeutic effects of the Chinese medications or because the clients did not understand their constitution (bodily functions) and took inappropriate medications. To study the client's knowledge of the Chinese medications, therapeutic effects and precautionary measures will be taken into account.

V DISCUCSSION

In light of the importance of promoting safe medication practice in Hong Kong so as to eliminate drug-related problems, the authors of this study suggest the following pharmaceutical plan (Panel 2). Firstly to constitute a working group in which pharmacists, nurses, doctors, Traditional Chinese medical practitioners, dietitians, statisticians and/or health care policy makers will be included. These experts will identify the drug-related problems in the community in Hong Kong and the available community resources that can be utilized to tackle the problems. A validated instrument, as mentioned earlier will be developed to explore the drug utilization patterns

Panel 1. Eighteen categories in a Chinese medicine formulary - A proposed instrument to study patterns of drug use

18 categories in a Chinese formulary:

a. Prescriptions of relieving exterior syndrome
b. Purgative prescriptions
c. Mediating prescriptions
d. Heating-clearing prescriptions
e. Prescriptions for warming the interior
f. Tonic prescriptions
g. Prescriptions for inducing astringency
h. Sedative prescriptions
i. Prescriptions for resuscitation
j. Prescriptions for regulating the flow of Qi
k. Prescriptions for treating blood disorders
l. Prescriptions for claming wind
m. Prescriptions for treating dryness syndrome
n. Dampness-eliminating prescriptions
o. Phlegm-eliminating prescriptions
p. Resolving prescriptions
q. Prescriptions for anthelmintics
r. Prescriptions for emetic

Panel 2. A proposed pharmaceutical plan to eliminate drug-related problems

1. Constitute a working group engaging representatives from varies health care professions, statisticians and policy makers.
2. Identify the drug-related problems in the community in Hong Kong
3. Identify the available community resources that can potentially be utilized to tackle the problems.
4. Develop and validate an instrument to explore the drug utilization patterns in the local community.
5. Recruit different populations from different age-groups.
6. Measure pattern of drug use including patients' drug knowledge and medication practices.
7. Develop an evidence-based and practical pharmaceutical plan to promote safe medication practice.

of the patients and other community citizens. By using the instrument, the amount of drug knowledge the citizens may have and their medication practices will be obtained. In order to obtain a comprehensive picture of the drug utilization patterns of the citizens in Hong Kong, it is recommended to recruit different populations from different age-groups, for instance, adolescents, adults and elderly people. According to the results of the drug utilization patterns, the working group will be able to develop evidence-based pharmaceutical plan to promote safe medication practice. For instance the working group will understand the inadequacy of the citizens using the OTC medications that include both Western and Chinese medications and that they will be able to provide counseling service in both the hospitals and in the community dispensaries. Practising OTC medications may not be a behaviour that is risky to health but lacking in knowledge in using inappropriate OTC medications will be harmful. Undoubtedly the extensiveness of the pharmaceutical care in promoting safe medication practices should be realistic. The authors suggest that the working group can organize campaigns in the community and prevention programmes in the schools as well as utilize multi-media means to promote safe medication practices. It is hoped that citizens in Hong Kong will benefit from this type of pharmaceutical care.

VI CONCLUDING REMARKS

To achieve the desirable therapeutic efficacy of "Drugs" and to eliminate drug-related problems are undoubtedly, the major foci of pharmaceutical care. The promotion of safe medication practice is also one of the best strategies to achieve the above purposes. The authors thus hope that the recommended strategy described and discussed in this paper can be taken into consideration by the relevant health professionals.

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Drugs for Summer

Windy Chan

Summer is the time for outdoor activities and adventures. Along with the growing trend of public health awareness, people are more concerned with the potential dangers in excursions and their preventions. Pharmacists have a key role giving professional advice on the employment of preventive measures. A few main issues are described in this article: mosquito bite avoidance, sunscreens, anti-perspirants and medical kits for travellers.

I MOSQUITO BITE AVOIDANCE [1 - 5]

Mosquitoes can act as vectors for a few potentially fatal infections. Of particular recent attention is Dengue Fever (DF). Brief details of DF are given in Table 1. At present, there are no effective vaccines for DF; personal protection against mosquito bites is therefore paramount at all times.

i) Feeding habits of mosquitoes [3]

Mosquitoes rely on body heat and moisture in targeting biting spots. Some perfumes, strong smells and human secretions, such as lactic acid, can also act as attractants. Dark clothing also looks more attractive to mosquitoes than light clothing.

Many species of mosquitoes tend to feed in late afternoon and evening. *Aedes* mosquitoes, vector of DF, are day-biting species with increased biting activities for 2 hours after sunrise and several hours before sunset.

ii) Prevention measures

Direct insect avoidance and physical barriers, such as wearing long-sleeves clothing and bed nets, are effective in combating infections. During outings, insect repellents are the mainstay of defensive strategy. The repellents are believed to work, after evaporation from skin, by interfering with chemical stimuli which attract mosquitoes.

iii) DEET [3-5]

There is a good range of effective repellents on the market. Among them, diethyltoluamide (DEET) has been relied on worldwide for over forty years. Many believe it is the first-line choice for use when visiting malaria endemic areas. It possesses a broad spectrum, and is effective against a wide range of mosquito species, as well as black flies, harvest bugs or chiggers, midges, ticks, and fleas.

DEET can provide acceptable levels of protection for three to four hours, much longer than other constituents. Reapplications are necessary for maintaining activity. In the UK, DEET of strength around 30 per cent product is recommended for best protection though products in the local market range from only 7 to 20 per cent.

DEET is relatively safe if properly used in adults. Toxicity from topically applied DEET products in adults, even in high concentrations, is extremely rare. Similar to other skin products, allergic skin reactions may happen, especially if left too long or even overnight causing occlusion of the skin. It is irritant to the eyes and mucous membranes. Care should be taken when applying it to the face. DEET can also be applied to clothing but as a plasticising agent, it can damage plastic objects that come into contact. Particular care should be taken regarding plastic glasses and watch faces.

Accidental oral ingestion of large volume can cause harms to the cardiovascular, respiratory and central nervous systems.

A prime concern is its safety in children. Reports of encephalopathy have been described since the introduction of DEET. Use strength lower than 10 per cent or alternatives if possible. Its use in pregnancy is discouraged though there has only been one documented case of harm to a foetus through the use of DEET.

Various dosage forms are available in the market. No significant differences in activities exist among the cream, gel or spray preparations. Adhesive appears having slightly longer duration but it should only be used on clothing.

iv) Volatile oils [4]

A number of natural products, with

Table 1. Dengue Fever

Causative Virus	✦ Flavivirus, virus serotypes DEN-1, DEN-2, DEN-3, and DEN-4 ✦ Closely related but antigenically distinct
Vector	Mosquito *Aedes aegypti* and *Aedes albopictus*
Incubation Period	Commonly 4 - 7 days
Clinical Manifestations	✦ Self-limited acute febrile illness accompanied by headaches, musculoskeletal pain, and skin rash, retro-orbital pain, anorexia, nausea and vomiting ✦ Dengue hemorrhagic fever can occur in secondary infection
Further information	✦ Tam V, Leung L. Dengue fever invasion - mosquito bite can cause fatality. HKPJ 2002; 11(4):146-153. (Ref. 2) ✦ CDC Dengue Fever Home Page http://www.cdc.gov/ncidod/dvbid/dengue/index.htm ✦ Department of Health Information Sheet on Dengue Fever/ Dengue Haemorrhagic Fever, September 2001 http://www.info.gov.hk/dh/useful/ltod/fs_dengue.htm ✦ Food and Environmental Hygiene Department, Local Vector Surveillance http://www.fehd.gov.hk/fehd/safefood/dengue_fever/indexc.html

Table 2. Correct use of insect repellents
Pharmacist advice for patients on using insect repellents :
• Apply only to exposed skin
• For use on the face, dispense repellent into the palms of the hands, rub together and then carefully apply to the face, avoiding the eyes and mouth
• Do not apply to broken or inflamed skin
• Wash repellent off hands after application to avoid contact with eyes, mouth or genitals. Also wash off repellent before going to bed
• If the effects seem to be wearing off, reapply more frequently than the time interval stated on the label. Sweating, abrasion or washing would remove repellents from the skin
• Apply carefully to children and do not apply to their hands to avoid ingestion
• When using a repellent for the first time, test the product on a small area of skin in case of allergy
• Insect repellents should generally be applied after sunscreen, as the sunscreen may occlude evaporation of DEET. However, there is evidence of a breakdown in sunscreen efficacy.

blends of volatile oils as active ingredients, have been promoted on the market. Published literature is only available to a significant extent for citronella oil which, though effective, has an extremely short length of action, often under one hour. Frequent reapplications are crucial. Another concern is the usefulness in mosquito severely infested areas while DEET remains more reliable. Fewer mosquito species are susceptible to the oils. It must also be made clear that natural products are not necessarily safe.

Choice of repellents is determined by the users' compliance, cosmetically acceptability and fears of adverse effects. A pragmatic recommendation is in a concordance approach: the repellent the person is willing to use regularly is better than the one found unacceptable, however efficacious it may be. Some points in the correct use of repellents are described in Table 2.

Until a better repellent becomes available, DEET-based repellents remain the gold standard of protection. However, prevention measures should never be restricted to insect repellents only. Promotion of good personal hygiene and environmental controls such as removal of stagnant water are critical.

Local guidelines on use of insecticides and education leaflets can be downloaded from the website of Agriculture, Fisheries Conservation Department at http://www.afcd.gov.hk/quarantine/animal.htm.

II SUNSCREENS [6-10]

Sunscreens are one of the best sellers in summer, traditionally used to prevent sunburn and tanning. Nevertheless, controversies have been brought up regarding the use of sunscreens. These include propositions that they increase rather than reduce the risks of cancers, hinder vitamin D synthesis in the skin, and possess unreliable potency when exposed to sunlight. Pharmacists should have good understanding of the scientific principles concerning sunscreens and the evidence for their effectiveness.

i) UV radiations

There are three bandwidths of UV radiation that have harmful effects on the skin: UVA (320 - 400nm), UVB (290 - 320nm) and UVC (200 - 290nm). UVA is further subdivided into short- and long-wave. About 80 per cent of the UV reaching the earth's surface is in the UVA range with the rest in that of UVB. Most UVC is filtered out by the ozone layer. UVB is mainly responsible for sunburn. Both UVA and UVB are involved with the process of tanning, the development of certain skin cancers and photoaging.

ii) SPF and star systems

To facilitate selection of an appropriate sunscreen, a system of measuring efficacy at screening against UVB has been developed - the Sun Protection Factor (SPF) rating. The SPF is the difference in time taken to burn between protected and unprotected skin. SPF 15 is usually good enough for daily activities. Sufficient thickness of application is essential for protection, or higher SPF should be used instead. [7]

For screening against UVA, some, but not all, manufacturers signify the Star system. Because of the long exposure time required before UVA-induced erythema becomes apparent, testing on human may not be achievable. Therefore, no universally accepted means of defining protection from UVA exists.

iii) Active ingredients in Sunscreens [9-10]

The ingredients in sunscreens fall into two broad classes:

- Absorbents, also called organic sunscreens, work by absorbing UV energy at a molecular level. Examples include para-aminobenzoic acid (PARA - less commonly used these days), esters of PABA, cinnamates and benzophenones (oxybenzone and mexenone), and dibenzoylmethanes (avobenzones). With the exception of avobenzone, they tend to be more effective in the UVB range.

- Reflectant or inorganic sunscreens act as a reflective barrier to both UVA and UVB radiations. Titanium dioxide is one of the most widely used compounds

It should be noted that only some ingredients are effective against UVA. Protection against UVA is also afforded by titanium dioxide and avobenzone and oxybenzone.

Proper use of sunscreens is safe. Local reactions can occur with the base formulation and/ or active ingredients but allergic reactions appear to be uncommon. Some tips on proper use of sunscreen are listed in Table 3. Importantly, sunscreen should not be the only measures against sunburn nor should it be used as a way of increasing exposure to the sun.

III ANTI-PERSPIRANTS[11-12]

Under the high ambient humidity

Table 3. Proper use of sunscreen
Pharmacist advice for patients on using sunscreen:
• Apply 30 minutes before sun exposure and reapply every two to six hours regularly
• Apply sufficient amount of sunscreen
• Apply higher factor sunscreen in severe sunlight.
• Pay particular attention to sensitive areas such as the soles of feet, backs of knees and nipples.
• Loss of protection can still occur with water-resistant products after immersion in water. Frequent reapplication would be prudent
• Potency of sunscreen can be reduced by improper storage, e.g., exposure to heat. Fresh bottle of sunscreen should be purchased for each summer

conditions during summer, sweating can be excessive enough that affects social life. The extent of hyperhydrosis (excessive sweating), generalized or localized, directs the choices of management. The causes of generalized hyperhydrosis may not be easily established but it may be secondary to underlying skin diseases (fungal infections; contact dermatitis), thyroid dysfunction or central nervous system disorders. Localised hyperhidrosis usually affect the palms, soles, groin and axillae. It happens as a natural response though stress or sometimes psychological factors can induce excessive sweating.

There are wide ranges of commercial brands of topical anti-perspirants. The main active ingredients are aluminium salts, such as aluminium chloride or aluminium chlorohydrate, formulated in alcoholic solvents. Aluminium salts, with their astringent and antiperspirant properties, are useful in mild and localized hyperhidrosis. The solution or spray should usually be applied at night onto dried affected areas and be washed out in the morning. Aluminium salts can be irritating and so do the fragrances contained in some brands. The solution should not be applied to wet, inflamed, broken, or recently shaved skin.

If aluminium salts treatment fails or the hyperhidrosis is extensively generalized, medical referral is warranted. Further treatment options include antimuscarinics, intradermal injection of botulinum A toxin and surgical excision of eccrine glands.

IV MEDICAL KIT FOR TRAVELLING [13-15]

Summer is a peak season for travelling abroad. Supplying medical kits to holidaymakers is an important task for pharmacists. Contents of a medical kit for a short trip are listed in Table 4. When travelling to more exotic destinations, a more specific range of items should be considered. Highlight is placed on the use of chlorinated tablets for water purification in which local people concern more after the outbreak of SARS. Vaccination is required for visiting some places. Information can be obtained from the Port Health Office, Department of Health at www.info.gov.hk/trhealth.

i) Water purification [14]

Chemical methods are frequently employed by travellers for water purification. Chlorination has long been used in the UK while iodination is preferred in the US. Spectrum of activities is similar though iodine possesses advantages in certain situations. With a better-tolerated side effect profile, being neutral on thyroid function, chlorine-based product would be more suitable and easily obtainable for most holidaymakers. Sodium dichloroisocyanurate (Puritabs) has been one of the market leaders. For Iodine, it is available in liquid (Tincture of iodine), crystals or tablets.

Recommendations and instructions on manufacturers' labels should be followed carefully. Any organic matter should be strained or filtered away before treatment. Chemical sterilization will take some time to complete, and treated water should be left for at least 30 minutes before drinking.

Travelers, however, should not assume treated water to be absolutely safe. For instance, chlorination alone may not kill some enteric viruses and parasitic organisms that cause giardiasis, amoebiasis, and cryptosporidiosis. Therefore, it should be emphasized that boiling remains the method of choice for sterilizing water.

V CONCLUSION

With increasing personal health and environmental awareness, people become more enthusiastic in guarding themselves against different kinds of potential hazards. Pharmacists should always keep themselves updated with current epidemics and risks, standing by at all times to offer professional advices.

Table 4. Medical kit

Basic First aid items	• Antiseptics • Plasters ± Bandage
OTC medicines	• Analgesics/ antipyretics • Loperamide/ Lomotil • Oral rehydration salts • Treatments for motion sickness • Antacids • Antihistamine

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Insights into Hormone Replacement Therapy (H.R.T.)

Chong, Donald

2 CE Units

I WHAT IS MENOPAUSE?

Menopause, the final menstrual cycle in a woman's reproductive life, is the result of decline in ovarian function with subsequent loss of the major ovarian hormones, estradiol 17-β (E2) and progesterone. After menopause, adipose (fatty) tissue becomes the primary site of estrogen production, where an androgen precursor from the adrenal gland is converted to estrone (E1), a much weaker estrogen than estradiol. Other ovarian hormones affected by menopause are progesterone, which is released by the corpus luteum following ovulation in pre-menopausal women, and androgens.

Menopause occurs naturally around the age of 50 years; however, undernourished women or those who smoke often experience menopause one to two years earlier. Smoking is thought to have anti-estrogenic effects related to an induction of accelerated estrogen metabolism or to the lower body weight in female smokers. Menopause occurs at any age if the ovaries are removed surgically. Although post-menopause is marked by the time after the last ovulation, it is difficult to determine clinically. Therefore, the post-menopausal period is often considered to begin 12 months after spontaneous amenorrhea. Measurements of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) can also be helpful in making the diagnosis.

II CONSEQUENCES OF MENOPAUSE AND ESTROGEN DEFICIENCY

The lack of estrogen leads to short-term and long-term consequences in women (Table 1). Estrogen replacement therapy (ERT) or hormone replacement (HRT), the replacement of estrogen plus progestin in women with a uterus, plays an important role in reducing its negative effects. It is generally agreed that post-menopausal women should receive high-quality counseling about menopause in general and about the decision to use ERT/HRT.

i) Vasomotor Instability

As estradiol concentration declines, 50% to 85% of women will suffer traditional menopausal complaints such as hot flushes, night sweats, irritability, palpitations, nausea and dizziness. These vasomotor symptoms result from a disruption of the thermoregulatory centre in the brain caused by the lack of feedback from ovarian hormones. These complaints vary in severity and duration from woman to woman. Over half of the women experience severe symptoms, over one-third have moderate symptoms, and 16% have only mild symptoms.[1]

Although symptoms generally diminish in time (12 to 24 months) even without treatment, some women experience symptoms for five years or more. Irregularities in the menstrual cycle in peri-menopausal women often are sufficient to cause vasomotor symptoms in some women up to ten years prior to menopause.

Table 1. Consequences of Estrogen Deficiency

	Consequences of Estrogen Deficiency
Short-term	* Vasomotor symptoms (hot flashes, night sweats) * Sleep disturbances * Fatigue * Exacerbation of depression/anxiety/mood disorder
Mid-term	* Vaginal dryness/atrophy with related pain with * intercourse * Breast atrophy * Loss of libido * Skin and hair dryness * Urinary difficulties
Long-term	Increased risk of: * Osteoporosis and tooth loss * Cardiovascular disease * Alzheimer's disease * Macular degeneration

ii) Genitourinary Atrophy

Tissues such as the vagina, vulva and areas in the bladder are rich in estrogen receptors. The lack of estrogen may result in atrophic changes and cause vaginitis, painful urination, painful intercourse and stress urinary incontinence.

iii) Psychological Symptoms

Insomnia and fatigue are commonly reported in peri- and post-menopausal women. Hormonal fluctuations also may be responsible for worsening post-menopausal syndrome (PMS) in peri-menopausal women and decreased libido in both peri- and post-menopausal women. Underlying mood disorders and anxiety may be exacerbated at menopause, but there is no evidence that menopause causes major depression, anxiety, severe memory lapses, or erratic behavior.[2] However, the patents' cultural attitudes toward menopause may also affect their psychosocial responses. For instance, an individual who is interested in seeking assistance for symptoms of menopause will respond differently to a woman who perceive the long-term consequences of estrogen deprivation inevitable.[7]

iv) Osteoporosis

The sustained production of estrogens in adolescents and young women is essential for the development and maintenance of healthy bone and peak bone mass. Estrogen deficiency at menopause results in rapid bone loss which is known as Type 1 or post-menopausal osteoporosis. Post-menopausal osteoporosis is the most common form of osteoporosis. Heavier women with higher production of estrone in the adipose tissue have less risk of developing osteoporosis than thin women. At the other end of the spectrum, elite female athletes who lose enough body fat to become amenorrheic also are at risk for loss of bone due to estrogen deficiency.

Estrogens act directly on bone cells through high-affinity estrogen receptors and appear to temper bone resorption, thus allowing for normal mineralization. Estrogen has a direct role in regulating bone metabolism through estrogen receptors on the osteoblasts (bone building cells) and osteoclasts (bone resorptive cells). Other effects of estrogen are less well-defined but may involve the modulation of one or more of the local bone-regulating factors released by bone or blood cells.[3] Without estrogen, the osteoclasts resorb more bone than the osteoblasts can replace. Estrogen is also thought to increase the efficiency of calcium absorption, promote the synthesis of calcitonin, and increase vitamin D receptors in osteoblasts. Rapid bone loss occurs soon after the estrogen concentrations decline even before menopause, and this is especially destructive to the trabecular bone of the vertebrae. Women who experience menopause before the age of 40 (natural or surgically induced) are at greater risk of osteoporosis because they experience fewer years with the protective effect of endogenous estrogen.

Although bone resorption (loss) and rebuilding occur throughout life; after menopause, there is a rapid loss of bone as the rate of bone resorption becomes much greater than bone formation. Accelerated bone loss diminishes exponentially with time, with most bone loss occurring during the first three to six years after menopause. However, the loss of bone can continue for up to two decades. Trabecular (spongy) bone, which is found in the vertebrae and the end of long bones, has the most rapid turnover rate and is at the greatest risk for significant decrease in bone mineral density. Women may lose up to 50% of their trabecular bone. Tooth loss and periodontitis have been attributed to osteoporotic changes in the jaw as well. [4,5]

Depending on the amount of bone present at the time of menopause, some women will begin experiencing "silent" fractures of the vertebrae within a few years after estrogen levels have fallen. Others may not experience clinical problems related to osteoporosis for a decade or more. Women at the greatest risk for developing significant bone loss after menopause are white and Asian women, thin women, female smokers, and those who do not get adequate exercise or calcium intake. Both women and men taking long-term corticosteroid are at risk for developing significant bone loss (secondary osteoporosis), but post-menopausal women are particularly vulnerable to fractures.

Screening post-menopausal women at risk for osteoporosis by measurement of bone density is recommended so that effective preventive or treatment measures can be taken to reduce the risk of fractures.[6] Unfortunately, large proportion of the populations at risk for osteoporosis and fracture have not been evaluated.

v) Heart Disease

Cardiovascular disease is currently the number one cause of death for women in the United States. Although many women fear breast cancer more than heart disease, 50% of women will die from heart disease or stroke, whereas only 4% will die from breast cancer.[7] The major risk factors for heart disease in both men and women include smoking, high blood pressure, dyslipidemia and obesity, but the loss of estrogen appears to be an independent risk factor for heart disease in women.[8]

vi) Other Sequelae of Estrogen Deficiency

Evidence suggests that long-term estrogen deprivation contributes to the development of Alzheimer's disease, lens opacity, and macular degeneration (particularly in women with surgically induced menopause). [2,9] The full effect of estrogen loss on skin is unclear, but cross-sectional data have demonstrated a correlation between the decline in skin collagen resulting in skin atrophy and the number of years after the onset of menopause.[2]

III HORMONE REPLACEMENT THERAPY

In the continuing search for an "ideal" hormone replacement, researchers have pursued variable doses of estrogens and progestins, different routes of administration, and new classes of compounds with the actions of estrogens hoping to minimize adverse effects. As a result, a variety of hormone replacement products are available in different dosage forms.

The potencies of the various estrogens vary considerably as do the qualitative differences (i.e., binding capacity and ability to induce a particular biologic response), making direct comparisons difficult. Similarly, progestins vary in potency and their abilities to produce estrogenic and androgenic effects.

i) Type of HRT

1. Estrogen

An estrogen may be defined as any chemical moiety that binds to the estrogen receptor (ER) and affects gene transcription to result in a biologic effect. The intricacy and complexity of estrogen action varies more than for other steroids. There are two-ER subtypes; namely ER-alpha and ER-beta, which have different cellular distribution and concentration in the target tissues such as the breast, uterus, bone, and brain. Receptor binding and subsequent events depend on tissue and cell type, as well as the presence of various

signaling, activating, and repressing factors. Non-genomic estrogen actions also occur in both ER-positive and ER-negative cells. This complexity helps to explain the range of biological responses (agonist, partial agonist, and antagonist) of various estrogens or estrogen-like compounds, such as estrogen receptor modulators (ERMs) and plant-derived estrogens (phytoestrogens), in different target tissues. [10, 11]

Pharmacologically, estrogens are often divided into three groups: synthetic estrogens, conjugated estrogens, and native human estrogens. Synthetic estrogens may or may not contain a steroid structure. Diethylstilbestrol and estrogens commonly used in oral contraceptives (ethinyl estradiol) are considered synthetic estrogens. Conjugated estrogens either are synthetically produced or originate from non-human sources.

Estrogen can be administered via multiple routes including oral, topical (vaginal creams, vaginal rings, and pessaries), transdermal (patches/gels), parenteral (IM, IV, SQ, and implants), and intranasal (investigational). Orally administered estrogen is subject to first-pass through the liver and it undergoes enterohepatic recirculation. Hepatic metabolism of estrogen is also responsible for the favorable effects on lipoproteins (< LDL, > HDL). Coagulation factors and renin substrate are also influenced by the hepatic metabolism of estrogen.

Estrogen delivered transdermally, vaginally, or parenterally is not subject to the hepatic first-pass effect. The non-oral routes of administration may be preferred in women at risk for gallbladder disease. Parenteral routes are less commonly prescribed because dosage titration is difficult and estrogen concentrations fluctuate mildly during the dosage interval. Vaginal preparations, while useful for treating genitourinary symptoms, have systemic absorption patterns too variable to be considered acceptable for prevention of osteoporosis.

2. Progestin

For women with a uterus, the addition of progestin protects against the overgrowth of the uterine lining from estrogen stimulation, a risk factor for endometrial cancer. The progestins used for HRT include the natural progesterone (micronized) and the synthetic derivatives of 17-alpha hydroxyprogesterone (medroxyprogrsterone acetate) and 19-mortestosterone (norethindrone, norethindrone acetate, levonorgestrel, norgestrel, and norgestimate).

The use of cyclic regimen (daily estrogen combined with cyclic exposure, usually 12 to 14 days of progestin results in periodic shedding of the uterine lining, thereby causing a menstrual-like bleeding. On the other hand, the use of continuous combined regimen (daily estrogen combined with daily low-dose progestin) attenuates the effects of estrogen on the lining and causes amenorrhea. Women will experience different patterns and amounts of vaginal bleeding and spotting depending on the dose and number of days per month the progestin is taken. [12]

ii) The benefits of HRT

The benefits of HRT are as follows:
a) Relief of menopausal symptoms
b) Prevention of osteoporosis
c) Prevention of cardiovascular disease

The administration of HRT may also reduce the risk of Alzheimer's disease, but data is less convincing.[13]

HRT may be offered to most post-menopausal or symptomatic peri-menopausal women, and their decision to use HRT will depend on the balance between the advantages and disadvantages of treatment that are explained to them.

1. Menopausal symptoms

Oestrogen is effective in reducing the severity and frequency of hot flushes and sweating. There is less evidence to show that oestrogen is effective in controlling other acute symptoms attributable to the menopause.[14] Although severe vasomotor symptoms may develop in some Chinese menopausal women, they are less common than in Caucasians.[15,16] Severe vasomotor symptoms are thus a less important indication for treatment in Chinese women.

2. Prevention of osteoporosis

Bone loss after menopause affects the femoral neck and lumbar spine in particular. The administration of

Table 2. Examples of preparations available in Hong Kong and doses
(HKCOG guidelines number 2 - revised January 2003)

Formulation	Active ingredients and recommended dosages	Trade name
Unopposed oestrogen		
Oral	Conjugated oestrogens 0.625mg daily	PREMARIN, CONJUGATED OESTROGENS JEAN-MARIE
Oral	Oestradiol 2mg daily	ESTROFEM
Oral	Oestradiol valerate 2mg daily	PROGYNOVA
Oral	Oestriol 0.27mg, oestradiol 0.6mg, oestrone 1.4mg	HORMONIN
Oral	Oestriol 1mg	OVESTIN
Gel	Percutaneous oestradiol gel 2.5g daily	OESTROGEL
Gel	Percutaneous oestradiol gel 1.5g daily	ESTREVA
Patch	Oestradiol 4mg patches (2 patches/week)	DERMESTRIL or ESTRODERM TTS
Intranasal	Oestradiol 150mcg/spray	AERODIOL
Combined cyclical (sequential)		
Oral	Oestradiol 2mg daily + dydrogesterone 10mg 14/28 days	FEMOSTON
Oral	Oestradiol 2mg 22 days/1mg 6 days + norethisterone acetate 1mg daily 10/28 days	TRISEQUENS
Oral	Oestradiol valerate 2mg daily + cyproterone acetate 1mg 12/28 days	CLIMEN 28
Oral	Conjugated equine oestrogens 0.625mg daily + medroxyprogesterone acetate 5mg 14/28 days	PREMELLE CYCLE
Oral	Oestradiol valerate 2mg daily + Medroxyprogesterone acetate 10mg 10/21 days	DILENA
Oral	Oestradiol valerate 2mg + levonorgestrel 0.15mg 12/21 days	KLIMONORM
Patch	Oestradiol 4mg patches (2 patches/week) for 2/52 followed by oestradiol 10mg + norethisterone acetate 30mg patches (2 patches/week) for 2/52	ESTROCOMB TTS
Continuous combined		
Oral	Conjugated equine oestrogens 0.625mg + medroxyprogesterone acetate 2.5mg daily	PREMELLE
Oral	Oestradiol 2mg + norethisterone acetate 1mg daily	KLIOGEST
Oral	Oestradiol 1mg + norethisterone acetate 0.5mg daily	ACTIVELLE
Oral	Tibolone 2.5mg daily	LIVIAL
Selective Estrogen Receptor Modulators		
Oral	Raloxifene 60mg daily	EVISTA

oestrogen is effective in preventing osteoporosis and osteoporotic fractures in these sites.[17] The decision to initiate HRT could be based on the measurement of bone mineral density (BMD) especially in women who are at risk of osteoporosis development (Table 3).

3. Prevention of cardiovascular disease

There is indirect evidence to suggest that the administration of oestrogen reduces cardiovascular risks by as much as 50%.[18] Oestrogen has been shown to improve serum lipid profile, reduce cholesterol uptake by blood vessel walls and increase blood flow due to arterial relaxation. Oestrogen may also have an antioxidant effect and it also increases insulin sensitivity. HRT confers cardioprotective effects in both patients who are currently receiving therapy or in those who have discontinued treatment. This benefit of oestrogen applies to current as well as previous users of HRT. The benefit of treatment is more evident in women at increased risk of cardiovascular diseases (Table 4).

iii) Disadvantages and risks of hormone replacement therapy

The main disadvantage of HRT is the necessity to receive treatment for a relatively long period of time. In addition, for women with uterus, the resumption of menstrual-like bleeding may be inconvenient.

The most common side effects of HRT are breast sensitivity or engorgement and fluid retention. These problems tend to improve within months of initiating treatment, but the dose of oestrogen given may be reduced to relieve the discomfort. It remains controversial whether HRT increases the risk of breast cancer.[19]

iv) Absolute contra-indications to hormone replacement therapy

Absolute contra-indications to HRT are existing breast carcinoma, endometrial carcinoma, venous thrombosis, and acute liver disease.

v) Prescription of hormone replacement therapy

Oestrogen may be administered orally, percutaneously, transdermally, or by using a subcutaneous implant. Vaginal administration of oestrogen is usually reserved for the short-term treatment of lower genital tract symptoms. For most women, the route of administration of oestrogen can be chosen according to their preferences. In patients with diabetes mellitus, hypertension, hypertriglyceridemia or a history of venous thrombosis, non-oral preparations are preferred to reduce first-pass effect.

1. Unopposed oestrogen therapy

Unopposed oestrogen therapy implies the use of oestrogen without a progestogen. In women who have had a hysterectomy, unopposed oestrogen should be prescribed. For those women who still have a uterus, a progestogen should be given in addition to oestrogen to prevent endometrial hyperplasia and carcinoma.[20] The prescription of oestrogen as well as progestogen is referred to as combined HRT, and this combination may be given either cyclically (sequentially) or continuously.

2. Combined cyclical (sequential) HRT

A cyclical (sequential) regimen implies that a progestogen is given on a cyclical basis (in addition to oestrogen). The cyclical use of progestogen usually results in regular 'withdrawal bleeding' at the end of each progestogen cycle. When prescribing HRT at the time of (or soon after) the menopause, a cyclical (sequential) regimen is less likely to cause irregular bleeding than would a continuous combined regimen. In a cyclical regimen, oestrogen is usually prescribed for 21 or 28 days while the progestogen is given for 10 or 12 days each month. A small percentage of women may become amenorrheic during cyclical treatment.

3. Continuous combined HRT

Continuous combined HRT can be given to women with an established menopause (>2 years), in which case both the oestrogen and progestogen are given on a daily basis. The aim of such a regimen is to maintain amenorrhea. Spotting is common during the first few months of treatment. An alternative to continuous combined HRT is the use of tibolone, a synthetic agent that has weak oestrogenic, androgenic, and progestogenic properties.

4. Selective estrogen receptor modulators

Recent data on a new class of drugs referred to as selective estrogen receptor modulators (SERMs) have suggested that these drugs reduce the risk of breast and endometrial cancer.[21] Although SERMs have a beneficial effect on the serum lipid level and BMD, they produce little or no improvements in acute menopausal symptoms. These drugs may thus be desirable for asymptomatic women who are anxious about or those at increased risks for the development of breast cancer. Selective estrogen receptor modulators may be prescribed whether or not the uterus is present.

5. Duration of hormone replacement therapy

No guidelines exist regarding the duration of HRT. As the treatment continues, the beneficial effects of HRT will be maintained. Studies on the effect of long-term HRT on breast cancer risks are currently underway.

IV MANAGEMENT OF MENOPAUSE

Table 3. Risk factors for osteoporosis

Risk factors for osteoporosis in women:
1) Prolonged oligomenorrhea / amenorrhea or premature menopause
2) Prolonged immobilization/inactivity
3) Excessive intake of alcohol or caffeine; smoking
4) Low body mass index, short stature, family history of osteoporosis
5) Use of drugs that increase the risk of osteoporosis, e.g., steroids, thyroxin, anticonvulsants
6) Medical conditions that increase the risk of osteoporosis such as:
Cushing's syndrome
hyperthyroidism
hyperparathyroidism
chronic disease of the liver or kidney
malabsorptive disorders
gastrectomy
rheumatoid arthritis

Table 4. Risk factors for cardiovascular diseases

Risk factors for cardiovascular diseases in menopausal women:
1) Existing cardiovascular disease
2) Family history of cardiovascular disease
3) Hypercholesterolaemia
4) Smoking
5) Diabetes mellitus
6) Hypertension
7) Obesity

HRT can be initiated at any time after the onset of menopause. The type of HRT regimen to use depends on the duration of menopause and whether a hysterectomy has been performed. Treatment may be started before the onset of menopause if symptoms of oestrogen deficiency develops, although irregular bleeding may be a problem in peri-menopausal women. In addition to using HRT, patients are reminded to attend to lifestyle modifications such as weight control and regular weight-bearing exercise.

i) Monitoring of women receiving HRT

Cervical smears should be performed routinely for all women with a uterus. As each visit, compliance with treatment, symptom control and drug-related side effects should be assessed. In patients receiving combined therapy, the bleeding pattern should also be monitored. Table 5 describes the examinations and investigations that are commonly performed in patients receiving HRT.

ii) Management of irregular bleeding during hormone replacement therapy

1. Bleeding during combined cyclical hormone replacement therapy

Some women will be amenorrheic during this course of therapy and a biopsy is not necessary. Bleeding should occur around the time of progestogen withdrawal. If bleeding occurs at times other than this or if it is persistently irregular, endometrial biopsy is recommended.

2. Bleeding during continuous combined hormone replacement therapy

Table 5. Follow-up of women receiving hormone replacement therapy

Visit	Recommended routine tests
At first visit	Blood pressure measurement; monitoring of levels of follicle-stimulating hormone, luteinizing hormone and oestradiol to confirm menopause (if clinical features are atypical); lipid profile; liver function tests; bone biochemistry; mammography; urinalysis
At each visit	Urinalysis; blood pressure measurement
Every 2 years	Physical examination; lipid profile; liver function tests; fasting glucose level; mammography
As indicated	Measurement of bone mineral density

Women using continuous combined HRT should achieve amenorrhea within about 4 months of starting treatment. Spotting in the first few months is common. Endometrial biopsy should be considered in women who develop irregular bleeding but who were previously amenorrheic when using this regimen.

3. Bleeding Patterns

There are two main types of bleeding pattern: withdrawal bleeding and irregular bleeding. Withdrawal bleeding may occur during the hormone-free period or at the end of the progestogen phase of treatment in patients receiving cyclical therapy. In peri-menopausal women, the occurrence of stable, regular withdrawal bleeding is an important treatment objective. In women receiving continuous estrogen treatment combined with continuous low-dose progestogens (mostly commonly in post-menopausal patients), the endometrium becomes inactive and there is a cessation of regular withdrawal bleeds (amenorrhea).

Irregular bleeding can be divided into spotting and breakthrough bleeding. Compared to breakthrough bleeding, spotting is light and does not require sanitary and hygienic measures. Irregular bleeding occurs at times other than at the end of, or after, the progestogen phase of the treatment cycle.[22, 23]

The volume, duration and frequency of bleeding may vary between individuals. However, precautions should be taken if the episodes are heavy, prolonged or very frequent. Low-dose unopposed estrogen is associated with a lower incidence of withdrawal and breakthrough bleeding.[24]

V THE PHARMACIST'S ROLE

Pharmacists need to stay up-to-date on current therapies related to women's health. These include peri-menopause, sexual health, lifestyle changes, osteoporosis, CVD, cancer and urogenital health, etc. Pharmacists also have an important role in providing education to other health professionals and peri- or post-menopausal women. For example, they can reinforce the importance of good nutrition, exercise, stress reduction, smoking cessation and adequate calcium and vitamin D consumption, etc. They should also be aware of the potential side-effects so that they can assist in resolving HRT-related problems.

Donald Chong is currently the Section Editor for the Pharmacy Practice Section of the HKPJ. He is currently working in the Regulatory and Medical Affairs in the Pharmaceutical Industry.

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Questions for Pharmacy Central Continuing Education Committee Program

2 CE Units

Insights into Hormone Replacement Therapy (H.R.T.)

1. ***Which of the following statements about post-menopause is/are true?***

(A) It is considered to be 9 months after spontaneous amenorrhea
(B) FSH and LH hormone levels may assist in the diagnosis of post-menopause
(C) It is considered to be 12 months after spontaneous amenorrhea
(D) Only FSH level is a critical factor for determining the stage of post-menopause
(E) Both B and C

2. ***Long term risks of estrogen deficiency include the following except:***

(A) Osteoporosis
(B) Macular degeneration
(C) Cardiovascular disease
(D) Parkinson's disease
(E) Alzheimer's disease

3. ***The benefits of hormone replacement therapy (HRT) include:***

(A) Relief of menopausal symptoms
(B) Prevention of cardiovascular diseases
(C) Prevention of osteoporosis
(D) A and B
(E) A, B and C

4. ***The disadvantages of HRT include:***

(A) Flu-like symptoms in 20% of women
(B) Re-occurrence of menses in all women
(C) Possible development of breast cancer
(D) Itchiness of the vagina
(E) All of the above

5. ***Absolute contraindications of HRT are:***

(A) acute liver disease
(B) venous thrombosis
(C) current endometrial carcinoma
(D) current breast carcinoma
(E) all of the above

6. ***Which of the following statements about Tibolone is true?***

(A) It cannot be used in surgical menopause
(B) It has weak estrogenic, androgenic and progestogenic properties
(C) It has strong estrogenic and progestogenic properties
(D) It is a type of estrogen
(E) It belongs to a class called Selective Estrogen Receptor Modulators (SERMs)

7. ***Which of the following is/are true about SERMs?***

(A) They have a favourable effect on lipid profile
(B) They reduce the severity of acute menopausal symptoms
(C) They are only to be used in patients with hysterectomy
(D) A & B
(E) A, B, C

8. ***Progestin is added to the regimen in HRT because***

(A) It helps to relieve menopausal symptoms
(B) It is used to prevent overgrowth of the uterine lining
(C) It is used to minimize the chance of ovarian cancer
(D) It is used to lessen the volume of menstrual blood
(E) It helps to prevent osteoporosis

9. ***Which of the following statements about HRT and its route of administration is true?***

(A) Estrogens and progestogens are used together in women with hysterectomy
(B) Estrogen can never be used alone
(C) Vaginal route is particularly useful for relief of lower-genital tract symptoms
(D) Oral route of administration is preferred in women at risk for gallbladder disease
(E) The hepatic "first-pass" effect is prominent for estrogen delivered via the vaginal route

10. ***Which of the following laboratory tests is/are recommended every 2 years in women receiving HRT?***

(A) Urinalysis
(B) liver function tests
(C) lipid profile
(D) A & B
(E) B & C

Pharmacy Conference 2004
"Patients and Pharmacists: In Sickness and In Health"
Welcome Message from the Chairperson

Lee, Vivian WY

23 April 2004

Dear friends and colleagues,

The time has come! It is my great pleasure to invite you to the 17th Hong Kong Pharmacy Conference which will be held on 9th and 10th October 2004 in Kowloon Shangri-La Hotel. Like previous years, the Organizing Committee from the six organizations including Chinese University of Hong Kong (CUHK), Hospital Authority (HA), Department of Health (DH), Pharmaceutical Society of Hong Kong (PSHK), Practising Pharmacists Association (PPA) and Society of Hospital Pharmacists of Hong Kong (SHPHK) has been working very hard on this year's program. I guarantee you that you will find this year's program a memorable and meaningful one.

The theme for this year's conference is "Patients and Pharmacists: In Sickness and In Health". During the pharmacy conference last year, we had emphasized the importance of partnership between the public and private healthcare sectors, the regulators and business enterprises, research institutions and pharmaceutical manufacturers. This year, the focus will be on the relationship between patients and pharmacists. The theme this year has highlighted the bonding of pharmacists and patients will be inevitable whether the patients are healthy or ill. Like other health care professions, our goal is to provide the best pharmaceutical care to our patients. In order to maintain a healthy relationship with our patients, we have to better equip ourselves. Therefore, the content of the conference this year will focus on the various areas that could improve our knowledge in providing the best pharmaceutical care to our patients.

The Organizing Committee has invited prestigious local and international speakers from USA and UK to deliver the programs. The conference program will start with a keynote speech delivered by our SARS[1] hero, Professor Joseph Sung, on "Taking care of our patients". Then, Prof. Jerry Bauman, Head of Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago (UIC) deliver the first theme speech on "Clinical Pharmacy in the United States: Progress and Challenges & How this service has benefited our patients". Mr. Jonathan McKinley, Assistant Director of the Sustained Development unit, Hong Kong SAR, will deliver our second theme speech. He will be sharing with us the importance of sustained development and self-enhancement. Our UK speaker, Mr. Steve Freeborn, will deliver the final theme speech on "Technology as the enabler in Patient Care & Patient Management". He is the director of Clinical Development, Head of Pharmacy Division, Ascribe, UK. After listening to our renowned speakers on the first day, we will conclude the first day program with our exciting dinner program. It is our tradition that the dinner program will be filled with surprises. It will definitely be your loss if you miss this joyful event.

On day 2 of the conference, we will start with early morning clinical case presentation. Dr. Lingtak Chan and Dr. Alan Lau from UIC will provide some case presentations in nutrition support and drug interaction management. They are both experienced clinical faculties at UIC and will definitely enlighten us with their valuable experience in US. Like previous years, we will also have 3 very exciting concurrent sessions. The themes of the concurrent sessions include clinical practice, safe medication practices and technology in practice. Our speakers at these concurrent sessions include both renowned local and international speakers. Their expertise will provide us with new insight, practical tips and perspectives to our daily practice as pharmacists.

In conclusion, we have placed the fourth theme speech on "The Pains and Gains of the first Public Private Partnership Program (4P) in Pharmacy Service - the Patients Referral Scheme on Drug Compliance and Counseling Service" at the end of the day 2 program. Ms. SC Chiang, Convenor of the Working Group on Drug Compliance and Counseling Service will share her experience in regards to this new project. Then, a special plenary session with an interview show on "Pharmacists and Patients Getting Together" will be hosted by Ms. Scarlet Pong. A panel of pharmacists from various sectors will participate at this plenary session.

As you can see, the program is packed with information, excitement and surprises. This year, to encourage more participation, we have maintained our low registration fee at HK$1000. For members of the three pharmaceutical societies, i.e. PSHK, SHPHK and PPA, an early bird discount of HK$200 will be available for registration before 1st September 2004. There will also be a special rate for pharmacy students from CUHK for HK $ 200. For this reasonable price, you will be able to attend valuable educational programs, enjoy a gourmet dinner with a very exciting dinner program, and network with other colleagues in our profession.

I encourage you to attend the conference to exchange information and share your views with fellow colleagues. Over dinner, lunch and coffee breaks you can catch up with those pals only seen once a year. I'd like to invite you to submit abstracts for poster presentations. The recent interesting works of yours could be shared with other colleagues at the conference.

In order to make this conference to be a successful one, I need your support and active participation. I look forward to seeing you at the conference.

Sincerely,

Vivian WY Lee
Chairperson, Conference Organizing Committee
Hong Kong Pharmacy Conference 2004

Pharmacy Conference 2004 Organizing Committee

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Last updated on 27/4/04

NEW INDICATION

COZAAR
(MSD)

Active ingredient:
Losartan potassium

New indication:
Hypertensive Patients with Left Ventricular Hypertrophy
COZAAR is indicated to reduce the risk of stroke in hypertensive patients with left ventricular hypertrophy (LVH). (see Race)

Dosage and administration:
Hypertensive Patients with Left Ventricular Hypertrophy
For hypertensive patients with LVH, the usual starting dose is 50 mg of COZAAR once daily. A low dose of hydrochlorothiazide should be added and/or the dose of COZAAR should be increased to 100 mg once daily based on blood pressure response.

Race. Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of COZAAR on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the overall LIFE study population (n=9193), treatment with COZAAR resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, COZAAR decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with COZAAR (p=0.03).

Side effects:
COZAAR was generally well tolerated in a controlled clinical trial in hypertensive patients with LVH. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with COZAAR as compared to atenolol (242 patients versus 320 patients, respectively, p<0.001). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of COZAAR or an adverse effect of atenolol.

NEW FORMULATION

NEXIUM IV
(AstraZeneca)

Active ingredient:
Esomeprazole sodium

New Formulation:
A vial contains esomeprazole sodium 42.5 mg, equivalent to esomeprazole 40 mg for intravenous injection or infusion. (10 vials per box)

Indications:
NEXIUM is indicated for gastroesophageal reflux disease in patients with oesophagitis and/or severe symptoms of reflux as an alternative to oral therapy when oral intake is not appropriate.

Dosage and Administration:
Patients who cannot take oral medication may be treated parenterally with 20-40 mg once daily. Patients with reflux oesophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily. Usually the iv treatment duration is short and transfer to oral treatment should be made as soon as possible.

Injection
40 mg dose - The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes.
20 mg dose - Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes. Any unused solution should be discarded.

Infusion
40 mg dose - The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.
20 mg dose - Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Any unused solution should be discarded.

Contraindications:
Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients of this medicinal product.

Precautions:
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with NEXIUM may alleviate symptoms and delay diagnosis.

Drug Interactions:
The decreased intragastric acidity during treatment with NEXIUM might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with NEXIUM.

Concomitant oral administration of 40 mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Side effects:
Common adverse reactions for esomeprazole administered orally or intravenously include headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting and constipation. (Note: Adverse drug reactions have been observed for the racemate (omeprazole) may occur with esomeprazole.)

Forensic classification:
P1S1S3

NEW PRESENTATION

PEGASYS
(Roche)

Active ingredient:
Peginterferon alfa-2a*

* recombinant interferon alfa-2a produced by genetic engineering from *Escherichia coli* conjugated to bis-[monomethoxy polyethylene glycol] of a molecular mass, M_n, of 40 000.

New Presentations:
PEGASYS 135 micrograms solution for injection in 0.5ml pre-filled syringe
PEGASYS 180 micrograms solution for injection in 0.5ml pre-filled syringe

Indications:
PEGASYS is indicated for the treatment of chronic hepatitis C in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis.

The optimal way to use PEGASYS in patients with chronic hepatitis C is in combination with ribavirin. This combination is indicated in previously untreated patients as well as in patients who have previously responded to interferon alpha therapy and subsequently relapsed after treatment was stopped.

Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin.

Dosage and administration:
Treatment should be initiated only by a physician experienced in the treatment of patients with hepatitis C.

The recommended dose for PEGASYS is 180 micrograms once weekly by subcutaneous administration in the abdomen or thigh given in combination with oral ribavirin or as monotherapy (see table 1). The ribavirin dose should be administered with food.

The duration of combination therapy with ribavirin for chronic hepatitis C depends on viral genotype. Patients with genotype-1 regardless of viral load should receive 48 weeks of therapy. Patients with genotype 2/3 regardless of viral load should receive 24 weeks of therapy (see table 1).

In general, patients infected with genotype 4 are considered hard to treat and limited study data (N=49) are compatible with a posology as for genotype 1. When deciding on the duration of therapy, the presence of additional risk factors should also be considered. For patients infected with genotype 5 or 6, this posology should be considered.

The recommended duration of PEGASYS monotherapy is 48 weeks.

Forensic Classification:
P1S1S3

Table 1. Dosing Recommendations for Combination Therapy

Genotype	*Pegasys Dose*	*Ribavirn Dose*	*Duration*
Genotype 1	180 micrograms	< 75kg = 1000mg	48 weeks
		≥ 75kg = 1200mg	48 weeks
Genotype 2,3	180 micrograms	800mg	24 weeks

ERRATUM

In the New Products Section of HKPJ Vol 13 Issue 1, the product brand name of Oseltamivir phosphate should read as "TAMIFLU" instead of "TAMIFUL". We express our sincere apology to the company.

THE POWER TO MOVE YOU

ARCOXIA®

(etoricoxib, MSD)

Before prescribing ARCOXIA®,
please consult the full prescribing information.

Therapeutic Class: ARCOXIA (etoricoxib) is a member of a class of arthritis/analgesia medications called Coxibs. ARCOXIA is a highly selective inhibitor of cyclooxygenase-2 (COX-2). **Presentation and Form:** 60 mg, 90 mg, 120 mg tablets. Box of 30 tablets for all strengths and box of 5 tablets for ARCOXIA 120 mg. **Indication:** ARCOXIA is indicated for symptomatic relief of osteoarthritis and rheumatoid arthritis, for treatment of acute gouty arthritis, for treatment of acute pain, including that related to primary dysmenorrhea and minor dental procedures. **Dosage and administration:** Osteoarthritis – 60 mg once daily; Rheumatoid arthritis – 90 mg once daily. Acute gouty arthritis – 120 mg once daily; Acute pain – 120 mg once daily. ARCOXIA 120 mg should be used only for the acute symptomatic period. ARCOXIA is administered orally. ARCOXIA may be taken with or without food. Mild hepatic insufficiency – less than 60 mg once daily; moderate hepatic insufficiency – less than 60 mg ***every other day.*** Severe hepatic insufficiency – not recommended. Renal insufficiency (creatinine clearance ≥30 mL/min) – no dosage adjustment is necessary. Advanced renal disease (creatinine clearance <30 mL/min) – not recommended. **Contraindications:** ARCOXIA is contraindicated in patients with hypersensitivity to any component of this product and with a history of asthma, urticaria, or other allergic reactions after aspirin or other NSAID's. **Precautions:** ARCOXIA is not recommended for patients with advanced renal disease. Close monitoring is advisable for patients with estimated creatinine clearance of 30 mL/min, pre-existing significantly impaired renal function, uncompensated heart failure and cirrhosis. Other precautions include considerable dehydration, pre-existing edema, hypertension, heart failure, and ischemic heart disease. Patients with a prior history of GI perforation, ulcers and bleeding (PUB), patient greater than 65 years of age are known to be at higher risk for a PUB independent of treatment. Persistently abnormal liver function tests, acute asthmatic attacks, urticaria, rhinitis. ARCOXIA may mask fever and is not a substitute for aspirin for cardiovascular prophylaxis. ARCOXIA can be used concomitantly with low-dose aspirin if indicated. Use of ARCOXIA should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus. Safety and effectiveness of etoricoxib in pediatric patients have not been established. **Drug Interactions:** Warfarin, rifampin, methotrexate, Angiotensin Converting Enzyme (ACE) Inhibitors, lithium, oral contraceptives. Aspirin may result in an increased rate of GI ulceration or other complications compared to use of ARCOXIA alone. At steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily). **Adverse Events:** Adverse events reported in clinical studies (≥2%) include asthenia/fatigue, dizziness, lower extremity edema, upper respiratory infection; hypertension; diarrhea, epigastric discomfort, heartburn, nausea; sinusitis; headache; urinary tract infection. Report from post-marketing experience include hypersensitivity reactions; dysgeusia; rash, pruritus, urticaria. **Overdosage:** In the event of overdose, it is reasonable to employ the usual supportive measures. Etoricoxib is not dialyzable by hemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

MSD

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Abstracts presented at

The Inaugural Asian Association of Schools of Pharmacy (AASP) Conference

Beijing, China, 4-6 June, 2004

Contents

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Pharmacy Research

Go further than ever before

Your potential to fight chronic hepatitis B has never been greater. With new Hepsera™ (adefovir dipivoxil), the risk of resistance is minimal.[1] So you can be confident of achieving key goals — long term viral suppression and effective disease control.

Hepsera™ (adefovir dipivoxil) is an advanced antiviral that has proven to be effective in both HBeAg+ and HBeAg-patients and those that have failed on previous treatment.[2-7] Hepsera™ (adefovir dipivoxil) helps you win and keep winning.

Hepsera is a registered trademark of the GlaxoSmithKline group of companies.

References : (1) Westland CE, Yang H, Delaney WE, et al. Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. *Hepatology* 2003;38:96-103 (2) Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *NEJM* 2003; 348:808-816 (3) Hadziyannis S, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *NEJM* 2003; 348:800-807 (4) Hadziyannis S, Tassopoulos NC, Heathcote EJ, et al. Two year results from a double-blind, randomized, placebo-controlled study of adefovir dipivoxil for presumed precore mutant chronic hepatitis B (0-96 weeks). *J Hepatol* 2003;38(suppl 2):143 (5) Schiff E, Willems B, Leung N, et al. Safety and efficacy of adding adefovir dipivoxil to lamivudine therapy in compensated chronic hepatitis B patients with YMDD variant HBV and a reduced response to lamivudine- 52 week results. *Hepatology* 2002;36(N0.4 Pt 2 of 2):636A (6) Mutimer D, Hann H, Buti M, et al. Significant clinical improvement following the addition of adefovir dipivoxil to lamivudine in decompensated patients with YMDD variant HBV and a reduced response to lamivudine - 1 year results. *Hepatology* 2002;36(N0.4 Pt 2 of 2):625A (7) Peters M, Hann HW, Partin P, et al. Adefovir dipivoxil alone and in combination with lamivudine suppresses YMDD mutant hepatitis B virus replication: 48 week preliminary analysis. *Hepatology* 2002;36(N0.4 Pt 2 of 2):374A

Abbreviated Prescribing Information

Product Name: Hepsera **Active ingredient:** Adefovir dipivoxil **Indications:** treatment of chronic hepatitis B in adults with evidence of active hepatitis B viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. **Contra-indication:** patients with previously demonstrated hypersensitivity to any components of the product. **Warnings and Precautions:** Doses higher than those recommended must not be administered. Patients with advanced liver disease or cirrhosis should be monitored closely during initiation of therapy. Exacerbations of Hepatitis after Discontinuation of Treatment: Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with Hepsera. Patients who discontinue Hepsera should be monitored at repeated intervals over a period of time for hepatic function. If appropriate, resumption of therapy may be warranted. Nephrotoxicity: Chronic administration of Hepsera (10mg/day) may result in nephrotoxicity. The overall risk of nephrotoxicity in patient with adequate renal function is low. However, this is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents. It is important to monitor renal function for all patients during treatment with Hepsera, particularly for those with pre-existing or other risks for renal impairment. Patients with renal insufficiency at baseline or during treatment may require dose adjustment. The risks and benefits of Hepsera treatment should be carefully evaluated prior to discontinuing Hepsera in a patient with treatment-emergent nephrotoxicity. HIV Resistance: Treatment with anti-hepatitis B therapies that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Hepsera has not been shown to suppress HIV RNA in patients; however, there are limited data on the use of Hepsera to treat patients with chronic hepatitis B co-infected with HIV. **Interaction:** Since adefovir is eliminated by the kidney, co-administration of Hepsera with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or these co-administered drugs. Ibuprofen 800mg three times daily increased adefovir exposure by approximately 23%. The clinical significance of this increase in adefovir exposure is unknown. While adefovir does not inhibit common CYP450 enzymes, the potential for adefovir to induce CYP450 enzymes is not known. The effect of adefovir on cyclosporine and tacroimus concentrations is not known. **Pregnancy:** There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Hepsera should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits. Women of child-bearing potential must use effective contraception. **Lactation:** It is not known whether adefovir is excreted in human milk. Mothers should not breastfeed if they are taking adefovir dipivoxil. **Undesirable effects:** posttreatment elevations in ALT were observed at a higher incidence in patients who had received 10 mg adefovir dipivoxil than in patients who had received placebo. **Dosage & Administration:** *Adults (18-65 years):* 10 mg once daily taken orally with or without food. *Children and adolescents (< 18 years) or Elderly (> 65 years):* Safety and efficacy have not been established. **Renal impairment:** The dosing interval of Hepsera should be adjusted in patients with baseline creatinine clearance, < 50mL/min using the following suggested guidelines (Table 1). Clinical response to treatment and renal function should be closely monitored in these patients. The pharmacokinetics of adefovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10mL/min; therefore, no dosing recommendation is available for these patients.

Table 1: Dosing recommendations in patients with renal impairment

	Creatinine Clearance (mL/min)*			
	> 50	20 - 49	10 - 19	Haemodialysis Patient
Recommended Dose and Dosing Interval	10mg every 24 hours	10mg every 48 hours	10mg every 72 hours	10mg every 7 days following dialysis

* Creatinine clearance caculated by Cockcroft-ault method using lean or ideal body weight.

Overdose: Doses of adefovir dipivoxil 500mg daily for 2 weeks and 250mg for 12 weeks have been associated with gastrointestinal side effects. If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Please read the full prescribing information prior to administration. Full prescribing information is available on request from Glaxo SmithKline Ltd. 23/F Tower 6 The Gateway 9 Canton Road Tsimshatsui Kowloon Hong Kong Tel: (852) 3189 8989 Fax: (852) 25061378 Website: www.gsk.com.hk

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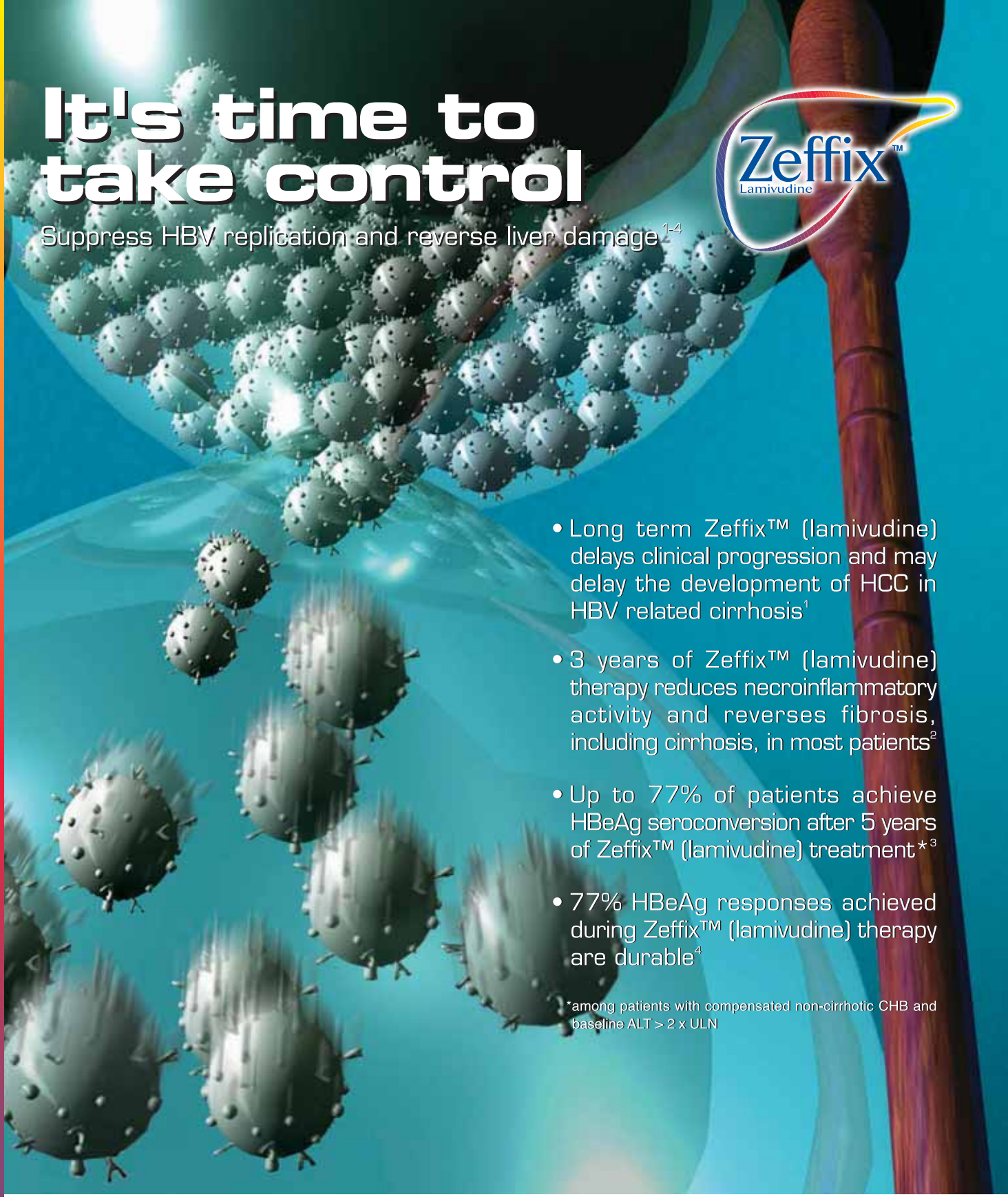

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*among patients with compensated non-cirrhotic CHB and baseline ALT > 2 x ULN

References: 1. YF Liaw, JJY Sung, WC Chow et al. Lamivudine delays clinical progression and reduces incidence of liver cancer in patients with HBV related cirrhosis – results of a prospective placebo-controlled clinical trial *J of Gastroenterology and Hepatology* (2003) 18 (suppl) Sep 2003; Abst No.179 2. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology*. 2003;124(1):105-17. 3. Guan R, Lai CL, Liaw YF Lim SG, Lee CM. Efficacy and safety of 5 years lamivudine treatment of Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2001; 16(Suppl): A60 (abst 187). 4. Dienstag JL, Cianciara J, Karayalcin S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. *Hepatology*. 2003;37(4):748-55.

Abbreviated Prescribing Information

Product Name: Zeffix Active Ingredient: Lamivudine

Indications: treatment of patients with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

Dosage & Administration: Adults and adolescents (≥ 12 years old): 100mg once daily. Children (2-11 years old): 3mg/kg once daily up to max. 100mg/day. Children (<2 years old): insufficient data to propose specific dosage recommendation in this age group. Renal impairment: lamivudine serum concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should therefore be reduced for patients with a creatinine clearance of <50ml/min (see Tables 1).

Table 1: Dosing Recommendation in Patients with Renal Impairment

Creatinine clearance (ml/min)	Adults and Adolescents (>12 years old)		Children (2 – 11 years old)	
	First dose of Zeffix	Maintenance Dose Once Daily	First dose of Zeffix	Maintenance Dose Once Daily
30 to <50	100 mg	50 mg	3 mg/kg	1,50 mg/kg
15 to <30	100 mg	25 mg	3 mg/kg	0,75 mg/kg
5 to <15	35 mg	15 mg	1 mg/kg	0,45 mg/kg
<5	35 mg	10 mg	1 mg/kg	0.30 mg/kg

Contra-indication: patients with known hypersensitivity to lamivudine or to any ingredient of the preparation

Warnings and Precautions: During treatment patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B. If Zeffix is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. If Zeffix is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) are increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of <50 ml/min. Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Hepatitis reactivation at discontinuation of lamivudine or loss of efficacy during treatment may induce severe and even fatal decompensation. It is recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate. For the treatment of patients who are coinfected with HIV and are currently receiving or are planning to receive an anti-retroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained.

Interaction: The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other drugs (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased lamivudine exposure by about 40%. Lamivudine had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. Zidovudine had no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Zeffix is therefore not recommended to be used in combination with zalcitabine.

Pregnancy: Use in pregnancy should be considered only if the benefit outweighs the risk. Zeffix administration is not recommended during the first three months of pregnancy.

Lactation: Following oral administration of lamivudine was excreted in human breast milk at similar concentrations to those found in serum (range 1 – 8 μg/ml).

Undesirable effects: In clinical studies of patients with chronic hepatitis B, Zeffix was well tolerated. The incidence of adverse events was similar between placebo and Zeffix treated patients. The incidence of laboratory abnormalities in chronic hepatitis B patients were similar in the Zeffix and placebo treated groups, with the exception of ALT elevations which were more common post-treatment in patients treated with Zeffix. In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported, although no relationship to treatment with lamivudine has been clearly established. Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however there is no evidence that these events were related to treatment with Zeffix

Overdose: If overdose occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialyzable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

Storage condition: Store below 30˚C.

Please read the full prescribing information prior to administration.

Abbreviated Prescribing Information Version 6 prepared in October 2003.

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N03ZX025/10-2003

Pharmacy Education Research and Practice in Asia

Chow, Moses S.S.

Asia pharmacy education, research and practice are diverse due to vast differences in Asian culture, education and government. Thus, there is a great need for Asian pharmacy educators, researchers and practitioner to get together to exchange and share their experiences, ideals and goals as well as to plan new future directions in enhancing the quality of education and training. With these purposes/objectives in mine, an initial Asian Pharmacy Educators Meeting (APEM) was held in Pattaya, Thailand April 26-28, 2001. This meeting was attended by over 100 pharmacy educators from Asia and was organized under the leadership of Dr. Sumon Sakolchai with support from Pharmacy Education Consortium of Thailand and many Thailand pharmacy schools. At the end of the APEM meeting, the Asian Association of School of Pharmacy (AASP) was formed and the initial 10 Members of Board of Directors and Officers of the Association elected. Subsequently, the Board approved the constitution and officially registered AASP in Singapore with the Secretarial Office established in Thailand (website www.AASP.network.org).

To move forward the objectives described above, AASP took the initiative and sponsor the Inaugural Pharmacy Conference in Beijing, June 4-6, 2004. This historic event provides a unique opportunity for all Asian pharmacy educators, researcher and practitioners to get together and to exchange ideas in advancing pharmacy education, research and practice.

This Inaugural Conference is co-sponsored by the School of Pharmaceutical Science Peking University and hosted by the Chinese Pharmaceutical Association (CPA). Together with AASP, an exciting program relating to newest thoughts and experiences in pharmacy education, research and practice has been developed. We are fortunate in that a number of prominent speakers from Asian institutions are willing to participate in the keynote speech, plenary sessions, symposiums and poster sessions. A special Pharmacy School Exhibition Poster Session is scheduled to allow exchange of pharmacy school education from different countries.

The keynote speech of the Inaugural Conference will be delivered by Professor Lloyd Sansom, University of South Australia. His topic on "Science Accessibility and Quality Use of Medicines - the need for integration" (Page A7) is timely and most relevant to "kick off" the academic sessions of this conference.

As the premier organization for all Asian pharmacy schools with an interest in pharmacy education, AASP devoted 2 plenary sessions on education and curriculum issues. Prof. Suresh of JSS College of Pharmacy, India (president elect) will speak and lead a discussion on "Core Curriculum Issues - New Emerging Pharmacy Curriculum Issues in Asia" (Page A7). Prof. Clarke Hazlett, Chinese University of Hong Kong, Hong Kong SAR will speak on "Innovative Teaching Techniques" (Page A7).

In addition to the plenary sessions, 4 symposiums have been organized, 2 on pharmaceutical science and 2 on pharmacy practice. The pharmaceutical symposiums include topics relating to pharmacogenomics/proteinomics and computational/combinational chemistry. The pharmacy practice symposiums encompass presentations of different pharmacy practice models and health information activities from different countries. In addition to these key presentations, more than 80 abstracts on education, research and practice have been accepted for poster presentation.

I am thankful to the co-chair of the Conference, Professor Zhang Lihe, Conference Secretariat, Mr. Liu Chunguang, Sunny, Professor Zhang Qiang of School of Pharmaceutical Science Peking University and members of the Board of AASP for their assistance and support in the program development, preparation and implementation of this Conference.

I hope this Inaugural Conference will provide an importance medium for all Asian pharmacy educators, researcher and practitioners to get together. I am sure this Beijing Conference will set a leading example for the future conferences to come. This is the first step for AASP, but a grant step for Asia pharmacy profession. I hope that all participants of this Inaugural Conference will be proud to participate in this first step in advancing Asian Pharmacy Education, Research and Practice.

Sincerely,

Moses S.S. Chow
President, Asian Association of Schools of Pharmacy

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Professor and Director
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L-1

SCIENCE, ACCESSIBILITY AND THE QUALITY USE OF MEDICINES - THE NEED FOR INTEGRATION

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The future of pharmaceuticals in the delivery of health care faces considerable challenges. While the drug discovery process races towards harnessing the new knowledge from a greater understanding of the molecular basis of disease, the cost of these discoveries is such that their place in therapeutics may never be realized for the majority of the world's population. Further, many of the new drugs will provide statistically significant benefits but the increment in average benefit will be small and the unit cost of the increment unsustainable unless pharmacogenomics can identify those patients who will receive the largest benefit. A patent life of 20+ years in the new area of molecular biology will also be difficult to sustain, due to the rapid expansion of knowledge in the discipline. This will result in the initial price of the new medicine being further increased in order to recoup R&D costs earlier in the drug's life. The evaluation of new agents will require the use of cost effectiveness analysis to ensure they represent value for money in an environment of limited resources for health and to maintain equity of access. The quantification of the benefit of a drug in clinical trials does not guarantee that such benefit will be achieved in clinical use and the role of the pharmacist in optimizing health outcomes from the quality use of medicines will be essential. The use of preventative health measures particularly related to life style and environment- related diseases (e.g. obesity, diabetes, C-V and respiratory disease) will require a greater emphasis in public health programs and thus in academic programs.

Pharmacy education must reflect these challenges for the health sector and the curriculum must be integrated in a continuum from drug discovery to health outcomes. Scientific principles must form the basis but the sub-disciplines of genomics, pharmacokinetics, pharmacoeconomics, molecular basis of therapeutics, and pharmacy practice must be integrated within a holistic curriculum. Separate streams of pharmaceutical science and pharmacy practice, so common in many pharmacy curricula world-wide, will be to the detriment of the role that pharmacists will need to play in the delivery of health care in the years ahead.

L-2

CORE CURRICULUM ISSUES - NEW EMERGING PHARMACY CURRICULUM ISSUES IN ASIA

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The schools of Pharmacy are being asked to make a shift in their educational paradigms from the Science based education outcomes to a more clinical or patient care centered skills and activities to provide ideal pharmacy practitioners care. Pharmacy education in the Asian Region has only recently endeavoured itself in this task when compared to their counterparts in Europe and U.S. Currently the problem is that in Pharmacy Practice based education in the Asian Region, no model or outcomes based framework for making this change has been demonstrated. All schools of pharmacy are currently grappling with the best and most cost effective means of bringing about this change but are looking forward to and also requesting other schools to share their experience to bring about this effective transition. Today no one has defined an assessment plan that can readily transfer successful models from one institution to the next.

AASP which addresses itself to this issue and suggest curriculum and programmes with well defined student outcomes, teaching methods and assessment strategies that lead to development of a competent pharmacy practitioner.

The presentation will highlight the key decisions that need to be taken in the political and social environment to shape practice based pharmacy education as means of providing effective pharmacy practitioners to the healthcare system.

L-3

INNOVATIVE TEACHING TECHNIQUES: SHIFTING FROM TEACHING PROGRAMMES TO LEARNING PROGRAMMES

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The transition from the Industrial Age to the Information Age has required educators in tertiary institutions to change how they fulfill their responsibilities as teachers.

The new learning environment is one in which information grows at such a rate that the existing knowledge base of a discipline will not remain current for long periods, and that accessibility to information has become much easier than the students' ability to evaluate which information is actually valid (i.e., knowledge). Accordingly, the new teaching paradigm is one in which both knowledge (i.e., pharmacy content) and the means by which the knowledge base is acquired (i.e., the process by which the pharmacy student learns that content) are now equally important learning objectives, and thus, both have become the responsibility of the pharmacy teacher to successfully address.

Pharmacy programmes normally recruit teaching faculty in reference to their research expertise. Although this strategy remains appropriate for any university-based programme, pedagogical skill is not necessarily a colliery of research expertise. Unfortunately, the research shows that pedagogical expertise cannot be achieved by simply practice nor do students regard it acceptable for their teachers to mimic teaching techniques that only address knowledge acquisition while ignoring their needs to acquire life long learning skills. The evidence established by over two decades of educational research with adult learners reveals how the above dilemma can be addressed successfully. This presentation will discuss some of this evidence and demonstrate one teaching technique by which students can students learn more and more quickly while also acquiring life long leaning skills.

S-1

GALACTOSYLATED LIPOPOLYPLEXES (LPD) FOR TARGETED GENE DELIVERY TO HEPACOCYTES

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A major goal of gene therapy is to obtain targeted vectors that transfer genes efficiently to specific cell types. The liver possesses a variety of characteristics that make this organ very attractive for gene therapy. Three novel galactosylated cholesterol derivatives were synthesized to prepare gene delivery carrier lipopolyplexes (LPD) with galactose residues as targetable ligands for liver parenchymal cells.

Anionic lipopolyplexes (lipid-polycation-DNA, LPD) were prepared by first mixing the plasmid DNA and protamine together. The resulted polyplexes were incubated for 10min at room temperature, following the addition of preformed anionic liposomes composed of DOPE, cholesteryl hemisuccinate (Chems) and galactosylated cholesterol derivatives. The morphology of LPD was observed by transmission electron microscopy. The diameter and surface charge of LPD were measured by photon correlation spectroscopy (PCS). Central composite design (CCD) was employed to optimize stable LPD formulation with small particle size. LPD size and LPD protection efficiency against nuclease were chosen as responses of CCD. The fields of protamine/DNA and Chems/DNA were set according to the size and zeta potential measurements of polycation-DNA complexes and LPD respectively. Transfection efficiency of optimized LPDs was evaluated by β-galactosidase assay.

An optimized LPD formulation was prepared, resulting in a particle size of 185.3 nm and protection efficiency of 80.22%. A high transfection activity to human hepatoma HepG2 cells was obtained by LPD in the presence of 50% serum. Meanwhile, the presence of 20 mM galactose significantly inhibited transfection efficiency.

Anionic lipid coating of polyplexes fulfilled the following functions. First, the coating shielded the positive surface charge of polyplexes that might cause aggregation of polyplexes upon exposure to the biological environment. Second, the shield of positive surface charges prevented the non-specific binding to cells and the lipidic coatings provided a site for galactose ligand attachment to obtain specific cellular uptake. Furthermore, the pH sensitive liposomes consisting of Chems and DOPE could provide endosomal disruption activity. Protamine sulfate, as a condensing agent could reduce the particle size of the complexes and the presence of nuclear localization signal in protamine's amino acid sequence could potentate gene expression by increasing the nuclear translocation of DNA.

Key Words: targeted gene delivery; galactosylated lipopolyplexes (LPD); central composite design (CCD); transfection efficiency

S-2

PHARMACOGENOMICS OF STATIN-INDUCED RHABDOMYOLYSIS

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A case-control association study was undertaken to identify genetic factors affecting susceptibility to statin-induced rhabdomyolysis in patients with hypercholesterolemia. One-hundred fifty-two single nucleotide polymorphisms (SNPs) or mutations of eight candidate genes were analyzed in 10 patients who showed abnormal increase in plasma creatine kinase (CK) or severe muscle symptoms and 25 control patients who did not show any increase in plasma CK or muscle symptoms during the course of statin treatment. Among 152 SNPs or mutations studied, only one SNP, T521C of organic anion transporting polypeptide-C gene *(OATP-C, OATP1B1, SLCO1B1)*, showed a significantly ($p<0.003$) higher frequency in patients with rhabdomyolysis than control patients when patients were selected for those taking pravastatin or atorvastatin. Since T521C could be detected in either of *OATP-C*15* and *OATP-C*15*, haplotype analysis was carried out. The result indicated that all the alleles having T521C in our patients were *OATP-C*15* and the frequency of this allele was still significantly higher in patients with rhabdomyolysis than control patients. To determine the effects of this haplotype on the function of OATP-C, we expressed *OATP-C*15* in HEK293 cells and studied the transporting activity of OATP-C for statins. The results indicated that intrinsic clearances of HEK293 cells expressing *OATP-C*15* for pravastatin and atorvastatin were more than 70% lower than those of wild type, suggesting that uptake of pravastatin and atorvastatin into hepatocytes decrease in patients with *OATP-C*15*. Overall, the results of present study suggest that *OATP-C*15* is one of the risk factors to acquire rhabdomyolysis in patients taking pravastatin or atorvastation.

S-3

PHARMACY EDUCATION AND PRACTICE IN THE PHILIPPINES COPING WITH GLOBAL TRENDS AND DEMANDS

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Pharmacy practice worldwide has been more patient-focused rather than drug-focused brought about by tremendous changes in Health Care Delivery System. In the Philippines, the needed change takes time due to some barriers. Despite such difficulty encountered, the PACOP has embarked on providing series of continuing education for faculty members geared toward more patient focused pharmacy education and practice, has identified the Core Competencies for Pharmacists in Different Area of Practice and have just recently prepared a new ethical- and patient-focused equipped with entrepreneurial skills.

S-4

PHARMACY EDUCATION AND PRACTICE IN INDIA: PAST AND THE PRESENT

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Pharmacy education and practice in India has long been oriented towards the pharmaceutical industry. Majority of graduate pharmacists here have still been employed in this sector, primarily in the areas of production, formulation, quality control and marketing. This has reflected in the phenomenal growth of pharmaceutical industry, whereas, apart from achieving self sufficiency in production and supply of most of the drugs, India stands as a net exporter of pharmaceutical formulations and APIs.

This growth has come at the cost of pharmacy practice in the country. Awareness in this area evolved more than a decade back in the country which resulted in the amendment to the ER in 1991 to include subjects in pharmacy practice. Following this, the need for involvement of pharmacists in direct patient care activities was recognised and discussions were mooted to identify the ways and means of achieving this. Even though slow to react, the pharmacy profession has tuned itself to the changing needs of the society. This was achieved with the help of support from experts in the field of pharmacy practice. JSS Mahavidyapeetha, a trust dedicated to the development of education in our country, started the first Masters in Pharmacy Practice programme and also established model centres for the practice of clinical pharmacy both in the government and private setup.

This has been followed with various educationists in the private sector providing higher education in pharmacy practice. Presently about 20 institutions are providing higher education in pharmacy practice in India. Apart from these, handful of corporate hospitals have also. However, most of these developments in education have occurred in South India. In the north, apart from the National Institute of Pharmaceutical Education and Research, Punjab, no other has so far started programmes in pharmacy practice. However, necessary ground work has been made here and in the near future, some of the premier institutions in North India will come up with such programmes.

Apart from evolving a new breed of pharmacists in pharmacy practice, steps have also been taken by various professional bodies such as Pharmacy Council of India, Indian Pharmaceutical Association etc. to reorient the vast majority of diploma holders in pharmacy who are largely placed in the hospital and community pharmacy sector and to develop competencies in the provision of pharmaceutical care. The recent developments evince clearly that the pharmacy professionals of our country have recognised the need for more focused patient care by the pharmacists and the profession is in transition state in evolving this concept. The future is bright for pharmacy practice in our country as the need is well recognised and the stakeholders are keen to achieve quality pharmaceutical care in the country.

S-5

PHARMACY PRACTICE IN AUSTRALASIA

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This joint presentation will examine the training of Pharmacists in Australia and NZ and Pharmacy Practice in these two countries. In Australia most Schools of Pharmacy offer a four year U/G (B Pharm) degree which enables graduates to register as Pharmacists after a pre-registration period. A similar academic training is also available in NZ. In Australia several new Schools of Pharmacy offer a 2 year M Pharm degree for candidates who already possess a tertiary qualification but not in Pharmacy. This degree also allows candidates to register as Pharmacists after registration training. In both Australia and NZ 80-90% of Pharmacy graduates undertake their registration training in Community Pharmacy and most practice Pharmacy in this area owning their own Pharmacy or working with other Pharmacists in a small business environment. These community Pharmacists dispense medicines generally on the prescriptions of medical practitioners. They also recommend Pharmacy-only medicines to the public and also recommend/sell over the counter (OTC) products. Some medicines are available from supermarkets/general stores but these have been judged to have large safety margins. In both countries Community Pharmacists also undertake medication reviews for patients. Only ~ 10% of graduates undertake registration training in Hospital Pharmacies, predominantly in the public hospital sector and gain employment in the government sector. An even smaller fraction of Pharmacy graduates work in Pharmaceutical Industry in either Australia or NZ as Industry generally requires/employs Pharmacy graduates with post-graduate degrees or training.

S-6

STRUCTURE-ACTIVITY RELATIONSHIP OF NEWLY SYNTHESIZED BOSWELLIC ACID DERIVATIVES AS APOPTOSIS INDUCERS OF LEUKEMIA CELLS

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Boswellic acids, isolated from the gummy exudates of *Boswellia serrata* Roxb and *Boswellia carterri* Birdw, belong to the pentacyclic triterpene class of compounds. It has been found that acetyl-11-keto-β-boswellic acid (AKBA, 3-acetyl-11-oxo-ursa-12-en-24-oic acid) is an inhibitor of topoisomerase I and 5-lipoxygenase and induces apoptosis in human leukemia, colon, hepatoma, and other malignant cell lines. Recently, it was found that α- and β-boswellic acid acetates without an 11-keto group also induce apoptosis in several leukemia cell lines. These data suggest that a group exists both in AKBA and in boswellic acid acetates is required for its apoptosis induction ability. To identify the moiety(s) of AKBA responsible for this apoptosis induction, a series of derivatives of AKBA, with various substitutions at positions 3 and 24, were designed and synthesized. The chemical structures of these derivatives were verified by the application of IR, NMR, and MS and then their apoptosis-inducing effects were determined in NB4 human leukemia cells. Structure-activity relationship of the data analysis indicated that the hydroxyl group at position 3 (but not the carboxyl group at position 24) is important for apoptosis induction. Converting the 3-hydroxy group of AKBA to either a 3-oxo or a 3-hydroxyimino group decreased the apoptosis-inducing ability of AKBA. Esterification of the 24-carboxyl group with a methyl or isopropyl group did not influence the apoptosis-inducing ability of AKBA.

S-7

HOMOLOGY MODELING OF LANOSTEROL 14α-DEMETHYLASE OF *CANDIDA ALBICANS* AND *ASPERGILLUS FUMIGATUS* AND STRUCTURE-BASED OPTIMIZATION OF AZOLE ANTIFUNGAL AGENTS

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The crystal structure of 14α-sterol demethylase from *Mycobacterium tuberculosis* (MT_14DM) provides a good template for modeling the three dimensional structure of lanosterol 14α-demethylase, which is the target of azole antifungal agents. Homologous 3D models of lanosterol 14α-demethylase from *Candida albicans* (CA_14DM) and *Aspergillus fumigatus* (AF_14DM) were built on the basis of the crystal coordinates of MT_14DM in complex with 4-phenylimidazole and fluconazole. The reliability of the two models was assessed by Ramachandran plots, Profile-3D analysis, and by analyzing the consistency of the two models with the experimental data on the $P450_{14DM}$. The overall structures of the resulting CA_14DM model and AF_14DM model are similar to those of the template structures. The two models remain the core structure characteristic for cytochrome P450s and most of the insertions and deletions expose the molecular surface. The structurally and functionally important residues such as the heme binding residues, the residues lining the substrate access channel, and residues in active site were identified from the model. To explore the binding mode of the substrate with the two models, 24(28)-methylene-24,25-dihydrolanosterol was docked into the active site of the two models and hydrophobic interaction and hydrogen-bonding were found to play an important role in substrate recognition and orientation. These results provided a basis for experiments to probe structure-function relationships in the $P450_{14DM}$. Although CA_14DM and AF_14DM shared similar core structural character, the active site of the two models were quite different, thus allowing the rational design of specific inhibitors to the target enzyme and the discovery of novel antifungal agents with broad spectrum. Based on the key functional regions in the active site of $P450_{14DM}$, a series of novel triazole antifungal agents were designed and synthesized. Results of preliminary biological tests showed that most of title compounds exhibited strong activity against the eight common pathogenic fungi. Several compounds showed higher antifungal activity and broader anrifungal spectrum than fluconazole and itraconazole, which was chosen for further development.

S-8

SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4,6-DIAMINO-2-ALKYL-1,2-DIHYDRO-1,3,5-TRIAZINES

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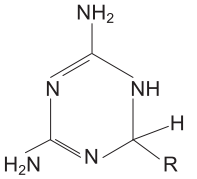
Cycloguanil, an antimalarial agent, contains the 4,6-diamino-2-alkyl-1,2-dihydro-1,3,5-triazine heterocycle in its chemical structure. There are several reports that also demonstrate that this heterocyclic structure is found in compounds that exhibit anticancer and antimicrobial activity. The search is still on-going to look for new therapeutic compounds that carry this heterocyclic structure. In our laboratory, much time has been focused on the study of this heterocycle and the following aspects of the triazine heterocycle will be presented.

a) Combinatorial synthesis of the triazine heterocycle and the screening for antifolate and cytotoxic activities.
b) Screening of differently substituted triazine heterocycle for antimicrobial activity.
c) Dimroth rearrangement of the triazine heterocyclic ring and new biological activity of the rearranged products.



4,6-diamino-2-alkyl-1,3,5-triazine

S-9

THE MALAYSIAN INITIATIVES IN HEALTH PROMOTION AND PHARMACY SERVICES THROUGH THE TELEHEALTH CONCEPTS

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Efficient telehealth services demand an effective integrated health services, with clear health vision, mission and is goal focused and addresses that connectivity must be predominantly by electronic means.

The existing primary, secondary and tertiary health care services in Malaysia are integrated and data are allowed to flow through mainly paper based health records. But, since the early 90's much efforts have been put in to use ICT as a mean for the connectivity e.g. LHP, PLHP, MCPHIE and CME services. One of the aims is to promote and create health through health promotion activities which is the balanced enhancement of physical, mental and social facets of positive health for the Malaysians, coupled with prevention of physical, mental and social ill-health.

Pharmacy through its services is in great demand to support the government initiatives. For examples, the Malaysian National Poison Centre which is operate basically by pharmacists, has developed various drugs and health programs e.g. websites, e-klinik, my.PCIS, smokeline, healthy campus portal and activities, VINDIS etc. (these will be included in the presentation) via electronic means and online system to promote and create health. Besides these efforts, teaching and research activities related to ICT e.g. Pharmacoinformatics are also emphasized.

S-10

DEVELOPMENT OF PHARMACY SERVICES BY PROVIDING A PATIENT WITH AN INDIVIDUALIZED MEDICATION NOTEBOOK

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The thing of "the medication notebook" is being provided to the patient each in our pharmacy. A record such as the name of the prescribed medicine and the quantity to take and the number of times is left in this notebook, and these are called drug history (medication history).

A doctor, dentist and a pharmacist can judge what kind of medicine is being used in how many periods from this notebook.

This notebook makes it possible for pharmacists to avoid duplicate medication by two or more medical facilities and give advise drug interaction.

Patients should feel safer when they carry it because pharmacists can easily check the drugs they taken and are taking. We have a patient know about the medicine which one takes by managing data on the medicine properly well, and we try to do synthetic advice about the self-control of the health.

S-11

PHARMACISTS' INVOLVEMENT IN IMPROVING ANTIDEPRESSANT MEDICATION COMPLIANCE FOR PATIENTS WITH CHRONIC DISEASES

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Objective: Evaluate and improve compliance of current antidepressant drug therapies for patients of chronic diseases.

Methods: A retrospective study used a self-conducted questionnaire to investigate the number of prescribed antidepressants at a large teaching institute from 2000-2002. Attempt to improve compliance included a series of depression and antidepressant educational series of lectures, as well as telephone counseling to address patients' questions.

Antidepressant inpatient prescriptions increased from 1.62% in 2001 to 2.98% in 2002. Medications were inappropriately used since the average course of treatment was less than two weeks. Outpatient surveys revealed a lack of patient knowledge in antidepressants and only 29% used medications as instructed by the physician. After four weeks of pharmacists' counseling, the patients' knowledge and compliance greatly improved. However, compliance may be further increased with public assistance to educate patients on effective use of medicine.

E-1

IMPLEMENTATION AND EVALUATION OF AN INTEGRATED FORMULATION WORKSHOP

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A workshop designed to promote the integration and application of information from the different disciplines in pharmacy was developed and introduced in the Formulation unit of study, at the end of the third year of the B Pharm program. Students worked in small groups using the problem-based learning approach. The objective of the activity was to illustrate how principles in drug formulation were interrelated with other aspects of the pharmacy curriculum and to give students the opportunity to apply the information obtained through didactic lectures. The problem-based learning approach also presented the opportunity for the development of generic skills such as working in a team, organizational skills and communication skills. A facilitator was present to guide students and ensure that all the relevant aspects of the scenario were discussed. Oral presentations were made by each group at the end of the 4-hour session. To evaluate whether the objectives of the activity were met as well as student responses to the workshop, a questionnaire was used. Both the presentations and the questionnaires suggested that the objectives were adequately met by this technique. Students enjoyed the group work and believed that they had benefited from it. Negative comments included issues such as the small tutorial room size and the time of day when the workshop was scheduled. Students indicated that the activity was very useful and requested more of these workshops. Although additional resources are required, this technique is effective in achieving the above objectives.

E-2

VISUAL IMAGE AIDED INSTRUCTION FOR BETTER SUBJECT COMPEHENSION

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The objective of this study was to develop interesting & effective visual images accompanied by audio-text, to help better student understanding of a subject. The results of this method were compared with conventional classroom learning. "Headache" was selected as the topic for the study. Students in the Second year B.Pharmacy curricula at the Allana college of pharmacy were randomized into three groups. One group of student viewed the visual images with audio- text & 2nd group listened to the section of text only. A third group watched unrelated visual images & served as control. Average pretest & post- test scores were calculated. The statistical analysis of data showed that pretest scores among the three groups did not vary significantly ($P>0.5$).

The students who viewed the image slides pertaining to headache showed a significant improvement in post-test scores ($P<0.001$).

The results suggest that "Visual image aided instruction", more effectively helped in enhancing student understanding of the subject compared to conventional lecture alone.

E-3

ESTABLISHMENT OF REFINED PHARMACEUTICAL COURSE OF ANALYTICAL CHEMISTRY

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The development of pharmaceutical science urged the birth of refined modern pharmaceutical course of analytical chemistry. The newly-compiled textbook merged the two traditional courses (analytical chemistry and pharmaceutical analysis) into one by cutting down the outdated knowledge which was not widely applied in practical work, by replacing the excessive examples of drug analysis with establishing principles of analytical methods, by rearranging most of the chapters from previous courses, and by enriching the course with new analytical methods and new territories of pharmaceutical analysis. The leading teacher was responsible for the primary course lectures, interspersed with profound lectures given by various visiting professors. Increasing percentage of designing experiments, based on right amount of traditional verifying experiments, helped improve the students' literature- consulting ability, team spirit and basic researching skills. Laboratories also provided sufficient time and ideal places facilitating effective bi-linguistic communication. Analytical informatics programming competition, among other extracurricular activities, was carried out successfully to consolidate the subject knowledge, to enhance the students' academic level, and even to pre-cultivate graduates. The refined course was adapted to specialty of pharmacy and students did profit a lot from its reasonable guidelines and multi-dimensional training patterns.

E-4

GRADUATION PROJECT FOR THE MASTER OF CLINICAL PHARMACY PROGRAM AT THE CHINESE UNIVERSITY OF HONG KONG

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As part of the Master of Clinical Pharmacy (MCP) Program offered by the Chinese University of Hong Kong (CUHK), students are required to complete a 10-unit course entitled "Graduation Project". The course spans the entire 2 years of the MCP program and requires the students to design and implement a practice-based project at their site of practice. The project should demonstrate pharmacist's impact on patient care, pharmaceutical research or administrative management. Students are expected to be solely responsible for idea initiation, planning, implementation, outcome measurement, result analysis and report writing of the project. Lectures and workshops that review the concepts of pharmaceutical care, pharmacoeconomics, epidemiology and pros and cons of various study designs were provided in the first semester of the curriculum. Under the supervision by the pharmacy faculty at CUHK, the projects could be finished as a group project or individual project according to the students' interests and practice settings.

For the program term 2003-2005, the 27 MCP students have based their project mostly in the scope of drug utilization evaluation, pharmacist intervention in disease prevention or control, and therapeutic drug monitoring. Patient subjects involved in the project are inpatients or outpatients of hospitals, nursing home residents or the community population. Over the span of the course, students will be assessed on their project proposals, review of peer proposals, written oral reports of study findings.

E-5

UNIQUENESS OF A MASTER OF CLINICAL PHARMACY PROGRAM

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Pharmacists play an important role in meeting the health care needs of the society. The traditional roles of pharmacist include medication compounding, dispensing and counseling. Ever since the introduction of pharmaceutical care practice concept, pharmacists in many western countries have developed new roles in various patient-focused activities such as aminoglycoside monitoring, anticoagulation and asthma management. Through implementation of these activities, the outcomes of therapy can be optimized and the risks can be minimized. The professional satisfaction of pharmacists can also be increased.

Provision of pharmaceutical care services requires knowledge and skills beyond the training provided by the bachelor of pharmacy degree. In Hong Kong, patient-focused care activities are slowly emerging. To meet the change in practice, the Master of Clinical Pharmacy program is developed. Master of Clinical Pharmacy is a 2-year part-time degree program. The program's objective is to equip practicing pharmacists with advanced clinical knowledge and skills in providing pharmaceutical care services. The poster will introduce the various aspects of the program in meeting its objective.

E-6

PHARMACOLOGY TEACHING MODEL FOR SEVEN-YEAR PROGRAM MEDICAL STUDENTS

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Facing the fast development of science technology, knowledge and information, we have established a Pharmacology teaching model for seven- year program medical students in our university. For many years we have performed the following teaching tasks.

1. Compile pharmacology textbook in English According teaching content, consulting newly published English and Chinese Pharmacology textbooks and reference books, we have written new English Pharmacology textbook. The book is designed to provide a complete, current and readable Pharmacology book both for seven-year program and foreign medical students. The book was printed in 1997(1st ed.), in 1999(2nd ed.) and in 2002(3rd ed.) It is also used by Medical School, Nankei University and Henan Medical University. After using this book for several years it shows that it is a practical, high quality basic science teaching material.

   In 2000 Pharmacology experiment guideline in English (3rd ed.) was accomplished. In 2003 a review test book in English was written. It includes multiple choices, filling the blanks, answering the questions.

2. From 1985 till now Pharmacology lectures have been given in English persistently by some professors. Pharmacology exam paper is in English and asks the students to answer the questions in English. Experimental reports are written in English by the students.

3. For raising teaching quality, we use elicitation-teaching method; prepare lessons collectively; connect pharmacology knowledge with clinic; train students' creativity. For elevating students' English level, we direct students to write abstracts and reviews.

4. We have invited foreign professors to give lectures and seminars. Thus, promote faculty members and students to understand new trend in Pharmacology.

5. For elevating the ability of young faculty members and graduate students, train them to read original English Pharmacology textbook once a week for 1.5 hours, and it is persisted for 20 years. This kind of training raises the listening comprehension, reading, speaking and writing ability of them. The purpose of that is to train them giving Pharmacology lectures in English. Encourage them to present papers in English when they attend academic meetings.

   In 1999 Pharmacology text book in English achieved 1st grade award given by Tianjin Medical University. In 2000 Pharmacology teaching model for seven-year program medical students got 2nd grade award given by Tianjin Municipal Educational Committee.

E-7

AN ASSESSMENT OF DRUG INFORMATION DATABASE PROGRAMS AS TOOL FOR DEVELOPING SENIOR PHARMACY STUDENTS' COMPETENCY IN DRUG INFORMATION PROVISION

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A case study-based, computer-based educational intervention for senior pharmacy students was designed to incorporate the use of two drug information databases, Efacts© and ProAccess© as source of information for therapeutic cases. These two databases were chosen from among six databases using a set of evaluation criteria. To design the educational intervention, twelve (12) clinical cases were formulated and evaluation tools were prepared. Evaluation was focused on determining the effectiveness of the two databases as instructional tool to enhance retrieval skills and application of retrieved information to clinical cases by pharmacy students.

Performance of the students in both parts of the post-tests remarkably improved using ProAccess© than Efacts©. Furthermore, the overall mean search time is shorter for ProAccess© than in Efacts©. While there was no significant difference between Efacts© and ProAccess© in terms of comprehensiveness and relevance, students considered ProAccess© to have satisfied the criteria for effectiveness in terms of user-friendliness.

Overall, the use of case study-based, computer-based educational intervention with drug information databases for pharmacy students taking Pharmacy Practice (Pharmacy 54) was beneficial as they were exposed to new method of learning which has potential for enhancing their competency in drug information provision. ProAccess© and Efacts©, as instructional tools, are effective in terms of their comprehensiveness and relevance to therapeutic cases encountered by students in Pharmacy Practice classes. However, ProAccess© was deemed more user-friendly by the students.

E-8

CULTIVATION OF CREATIVE BIOMEDICINE TALENTS

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To meet the challenge of biotechnology and bioeconomics, our country need more talents who know science, technology and marketing operation, and can do R&D and administration works in the field of biomedicine. The School of Life Science and the School of Pharmacy, Fudan University, with different discipline and speciality, united for establish the "State Cultivate Base for Life Science and Technology Talents". The train objective of seven-year graduate education is to cultivate innovative and complex type, high qualities talents, who engage in R&D and management of new technology and new products in biomedicine. The curriculum frameworks are different from traditional bioscience and pharmacy. The specialties are de-emphasized; instead, the foundation and ability cultivation are emphasized. The different courses are mutual associated and coordinated. The credit system is implemented to put more room for students to study knowledge on their own initiative, and to practice in labs and even in corporations.

E-9

EDUCATION AND RESEARCH OF PHARMACEUTICAL ENGINEERING IN TIANJIN UNIVERSITY

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The Pharmaceutical Engineering in Tianjin University (TJU) is a new interdiscipline based on our traditional dominating subjects such as chemical and biochemical engineering and technology, merged with biotechnology and pharmaceutical sciences. Since its inception in 1999, 30 B.S., 67 M.S. degrees have been awarded. There are a total of about 210 undergraduates and 201 graduate students (193 M.S. students and 8 Ph. D. students) enrolled in the program.

The department has grown in strength to 25 faculty actively involved in teaching and research. Among our faculty, there are two academicians of Chinese Academy of Engineering, one academic member of Ministry of Education, 10 professors and 8 associate professors. Altogether 7 supervisors are authorized to direct doctorate students and 18 supervisors for M.S. students.

It has formed its own special orientation of research: (1) plant cell culture and biopharmaceutical engineering; (2) research of Chinese traditional medicine; (3) pharmaceutical crystallization engineering; (4) pharmacokinetics; (5) experimental bioinformatics; (6) pharmaceutical separation.

The department provides extensive laboratories and centers to support scientific research. They are the State Research Center of Industrialization for Crystallization Technology (SRCICT), Tianjin Industrial Center for Biopharmaceuticals and Chinese Traditional Medicine Modernization, Tianjin Key Laboratory of Molecular and Pharmaceutical Engineering, Platform of Pharmaceutical Engineering, Laboratory of Biopharmaceutical Pilot scale-up, Laboratory of Cell Culture and Molecular Biology.

The department has many advanced instruments for pharmaceutical engineering and related research, including two-dimensional gel electrophoresis system, NMR, CD spectrum, LC-ESI-MS/MS, fluorescence microscope, super minicomputers for drug design and molecular modeling, etc.

Many state research projects are accomplished or undergoing, including national "863" project, projects of National Science Foundation of China (NSFC) and international academic cooperative projects with scientist of USA, Germany, and Finland in recent years. Altogether about 300 papers have been published in last four years. Among them about 100 papers are recorded by SCI and about 30 papers are educational papers. Two awards of National Scientific Progress and one of National Creativity were granted by the central government.

The main achievements are as followings: (A) The new technique for pharmaceutical crystallization and purification was developed and used commercially; (B) Modes and batch process of pharmacokinetic data were optimized and applied in drug evaluation; (C) Mechanism of signal transduction of plant cells on regulation of secondary metabolite was analyzed; (D) One novel drug from microbes was discovered and show high potential of inhibiting HIV PR; (E) A natural anti-tumor drug was efficiently delivered.

E-10

EMERGING UNDERGRADUATE EDUCATION OF PHARMACEUTICAL ENGINEERING IN CHINA

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Pharmaceutical engineering is a new inter-disciplinary subject to meet with the needs from modern medicine industry. The undergraduate program of pharmaceutical engineering in China was initially set up in 1998 and master of engineering degree program in this field was offered simultaneously, and Ph. D. program in 2003. Up to now, undergraduate program for pharmaceutical engineering was provided in more than 100 universities or colleges. They are 53 technology universities, 18 comprehensive universities, 17 medical universities, and 16 other universities. In this program, more than 15, 000 students are enrolled in China.

The undergraduate program in Pharmaceutical Engineering strives to instill the fundamental knowledge, creativity, and confidence students need to meet the many professional challenges after graduation. Program objectives are intended to help students attain subject knowledge, acquire an appreciation for life-long learning, and develop skills in analysis and design, teamwork, and oral and written communication necessary for a successful career.

It provides curriculum involved in the following 8 main modules with some special curriculums such as pharmaceutical separation engineering, pharmaceutical technology, design for pharmaceutical equipment and engineering and QC of pharmaceutical production. (A) Mathematics and physics module: Advanced mathematics, applied mathematics, and physics. (B) Chemistry module: inorganic chemistry, organic chemistry, analytical chemistry, and physical chemistry. (C) Pharmaceutics module: drug design and synthesis, pharmacology, pharmaceutical chemistry, pharmaceutical analysis, and phamarcokinetics. (D) Biology and biotechnology module: biochemistry, microbiology, molecular and cellular biology, life science and biotechnology. (E) Engineering module: mechanical graphing, electricity and electronics, computer and network technology, process control, technological economics, management for industrial enterprises, industrial safety and environment protection. (F) Pharmaceutical engineering module: principles of chemical engineering, introduction to pharmaceutical engineering, pharmaceutical separation engineering, pharmaceutical technology, management of pharmaceutical quality, pharmaceutical equipment and engineering design, special experiment and industrial practice. (G) Human and society module: Philosophy, history, foreign language, economics, law, politics, art, and literature. (H) Optional module: other courses provided by the university.

E-11

PRACTICE OF CULTIVATING CREATIVE PHARMACEUTICAL TALENTS IN COMPREHENSIVE UNIVERSITY

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Abstract: The article systemically summarizes the pattern of nurturing creative character in the School of Pharmaceutical Sciences, Sun Yat-sen University, and has an analysis, a discuss and a conclusion in the aspects of education conception of pharmaceutical school in the university, the cultivation system of creative character, the platform of undergraduate course, and the cultivation of general ability especially in the innovation of general ability.

Key words: comprehensive university; innovation; pharmaceutical talent; cultivating

E-12

THE COMPARISON OF PHARMACEUTICAL CURRICULA BETWEEN SMMU AND US SCHOOLS

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Pharmaceutical care has shown great influence in the pharmaceutical education and pharmacy practice. However, improving the quality of pharmaceutical service in china is a rather complicated matter. There are several ingredient limit the development of pharmaceutical care, even that of the clinical pharmacy. Such factors include the deficiency of national policy, the absence of incentive program and the unsuitable professional education. Above all, educational program is the most important factor.

The Pharm.D. Degree is the entry-level of pharmaceutical practicant in USA. The curriculum of Pharm.D. program is patient-oriented and problem-based. In China, some pharmacy schools have the clinical pharmacy program, and a few are discussing the feasibility of Pharm.D. program. The Second Military Medical University pharmacy school (SMMU) is one of them which will have great changes in curriculum. It is necessary for the school manager to make a thorough investigation.

The research compared the current pharmacy BS curriculum of the SMMU pharmacy school and Pharm.D. program of American schools. The American schools were selected according to U.S. Pharmacy Schools Ranking in 1998 by US News. The research collected the pre-pharmacy and Pharm.D. curriculum of U.S. schools ranking from 1 to 20, and 11 schools' data were obtained through their website. The curricula were categorized to seven groups and summarized by credits. Considering the differences of schools, we calculated credit proportion of each group. The curriculum of pharmacy BS in SMMU was categorized in the same way.

The curriculum of SMMU is composed of much basic science and pharmaceutical science, and US schools think much about clinical science and social pharmacy. To endue students with the ability and skill of pharmaceutical care, the SMMU pharmacy school should extend the school year and introduce some new courses such as physical assessment. And some courses having closely relationship with pharmaceutical care should been enhanced, e.g. biopharmaceutics & pharmacokinetics and therapeutics.

E-13

WORK FOR EXPERIMENT INSTRUCTION SYSTEM OF PHARMACEUTICAL ENGINEERING SPECIALTY IMPROVEMENT, BASED ON PRACTICAL EDUCATION PURPOSE

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Experiment instruction is a key link of qualified practical talents training. Any instruction method is not substituted for it. Pharmaceutical engineering specialty is a discipline by which technique practical talents are trained. Experiment instruction plays a much more important role in talents training program. It is an important content to form experiment instruction system of pharmaceutical engineering specialty improvement in reforming educational system. Practical teaching system should conform to the educational law in which instruction is given from easy to the difficult, and step-by-step. It is formed of three phases, the first is the basic skill experiment, to train students basic operation skill; the second is the comprehensive skill experiment, to train students the ability to use knowledge in a comprehensive way; the third is designable experiment, to train students the ability to bring forth new ideas, to enlighten and develop students' exploring spirit.

P-1

THE MEDICINES, THE PRESCRIPTIONS AND THE PHARMACISTS IN INDIA

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In India there are about 8000 pharmaceutical manufacturers that produce medicines worth about $8 billion of which $ 1.8 billion worth are exported. More than 25 pharmaceutical companies are approved by the US FDA. In comparison to US, our companies are small and their total out put in dollar terms is very limited. Since the Indian prices are 10 to 20 times lower than that of global prices, the international value of our produce and its volume is large and our share of the global market significant.

Studies have shown that modern drugs are reachable to about 65% of the population and to the rest (35%) the access is poor. The WHO and the other international organizations have been concerned about this and attempts have been made to work out a methodology to remedy this lacuna in our health care system at several forums. The list of schedule H (prescription only drugs) is very large and the rules under the Drugs Act are not strictly enforceable, resulting into frequent sale without the prescription. This results into irrational use of drugs. Besides other measures it has been suggested that the community pharmacist be encouraged and strengthened to provide medicines to the needy, A group of professional bodies including the representatives of the WHO have evolved some guiding principles to strengthen the community pharmacist to help increasing availability of appropriate drugs for the people and to advise the patient on their safe and effective usage. This will require a change in legislation for 1) Minimizing the list of prescribed drugs 2) Drawing out of a positive and comprehensive list of OTC drugs (many of which are already being distributed by the health workers in the National Health Programmes). 3) Improving knowledge and skills of the community pharmacists through education and training by short term courses.

P-2

SUPPLEMENTAL INFORMATION OF OFF-LABEL DRUG USE

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Study Objectives: Off-label use of drugs is frequently seen in pediatric, obstetric, and psychiatric units of Japan, for treatments that are not indicated by The Ministry of Health, Labor, and Welfare. This is an opportunity for pharmacists to critically evaluate the literature, supply drug information, and advise other healthcare professionals of proper off-label use. Therefore, the purpose of this study is to establish a model procedure to collect drug data from available clinical studies and format it for easier use for Japanese pharmacists.

Method: Methylphenidate was selected as the model study for its off-label use in attention deficit hyperactive disorder (ADHD). Drug information on methylphenidate for ADHD was collected using Micromedex, the Drug Information Handbook, Drug Facts and Comparisons, and other clinical study publications. A template of the off-label information sheet and questionnaire was distributed to 13 clinical pharmacists for evaluation and suggestions. Upon their recommendations, revisions were made.

Result & Discussion: The original information sheet included etiology and epidemiology of the disease, treatment objectives and monitoring, a treatment flowchart, inclusive of general comments. Revisions included a summary of study outcomes, a drug-drug interaction table, probabilities of adverse drug reactions, and a more familiar standard format, like the package insert. This methylphenidate information sheet will now be the model format for future information gathered for off-label use of drugs.

P-3

PHARMACISTS' ROLE IN MEDICATION MANAGEMENT IN A PATIENT UNDERGOING CONTINUOUS HEMODIAFILTRATION

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Background: Excessive humoral mediators play an important role in the pathogenesis of organ failure. Continuous hemodiafiltration (CHDF) is used intensive care units (ICU) in Japan to remove these mediators from hypercytokinetic patients with systemic inflammatory response syndrome (SIRS). The pharmacokinetic management of drugs varies for patients that undergo CHDF.

Description: This presents an opportunity for ICU pharmacists to assist in patient care. This is a case report of a 72-year-old male with severe acute pancreatitis admitted to the ICU for increase of serum amylase, abdominal pain with complications of chronic renal failure upon transfer from a previous secondary care hospital. While undergoing CHDF, he was administered empiric imipenem/cilastatin, followed by micafungin plus fosfluconazole, and arbekacin, a novel semi-synthetic aminoglycoside founded in Japan for methicillin resistant *Staphylococcus aureus* (MRSA). Pharmacists participated in fungal selection, evaluated kinetics prior to drug administration, and monitored arbekacin blood concentrations for dosing alterations when CHDF was held.

Conclusion: Pharmacists' active role in patient care contributed to appropriate administration of drug without adverse effect events or toxic occurrences.

P-4

COMMUNITY PARTICIPATION IN PRIMARY CARE UNIT: ROLES OF PHARMACISTS

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The World Health Organization has challenged the health services of developing countries to promote participation by communities. Since 2001, the Thai government has adopted this concept by organizing a root-end network structure, so-called primary care units. This study investigated the level of community participation from the point of view of health care workers in Mahasarakham, a district with about 1 million populations. A set of structured questionnaires was designed. The expected roles of pharmacists that would fit in with this concept were reviewed. All of the workers at the total of 11 Contracting Units of Primary Care (CUP) of Mahasarakham answered the questionnaires. Most of the respondents (60 in total) were 40-49 yrs (43%) and had worked at least 5 yrs (37%) as health care workers. 70% of the respondents informed that the Local Authorities contributed financially and 85% of the CUP committees were composed of the elected Local Authorities representatives. The activities, which the health care workers expected community participation were consecutively listed as follows: open-air exercise (45%), disease prevention (38%), home care visits (36%), health education (36%). The activities which the health care workers provided with high community participation were consecutively listed as follows: open-air exercise (22%), herbal use (18%), disease prevention (17%), home care visits (17%), health education (17%). There were some helpers from the communities participated in the routine services of these CUPs. There are some roles for pharmacists in the community such as consumer protection and herbal use. Methods used to achieve this goal are likely to be various types of training and home care visits. Our current review leads to conclude that pharmacists played very little roles in community participation and the levels of the current community participation in the health care provision at these primary care setting were organization and contribution. There was no evidence to support the level of empowerment of community participated in health care provision.

P-5

THE EXTENT OF COMPLIANCE AMONG ELDERLY PATIENTS

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Medications are probably the single most important health care provision in preventing illness, disability and death in the geriatric population. New pharmaceutical products provide hospital pharmacists with valuable tools for upgrading quality of life. With the steady increase of advanced medical disorders along with the drastic surge in the number of marketed prescribed drugs, patient compliance to medication regimens has become increasingly complicated and problematic. The objective of the study is to find out the extent of compliance among geriatric patients and to determine whether there is any significant association between demographic, socio-economic status, awareness about the disease and other variables with non-compliance. Elderly patients above the age of sixty years who had attended Medicine Unit of Christian Medical College and Hospital for the treatment/review and outpatient pharmacy dispensing counter were included in the study. An interview was conducted with each patient based on a semi-structured questionnaire which consists of questions about demographic, socio-economic, cognitive skills, treatment schedule, awareness about the disease/disorders and so on. The data collected were statistically analyzed and determined whether there is any significant association of the variables with regard to the non-compliance. The compliance score was calculated using two aspects, one on the number of days on medication and the other on the total days prescribed with medicines. Accordingly, the elderly patients were categorized as excellent compliant patients [100%], good compliant patients [90-99%] and non-compliant patients [<90%]. The several risk factors associated with the patients' attitude contributed to the percentage of compliance are also identified. Economical status was found to be the major contributor to non-compliance. Illiterates and those with elementary education showed more non-compliance. Those who stick to their follow-up appointments showed considerable improvement in compliance.

P-6

USE OF EXTEMPORANEOUS PREPARATIONS IN PAEDIATRIC PATIENTS ATTENDING A TEACHING HOSPITAL

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The aim of the study was to assess the use of extemporaneous preparations in paediatric patients. A total of 400 paediatric patients who visited a teaching hospital during the one-year period of 2002 were selected at random. Data of these patients were obtained from the Pharmacy Information System (PIS). Eighty of these patients (20%) were dispensed with at least one extemporaneous preparation during this one-year period. Out of a total of 4205 medications dispensed, 180 (4.3%) were extemporaneous preparations. Diuretics were found to be the main group of medications made into extemporaneous preparations (24.4%). This was followed by ACE inhibitors (10.6%) and oral iron preparations (8.9%). A majority of the extemporaneous preparations (78.3%) were dispensed to patients aged one-year and below. Tablets were the main dosage form used to prepare oral liquid preparations. In conclusion, extemporaneous preparations were often dispensed to paediatric patients. However, the stability of these preparations and its acceptability to patients has not been investigated. More incentives should be considered by authorities concerned to encourage more participation from pharmaceutical manufacturers in such investigations.

P-7

THAI VERSION OF THE QUALITY-OF-LIFE IN EPILEPSY INVENTRY: COMPARISON BETWEEN THE QOLIE-31 AND THE QOLIE-10

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Objective: To determine the correlation between the QOLIE-10 and the QOLIE-31 in Thai epileptic patients.

Design: Prospective, analytical design.

Methods: A study of 89 patients with epilepsy was undertaken at 2 seizure clinics in Thailand. Patients completed both the QOLIE-10 and the QOLIE-31 by themselves on the same day. Internal consistency, reliability coefficients in subscale and total score, correlation coefficients, discriminant validities were all studied.

Results: Internal consistency reliability coefficients (Cronbach alpha) of the QOLIE-10 in three subscales were 0.60 (epilepsy effects scale), 0.33 (mental health scale), and 0.64 (role function scale). Internal consistency reliability coefficients of the QOLIE-31 ranged from α= 0.47 (energy-fatigue) to α= 0.80 (seizure worry).The QOLIE-10 correlated well with the QOLIE-31 when QOLIE-10 components and total scores were calculated from the QOLIE-31 scores (range from 0.59-0.87). Correlation for the QOLIE-10 and the QOLIE-31 that were completed by the patients on the same day ranged from 0.30 to 0.78. The QOLIE-10 and the QOLIE-31 total scores were sensitive to differences in the seizure frequency categories. (P=0.004, 0.019, respectively).

Conclusion: The QOLIE-10 correlated well with the QOLIE-31 and can be used for Thai epileptic patients to discriminate among seizure groups.

P-8

PHARMACIST MONITORING OF WARFARIN-RELATED PROBLEMS IN OUTPATIENT ANTICOAGULATION CLINIC

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This research was to compare patient outcomes between the pharmacist-assisted anticoagulation service and usual medical care in ambulatory patients, Mahasarakham hospital, which was conducted in outpatients receiving warfarin therapy at cardiovascular clinic. The patients were randomized into two groups; 40 in the control group and 37 in the study group.These groups were compared by anticoagulation control, warfarin-related problems and patients' knowledge. Baseline characteristics of the two groups were no statistical difference. The pharmacist identified warfarin-related problems and provided counseling to the study patients. Over one-year follow-up period, the results showed that the number of patients in the study group (31.3%) were significantly more likely to be detected anticoagulation control than those in the control group (22.2%; p = 0.024). Warfarin-related problems in the two groups included bleeding (5.8% vs 3.7%), thromboembolism (0.8% vs 0.9%), drug interactions (6.2% vs 9.4%), and non-compliance (11.5% vs 7.3%) in the study group versus the control group, respectively. The major problems needed pharmacist interventions to physician in study group were incorrect prescription orders of warfarin, too low dose of warfarin and prescribing error of concomitant drugs. All problems addressed could be resolved by providing recommendations to physicians. Additionally, knowledge score of the study group was significantly higher than that of the control group (5.8$\pm$2.0 vs 6.8$\pm$1.4; p = 0.038). As demonstrated in this research, the pharmacist's counseling in anticoagulation clinic could contribute to the appropriate approaches for enhancing anticoagulation control and patients' knowledge. Therefore pharmacist's role in anticoagulation clinic could improve the patient outcomes.

Keyword: warfarin, anticoagulation clinic, counseling

P-9

A CONCEPTUAL-THEORETICAL-EMPIRICAL SYSTEM OF KNOWLEDGE FOR GUIDING PHARMACY PRACTICE, EDUCATION, ADMINISTRATION AND RESEARCH: THE MANIFESTO ON PHARMACEUTICAL CLINICAL TECHNOLOGY

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Objectives: The purpose of the manifesto is to provide a medical, scientific, theoretical, educational, professional and legal basis for expanded scope of pharmacy practice by including Pharmaceutical Clinical Technology (PCT). PCT is the rational, effective, safe and cost efficient use of medical technologies (e.g., devices, instruments, single use items, diagnostics) and medications used in the prevention, diagnosis and treatment of human disease. For the past 30+ years, PCT has been practiced and taught in Europe.

Methods: The manifesto on PCT was created using the conceptual-theoretical-empirical systems approach described by Fawcett. This method involves defining those elements of practice that are unique to the discipline, establishing the theoretical basis upon which the discipline is practiced and describing the empirical tools used in the day-to-day performance of professional activities. This collaborative inquiry process was undertaken by a multi-disciplinary team and then subjected to the critical review of over 150 senior experts from the fields of pharmacy, medicine, biomedical engineering, systems engineering and nursing meta-theory. In addition, the evolving MANIFESTO was subjected to the critical review of more than 10 experts in pharmacy law.

Results: A vigorously revised and highly refined document was generated that provides a clear conceptual-theoretical-empirical system of knowledge for guiding pharmacy practice, research and education.

Implications: A manifesto which calls for the implementation of PCT as a means for expanding the scope of practice and for establishing a conceptual-theoretical-empirical basis for pharmacy practice, education and research is gaining wide acceptance among academic and practicing pharmacists worldwide.

P-10

THE ROLE OF THE DRUG NOTE AS TOOL FOR THE SELF MANAGEMENT OF DRUG AND PATIENTS' HEALTH

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Objective: Information supply regarding drugs is one of the major factors to promote proper use of drugs. In each country various efforts are made to achieve proper use of drugs by patients. In Japan pharmacists' technical charges of are admitted for prescribed drugs in addition to the cost of the drug itself. Such charges include technical service for management of patients' information and information supply based on this. There are two kinds of information media to be provided together with medication guidance. One is paper media to provide information of drugs and the other is the Drug Note. Drug Note distributed to patients through pharmacies across the country as a tool for the supply of drug information and communication with patients.

There are a number of kinds of Drug Notes including those published by Japan Pharmaceutical Association. This document introduces the role of the Drug Note and the health insurance system as well as newly developed women's Drug Note.

Methods: The relationship between Drug Notes used in Japan and the health insurance system is analyzed. Women's Drug Note was newly developed as a tool to support women's health.

Result & Conclusion: Pharmacists are not only required to achieve that the drugs are used properly but also to contribute to preventing diseases and promoting health. It is essential to understand one's physical condition thoroughly for self-management of health. There will be a demand to develop a tool to enable recording of while there is no problem with health.

Women's Drug Note was developed to record physical changes as well as drugs or health food taken. 20,000 copies have been sold so far and are used as a tool for health self management by healthy women and patients.

P-11

PRIMARY CARE SERVICE OF UNIVERSITY PHARMACY IN UNIVERSAL HEALTH CARE COVERAGE IN THAILAND (PRELIMINARY STUDY)

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University Pharmacy was subcontractor of Mahasarakham Hospital that is Contracting Unit for Primary care (CUP) under the Universal Health Care Coverage (UC), the government policy of Thai health insurance in 2001 and serviced with clinical practice guideline to study the pattern of community pharmacy in health care service system. The objective was to study the pattern and outcomes of primary care service of University Pharmacy. The outcome objectives were divided into 3 dimensions, clinical outcomes, humanistic outcomes and economic outcomes. This is descriptive study, collected data with developed questionnaire. The questionnaires consist of 3 parts, general data, clinical outcomes data and humanistic outcomes data. The study conducted during January to March 2004. 135 patients who using primary care service in University Pharmacy between May - December 2003, completed the questionnaires. The results, most of patients were women (51.4%). The patients' age between 1-75 year, average age was 25 years old. The patients' education was primary education (24.4%). Most of them were student (27.8%) and their incomes were less than 2,000 baht (43.0%). The kind of UC insurance of the patients was free service (53.3%). Approximately twenty four percent of the patients were come with fever (24.4%) and common cold (10.4%). Ninety two percent of patients' received counseling by pharmacist about disease, drug use and ADR management and self practice for behavior modification. After 1 week the symptoms were disappeared (68.9%) and good better before visited (28.1%). Ninety percent of the patients' were agree with good compliance. All of them were satisfied of the service, convenient to access, waiting time, time, process and quality of service and treatment outcomes. This pilot study was new innovation of community Pharmacy in primary care service in Thailand. The study should develop and performed to improving the role of community pharmacy to improving good health and rational used of drug to Thai people.

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P-12

APPLICATION OF PHARMACOECONOMICS IN PRACTICE AND RESEARCH IN SINGAPORE

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Pharmacoenomics is a relatively new science that borrowed from several disciplines including health economics and evidence-based medicine. Many factors contribute to the development of this new discipline; however, the major driving force behind this discipline is the need for more accountability due to the disparity between demands and supply in healthcare. Potentially the rational use of pharmacoeconomics can improve the allocation of resources and has been employed for evaluation of the usefulness of drug therapies, policy analyses and cost-benefit analyses for medical treatments in many western countries. In other words, at the macro-level it can be used to assist in overall drug policy decision and at the micro-level it can assist in determining whether costly new drugs or technologies should be used after considering all cost-offsets such as reducing the need for hospitalisation or by enabling the patient to return to the workforce earlier. The current paper will describe and discuss the experience of using pharmacoeconomics in clinical practice and research in Singapore.

P-13

PHARMACY PRACTICE, A PARADIGM SHIFT IN COMMUNITY PHARMACY SET UP IN INDIA

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Pharmacy Practice is now considered as a system that does not just sell medicines but works simultaneously for disease awareness, disease detection, disease management and Patient compliance. The Community Pharmacy Stores are best outlets in India, to practice this concept. The care is provided through various disease state management camps, like hypertension, diabetes, asthma, arthritis, BMD, derma care and eye care. Over 300 such camps were conducted through our Medicine Shoppe outlets in the state of Maharastra, Gujarat & Karnataka in India, serving more than 4000 people. Outcomes of such camps have been very positive. Results also showed how health information can be reached to the people through this kind of pharmacy practice activity.

P-14

PHARMACIST SERVICE ACTIVITIES DEVELOPMENT: APPLICATION OF LEVITT'S TOTAL PRODUCT CONCEPT TO EVENT BASED OF PATIENT DEMAND PRACTICE ENVIRONMENT

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The objectives of this study were to 1) identify, group and label pharmacist service activities into pharmacist service construct, and 2) apply and test Levitt's Total Product Concept Model to the domain of pharmacist service activities. Data for the analysis were gathered in winter 1999 by mail survey in Dane County, Wisconsin, USA. Systematic random sampling was applied in selecting 500 samples from the purchased mailing list. Twenty-nine pharmacist service activities identified primarily from previously developed scales for community pharmacy patronage were used in this study. The respondents were asked to rate the importance of each pharmacist service activities (of scale 1 = of no importance to 5 = great importance) and check the experienced box provided at the end of the importance scale if they had ever experienced it. Factor analysis was conducted as an exploratory technique to examine the dimensional structure of the constructs and the designation of individual pharmacist service activities to measure the dimensions. Then, total product concept groupings based on extent of consumers' experience with each pharmacist service constructs were applied. The response rate was 58.80 percent. Four factors above the break in the screen-plot were found to explain 57.94 percent of the variation. Eigenvalues for each of these four factors were equal or greater than 1.225. The factors extracted represented four dimensions and were labeled as 1) Non-prescription Drug Consultation and Monitoring Activities, 2) Medication Consultation and Monitoring, 3) Medication Administration and Management Activities, and 4) Educational and Informatic Activities. Based on Levitt's model of the Total Product Concept using consumers' percent experience criteria, Prescription Drug Consultation and Monitoring Activities fitted in Expected Product/Service Component. While Medication Administration and Management could fit well under Augmented Product/Service Component, and Non-prescription Drug Consultation and Monitoring Activities and Education and Informatic Activities Dimensions could fit well into the Potential Product/Service Components.

Key words: pharmacist service activities, Levitt's total product concept, patient demand

P-15

INSTRUCTION OF MEDICATION AND MANAGEMENT OF EFFECT AFTER ADMINISTRATION OF CORTICOSTEROID IN INTERSTITIAL PNEUMONIA

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Background: Intractable interstitial pneumonia (IP) symptoms such as dyspnea may be resolved with administration of corticosteroids. Although corticosteroids have many adverse effects, it is important to maintain compliance for improvement of symptoms. This case study is an example of effective steroid management by a pharmacist at Kawakita general hospital in Japan.

Case Description: A 72-year-old Japanese female was hospitalized for chief complaint of dyspnea upon effort due to idiopathic bronchiolitis obliterans organizing pneumonia (BOOP). Upon physical examination, chest auscultation revealed rates with fine crackles. Methylprednisolone 500 mg was administered intravenously once daily for three days, as a semi-pulse therapy. This was followed by a secondary treatment of 30 mg oral prednisolone taper every two weeks in five-milligram increments.

Conclusion: Within one week of initial therapy, her shortness of breath subsided and rates diminished. The patient's recovery can be attributed to reinforcement of compliance via bedside counseling by the pharmacist. Furthermore, pharmacist intervention in adverse effect management allowed the patient to continue therapy as scheduled.

P-16

A CASE REPORT ON PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

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Objectives: Nausea and vomiting are some of the adverse effects of chemotherapy agents and are difficult symptoms to resolve in a cancer patient. If symptoms continue, it may cause dehydration, electrolyte disturbances, poor nutrition status, etc. Thus, it is important to prevent chemotherapy induced nausea and vomiting (CINV) to maintain the patient's quality of life (QOL) and uphold chemotherapy schedules.

Methods: A 73-year-old patient with Hodgkin's disease was admitted in January 2004, for intravenous administration of the chemotherapy regimen, ABVD (Doxorubicin 45mg, Bleomycin 15mg, Vindesine 3mg, Dacarbazine 680mg, on days 1 and 15). After administration of the first cycle of ABVD and a single antiemetic, granisetron 3mg IV, nausea and vomiting occurred on day 3, following delayed nausea on days 3 to 7. According to the National comprehensive Cancer Network (NCCN) 2003 guideline, ABVD therapy has the highest level of emetogenic potential due to the presence of high-risk emetogenic agents such as dacarbazine and doxorubicin. Furthermore, delayed nausea may be attributed greatly to doxorubicin.

Results & Conclusion: To prevent further delayed nausea occurrences, the pharmacist suggested continuation of an oral 5-HT3 blocker on days 2 to 4 and the addition of dexamethasone 4mg IV, following oral administration on days 2 to 4 of the next cycle. Unfortunately, the patient was not prescribed any additional therapy other than a previous antiemetic agent for day 15. As a result, nausea and vomiting occurred on the day after chemotherapy administration. The patient then received the original pharmacist recommended therapy plus metoclopramide 10mg IV, and symptoms subsided without dehydration or electrolyte disturbances. Hence, it is important for pharmacists to prevent CINV in order to maintain the patient's scheduled chemotherapy regimen and the patient's QOL.

P-17

THE ANALYSIS OF ACUTE DRUG POISONING IN ADVANCED EMERGENCY CRITICAL CARE CENTER

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Introduction: Many patients needing drug poisoning care are admitted to the critical care department. At the Nippon Medical School hospital, pharmacists are permanently stationed at intensive care units (ICU) in the critical care department. The role of the ICU pharmacists, in acute drug poisoning, is to provide physicians with the information of the occurrence, mechanism of poisoning and pharmacokinetics of drugs. In acute drug poisoning, information is often incomplete and record keeping is unorganized. Therefore, the poison sheet was created by pharmacists to provide an accurate record of labs, diagnosis, and treatment for each acute drug poisoning incident.

Subject & Result: Since the implementation of the poison sheet, patient data can be collected and organized to find population trends. During the period of January 1, 2002 to March 2004, 209 patients with acute drug poisoning were admitted to the critical care department. The patients were predominantly female (76.2%) and relatively young (average age of 34 years). Database trends found an average of 4.8 kinds of medications taken upon drug poisoning were most common class of drugs were benzodiazepines for anti-anxiety. Information gathered on patient populations will be useful for doctors in anticipating drug poisoning patterns such as overdose or suicidal events.

Conclusion: Pharmacists can now use the drug poisoning sheets as quick reference for previous incidences to evaluate and manage future events.

R-1

EFFECTS OF SUCROSE STEARATES ON MELT PELLETS PREPARED IN A HIGH SHEAR MIXER

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Objectives: To study the effects of sucrose stearates on agglomeration and dissolution characteristics of melt pellets containing lactose, chlorpheniramine maleate and hydrogenated cottonseed oil (HCO).

Materials: Crystalline α-lactose monohydrate and chlorpheniramine maleate in a weight ratio of 24:1 were used as solid bulk materials. 23-25% v/w HCO and 0-0.6% w/w sucrose stearates S170, S770 or S1570, expressed with respect to the weight of solid bulk materials, were used as meltable binder and additives respectively.

Methods: Melt pelletization was carried out in a laboratory scale vertical high shear mixer. The size and size distribution of melt pellets were determined by using sieves. The percentage of material adhesion on mixer was calculated as weight percentage of unrecovered materials after processing. Drug release was evaluated using the USP dissolution paddle method at 50 rpm and simulated gastric fluid as dissolution medium.

Results: The addition of sucrose stearates S770 and S1570 promoted pellet growth and lowered the percentage of material adhesion at additive concentrations lower than those of sucrose stearate S170. The melt pellets released more than 80% of the drug content by an hour. Without sucrose stearates, the drug release was slower and best described by the Higuchian model. However, with sucrose stearates, drug release rate was faster and the release kinetics deviated from the Higuchian model.

Conclusion: Sucrose stearates promote pellet growth and prevent loss of materials by reducing adhesion to the mixer. They are useful as agglomeration additives. The release kinetics of the melt pellets was altered when sucrose stearates were added.

R-2

COMPARISON OF ROUNDNESS DESCRIPTORS FOR QUANTIFYING THE SPHERONIZATION PROCESS OF EXTRUDATES IN A SPHERONIZER

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Objective: To use roundness descriptors for quantifying spheroid development during spheronization.

Method: Spheroids were produced by extrusion spheronization using a fixed ratio of water, lactose and microcrystalline cellulose. Extrusion screen of 1 mm was used. Extrudates were spheronized for 10 mins and sampling was carried out at 2 mins interval. Experiments were triplicated. Shape analysis was carried out using image analysis. ANOVA and post-hoc Fisher's LSD test were carried out to compare the usefulness of roundness descriptors such as aspect ratio, circularity, sphericity and e_R in describing spheroids roundness during spheronization.

Results: Roundness of spheroids improved during the course of spheronization. All roundness descriptors were equally effective in detecting improvements in roundness up to 6 mins of spheronization. Aspect ratio was most discerning in describing improvement in roundness. Circularity could not detect improvement in roundness beyond 6 mins of spheronization.

Conclusion: Aspect ratio is a robust descriptor of roundness when used to monitor improvement in roundness during the spheronization process.

R-3

PREDICTION OF HYDROPHILIC/HYDROPHOBIC GEL PROPERTIES OF NON-AQUEOUS GEL MATRICES USING DYNAMIC CONTACT ANGLES

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Objective: To characterize the hydrophilic/hydrophobic properties of non-aqueous Gantrez gel matrices using dynamic contact angles of water and isopropylmyristate (IPM).

Materials and Methods: Gels of different concentrations were prepared using Pharmasolve (ISP, USA) as the solvent and Gantrez AN-169 (ISP, USA) as the gelling agent. Water and IPM contact angles, θ_w and θ_i, respectively and standing volumes, V_w and V_i, respectively on the gel surfaces were measured over 3 mins using the contact angle analyser (FTÅ200) and analysed by a drop shape analysis method.

Results: θ_w and V_w decreased by first order kinetics whereas V_i decreased by zero order kinetics. Both liquids showed lower rate constants for higher polymer concentrations. For every comparable time point, $\theta_i<\theta_w$ and $V_i<V_w$ were observed. Reduction in θ and V values indicated liquid spreading and absorption into gel matrices, respectively. In general, the coefficients of variation (C.V.) of θ_w and V_w were comparable whereas C.V. of θ_i was lower than that of V_i.

Conclusions: Rapid spreading and absorption of water (polar) and IPM (non-polar) indicated that non-aqueous Gantrez gel matrices had both hydrophilic and hydrophobic properties, with predominance of the latter. From the comparison of the C.V. of θ and V for both water and IPM, θ seemed to be a better predictor of the hydrophilic/hydrophobic properties in the gel matrices. The measurement of these properties enables better prediction of skin compatibility for formulated gel matrices to be used as topical drug delivery systems.

R-4

COMPARATIVE STUDY OF PELLET MASS FLOW IN THE PRECISION COATER AND WURSTER COATER

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Objective: To evaluate the pellet mass flow rate (MFR) in the Precision coater and Wurster coater at different column clearances.

Materials and Methods: The two coaters were fitted with the same air handling system (MP1, GEA-Aeromatic Fielder, UK). 700 g of HPMC film coated sugar pellets were placed in the chamber. The time taken (cycling time) for all the pellets to traverse through the column was determined. MFR was calculated by dividing the mass of pellets by the cycling time. The distance between the air distribution plate and the lower end of the column (column clearance) was varied. The MFR values at different column clearances were obtained for the Precision coater and Wurster coater.

Results and Discussion: For both coaters, the MFR increased, reached a peak, then decreased with increasing column clearance. However, MFR in the Precision coater was relatively lower and showed a greater range than that in the Wurster coater. This indicated that the impact of the column clearance on the MFR was greater in the Precision coater than in the Wurster coater.

Conclusions: Column clearance has a greater influence on the MFR of pellets in the Precision coater than the Wurster coater. The column clearance should be appropriately adjusted to ensure proper flow of pellets during coating.

R-5

LIQUID PHASE COATING TO SUSTAIN DRUG RELEASE FROM ALGINATE MICROSPHERES

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Objective: To explore a liquid phase coating technique to prepare Eudragit-coated alginate microspheres for sustained drug release.

Methods: Alginate cores containing paracetamol were prepared using an emulsification method. The cores were then coated at different core:coat ratios in an emulsion of coating polymers. Paracetamol was the model drug used. The morphology, drug loss during coating and dissolution profiles of microspheres were determined. Dissolution test was carried out using the paddle method at a stirring speed of 50 rpm at 37ºC in simulated gastric (SGF) and intestinal (SIF) fluids.

Results: The coated microspheres consisted of agglomerates that were generally spherical in shape, with mean size ranging from 354 to 807 microns. The release of paracetamol from coated microspheres in SGF and SIF were retarded. Release rates of Eudragit RS100-coated microspheres were comparable. In contrast, drug release from Eudragit S100-coated microspheres was significantly faster in SIF than in SGF. It was also found that drug release decreased with increasing core:coat ratio. The mechanism of drug release from microspheres coated with different types of Eudragit and the gradual evolution of release kinetics with core:coat ratio will be further discussed.

Conclusion: Alginate microspheres were successfully coated using a liquid phase coating technique. The coated microspheres showed little drug loss during coating and significantly retarded drug release in *in vitro* dissolution test. The novel coating technique is useful for development of controlled delivery systems.

R-6

COMPARING THE FLOW DETERMINATION METHODS USING LACTOSE POWDERS

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Objectives: This study reports the investigative work on the application of avalanche flow to several grades of lactose and compares the results with other flow determination methods.

Materials: Lactose monohydrate powders - 80 M, 100 M, 125 M, 150 M, 200 M, 350 M, 450 M (DMV International, The Netherlands) were equilibrated at 30, 50, 75 % RH, 25ºC for 72 h in a humidity chamber.

Methods: Powder avalanches of the equilibrated lactose powders were determined and their flow indices calculated. Bulk and tapped densities, Carr indices and Hausner ratios were derived for the respective lactose grades from tapping studies. Repose angles and angles of fall were measured using a powder tester (Hosokawa Micron Corporation, Japan).

Results: Regardless of the flow method employed, the ease of powder flow decreased with increasing particle size with the exception of Lactose 80 M. This was attributed to the increased frictional and electrostatic forces acting on smaller particles which impeded their flow.

Conclusions: Compared to the other flow parameters, avalanche flow indices calculated from the avalanche results were able to differentiate between the various lactose grades very well especially at 50 % RH. Furthermore, avalanche flow results compared favorably with the existing methods which were unable to differentiate powders that were highly cohesive and poor flowing.

R-7

PHOTODYNAMIC THERAPY USING HYPERICIN IN THE CHICK CHORIOALLANTOIC MEMBRANE MODEL

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Introduction: Photodynamic Diagnosis (PDD) and Photodynamic Therapy (PDT) utilize photosensitizing agents for photodynamic diagnosis and treatment of superficial cancers. Hypericin is a potent and promising photosensitizer for the treatment of cancer. The chick embryo chorioallantoic membrane (CAM) model had been used for testing photosensitizers' ability to induce vasculature damage as the primary target in PDT. The CAM model has several advantages including its simplicity, rapidity, sensitivity, ease of performance and its relative cheapness and thus suitable for large-scale screening.

Objective: To assess photodynamic therapy (PDT) effects of hypericin on CAM model.

Materials & Methods: Fertilized chicken eggs were disinfected with 70% ethanol before placing them into trays with blunt end upwards aseptically. They were incubated at 37ºC in a 37.4ºC and 60 % humidified atmosphere inside an incubator. On day 7 of embryo age (EA 7), a window was opened at the apex to create a false air sac. A dose of 2 mg/kg per embryo was used for topical application. The blank solutions without hypericin were used as controls. The solutions were applied on CAM and incubated for 30 min in the dark. The vascular damage induced by light was quantitatively measured using image-processing technique.

Result & Conclusion: The hypericin treated CAM had a vessel regression as compared to the control. Hypericin showed antivasculature effect.

R-8

CRYOMILLING OF COPOLYVIDONE AND ITS INFLUENCE ON ASPIRIN RELEASE FROM ASPIRIN-COPOLYVIDONE MATRIX TABLETS

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Objective: To investigate the effect of different temperatures and rotor speeds of the cryogenic mill on the extent of particle comminution of copolyvidone (Plasdone S630) and the effect of milled S630 on aspirin release from aspirin-S630 matrix tablets.

Materials and methods: S630 (ISP, USA) was cryogenically milled (Globin, Nara, Japan) using different rotor speeds (2000, 6000, 10000 rpm) and temperature conditions (-20, -60, -100 ºC). Aspirin loaded S630 matrix tablets were prepared by direct compression using a single punch tablet machine. Dissolution studies (method 2, USP) were carried out on the prepared tablets.

Results: Rotor speeds of 10000 and 6000 rpm reduced the median S630 particle size by over 50 % as compared to the unmilled powder. Temperature changes from -20 to -100 ºC was found not to have a significant influence on the cryomilling of S630. Different S630 median particle sizes resulted in different rates of aspirin release from the matrix tablets. Aspirin release kinetics conformed best to the Hixson Crowell's release equation.

Conclusions: The extent of S630 particle size reduction was speed dependent when cryogenic milling was carried out. The rate of aspirin release from S630 matrix tablets was affected by the particle size of the constituent S630 particles.

R-9

INFLUENCES OF ADDITIVES ON THE STABILITY OF ASPIRIN IN COATING SOLUTIONS

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Objectives: To investigate the influences of additives on the stability of aspirin in coating solutions.

Materials & Methods: The levels of aspirin degradation in aqueous solutions in the presence of different additives were determined using HPLC. The additives used in the studies included surfactant sodium lauryl sulfate (SLS), organic acids such as citric acid, oxalic acid and phthalic acid, and a copolymer of N-vinyl-2-pyrrolidone and vinyl acetate (Plasdone® S630, ISP).

Results: SLS increased the degradation of aspirin by increasing the solubility of aspirin in aqueous solutions. Citric acid and phthalic acid were able to improve the stability of aspirin by lowering the pH of the solution and converting the aspirin into the unionized form. Oxalic acid increased the hydronium ion-catalyzed hydrolysis of aspirin instead at very low pH. S630 showed a concentration-dependent stabilizing effect, which might be due to the formation of hydrogen bonds between carbonyl groups of S630 molecules and hydroxyl groups of aspirin molecules. The hydrophobic vinyl acetate chains of S630 molecules might also account for the stabilizing effect by shielding the aspirin molecules from attacking species such as hydroxyl or hydronium ions.

Conclusions: Additives used had varying effects on aspirin stability in aqueous solutions. Citric acid, phthalic acid and S630 improved the aqueous stabilityof aspirin whilst oxalic acid and SLS increased its degradation.

R-10

INVESTIGATION OF MELT POLYMER PROPERTIES ON SPRAY-CONGEALED MICROPELLETS

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Spray congealing is mostly employed for hydrophobic matrix materials to sustain drug release. The use of spray congealing for hydrophilic matrix materials to improve the dissolution of water-insoluble drugs is a more recent development. The influence of hydrophilic polyethylene glycols (PEGs) on the physical properties of spray-congealed micropellets produced has not been extensively reported. Hence, this formed the objective of the present study. PEG 3350, 6000 and 8000 spray-congealed micropellets were produced using a two-fluid spray atomiser. The size and size distribution, shape and calorimetric properties of the micropellets were evaluated. Discrete and relatively spherical micropellets were successfully produced from the different types of PEG by spray congealing using optimised processing conditions. The median diameters of the micropellets ranged from 98 to 126 μm, with size span of 1.8 to 2.3. Micropellets prepared from the three grades of PEG showed no significant difference in shape, as indicated by the aspect ratios, roundness and shape factors. The molecular weight and viscosity of the PEGs had no significant effects on the size and size distribution, as well as the shape of the micropellets. Calorimetric properties of PEG were found to change after spray congealing. As all the batches of micropellets had acceptable physical properties, the PEGs used are suitable for production of micropellets by spray congealing. The varying water solubility/miscibility of the PEGs is potentially useful for modulating dissolution of drug.

R-11

THE EFFECT OF CROSSLINKING CATIONS ON THE ANTIBACTERIAL ACTIVITY OF ALGINATE MICROPELLETS

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Objective: To investigate the effect of crosslinking cations on the antibacterial activity of alginate micropellets.

Materials and methods: Alginate micropellets were prepared using an extrusion method. Calcium chloride, copper sulphate and zinc chloride were used as crosslinking agents while sulfadiazine sodium was used as the model antibacterial compound. The antibacterial activities of sulfadiazine sodium and the blank alginate micropellets were evaluated using *Staphylococcus* aureus as the test organism.

Results & discussion: The antibacterial activities of calcium alginate and zinc alginate micropellets were comparable with that of sulfadiazine sodium (10 mg/ml) while that of copper alginate micropellets was markedly higher. When the micropellets were combined with sulfadiazine sodium, the activity of the antibacterial compound was affected to different extents.

Conclusion: Alginate micropellets crosslinked with calcium, zinc and copper ions exhibited significantly different antibacterial activities. They also affected the antibacterial activity of sulfadiazine sodium to different extents. Copper alginate showed higher antibacterial activity than sulfadiazine sodium and is potentially useful for wound care.

R-12

GLUTATHIONE (GSH) AND mRNA EXPRESSION OF GSH SYNTHETIC AND UTILIZATION ENZYMES ARE INCREASED IN DRUG-RESISTANCE NEUROBLASTOMA CELL LINES

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Neuroblastoma (NB) cell lines established at patient relapse often manifest multi-drug resistance (MDR), including high-level alkylating agent resistance. Alkylator resistance in NB cell lines can be overcome by buthionine sulfoximine (BSO)-mediated GSH depletion. To determine if GSH and GSH synthetic/utilization enzymes were increased in alkylator-resistant NB, we studied 17 NB cell lines: 8 drug sensitive lines (Drug-Sens, 7 obtained at diagnosis), 3 moderately drug-resistant lines established post-chemotherapy (Post-Chemo), and 6 high-level multi-drug resistant cell lines obtained after intensive chemotherapy (MDR). We measured basal levels of GSH (nmol/mg protein) by the DTNB-GSSG reductase method, mRNA expression (ratio to 18S) of γ-glutamylcysteine synthetase (regulatory, γ-GCSr and catalytic, γ-GCSc subunits), GSH peroxidase (GPX), and GSH-S-transferase (GST) by quantitative TaqMan RT-PCR. We also determined the concentrations of melphalan (L-PAM), carboplatin (CBDCA) and etoposide (ETOP) lethal for 90% of cells (LC_{90} in μg/ml) derived from cytotoxicity dose-response curves generated with DIMSCAN (a digital imaging fluorescence cytotoxicity assay). GSH-depletion induced by BSO significantly increased the cytotoxic response of MDR NB cell lines to L-PAM and CBDCA ($P < 0.001$), but not to ETOP ($P > 0.05$). GSH and γ-GCSr were associated ($P < 0.01$) with L-PAM and CBDCA LC_{90}, but not with ETOP LC_{90}. Elevated GSH, γ-GCSr, GSTμ, or GSTπ was observed in both p53 functional and p53 non-functional MDR NB cell lines. CHLA-122 (Drug-Sens) + CHLA-136 (MDR, p53-wild-type/functional) and SK-N-BE(1) (Drug-Sens) + SK-N-BE(2) (MDR, p53-mutated/non-functional) are paired cell lines established from the same patients at diagnosis and after intensive chemotherapy. CHLA-136 and SK-N-BE(2) exhibited a 1.3 to 2.5-fold increase in GSH, γ-GCSr, and GSTμ/GSTπ ($P < 0.05$) vs CHLA-122 or SK-N-BE(1). Thus, elevated GSH (reversible by BSO) and elevated mRNA expression of γ-GCSr/γ-GCSc and GSTμ/GSTπ were associated with drug resistance. These data further support GSH-depletion by BSO as a strategy to overcome alkylating agent resistance in neuroblastoma.

R-13

THALIDOMIDE, A TUMOR NECROSIS FACTOR-α INHIBITOR, AMELIORATED THE DOSE-LIMITING TOXICITY OF IRINOTECAN IN RATS

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CPT-11 is a topoisomerase I inhibitor used to treat colorectal cancer, but myelosuppression and diarrhea are its major dose-limiting toxicities. This study aimed to investigate whether thalidomide, a tumor necrosis factor-α inhibitor, modulated the toxicities of CPT-11 in rats. Rats were treated with CPT-11 alone at 60 mg/kg (i.v.) for 4 consecutive days, or in combination with thalidomide (100 mg/kg, i.p.) for 8 consecutive days starting one day before the first CPT-11 injection. Blood cell counts and the incidence of acute and delayed-onset diarrhea were monitored. Treatment of CPT-11 for 4 days caused serious diarrhea and marked decreases in neutrophil and lymphocyte number. Co-administered thalidomide significantly ameliorated these toxicities. A single-dose kinetic study in the rat showed that concomitant thalidomide significantly decreased the area under the plasma concentration-time curve (AUC) of SN-38 (the active metabolite) and increased the AUC of CPT-11. In contrast, co-administered CPT-11 did no significantly alter the pharmacokinetic parameters of thalidomide. Pharmacokinetic interaction appeared to provide partial explanation for the protective effect of thalidomide and the studies on the role of pharmacodynamic component is undergoing.

R-14

PHARMACOKINETICAL CHANGES OF OFLOXACIN IN HEPATIC FIBROSIS RATS

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Objective: Probe into the changes of drug-metabolizing function of liver and small intestine, further investigate the pharmacokinetical changes of ofloxacin and potential mechanism in hepatic fibrosis.

Methods: Activities of drug-metabolizing enzymes of liver and small intestine were measured, spectrofluorimetric determination were used to monitor the concentration of ofloxacin in plasma of rats after intravenous injection and oral administration, pharmacokinetical parameters and absolute bioavailability were computed.

Results: In hepatic fibrosis the activities of phase I enzymes in liver – 7-ethoxyresorufindeethylase (CYP1A), aniline hydroxylase (CYP2E1), erythromycin N-demethylase (CYP3A) and glutathione S-transferase (GST) reach the 68%, 56%, 81% and 59% of the control. Meanwhile the activities of phase II enzymes – uridine diphosphateglucuronate transferase (UDPGT), α-, π- GST of small intestinal mucosal epithelial cells decreased 15%, 36% and 57% respectively, however, the activities of CYP3A, CYP1A1 and CYP2E1 enhanced 2.2-, 0.6- and 0.3-times respectively, in comparison with control group. The pharmacokinetics research discovered that the concentration-time curves of ofloxacin fitted to two-compartment open model after intravenous injection, in hepatic fibrosis the area under the curve(AUC) and half-time of distribution($T_{1/2\alpha}$) increased 12.4% and 137.8%, whereas, the rate constant of distribution(K_{12} and K_{21}), apparent volum of distribution(VI) and clearance(CL) decreased 68.7%, 53.6%, 8.2% and 12.5% respectively as compared with control group. Otherwise, the concentration-time curves fitted to one-compartment open model after oral administrate ofloxacin, the half-time of absorbing($T_{1/2(K01)}$), half-time of eliminating($T_{1/2(K10)}$) and peak time(T_{max}) enhanced 50.4%, 41.5% and 38.2% but the AUC and peak concentration(C_{max}) reduced 14.7% and 24.1% when the liver fibrosis group was compared with the control. The absolute bioavailability of hepatic fibrosis group came to 75.9% of the control.

Conclusion: In liver fibrosis the activities of phase I and II enzymes in liver were distinctly decreased, at the same time in small intestinal mucosal epithelial cells phase II conjugations decreased but phase I oxidations increased. The absorbing, distribution and eliminating of ofloxacin were slower, the absolute bioavailability and C_{max} were reduced in status hepatic fibrosis.

Key words: hepatic fibrosis; pharmacokinetics; absolute bioavailability; phase I and phase II enzymes; liver; small intestine

R-15

DETERMINATION OF TRIBUTYRIN AND ITS METABOLITE, BUTYRATE IN WISTAR RAT PLASMA SAMPLES BY GAS CHROMATOGRAPHY - MASS SPECTROMETRY

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A gas chromatographic (GC) method with mass spectrometric (MS) detection was developed for the determination of tributyrin and its metabolite, butyrate in rat plasma. Following precipitation of protein with acetonitrile, the analytes were separated on a DB-5ms capillary column with helium as carrier gas. Phenylmethyl sulfonyl fluoride (PMSF), an inhibitor for serine proteases, papain and acetylcholinesterase was required to inhibit the activity of enzyme(s) responsible for the hydrolysis of tributyrin in blood samples. The enzyme inhibitor in 5 mM was added immediately into the blood samples after collection to prevent the hydrolysis. The linearity for tributyrin and butyrate was within the concentration range of 0.1-2.0 μM and 1-20 μM, respectively. The coefficients of variation for intra-day and inter-day assays for tributyrin were all <10%; whereas the coefficients of variation for intra- and inter-day assays for butyrate were <10%, except for the low concentration of 1 μM, it was <20%. The accuracy for all concentration determinations ranged from 96.0 to 110.0%. The limit of quantification (LoQ) was 0.1 μM for tributyrin and 1.0 μM for butyrate. The present method was an improvement over the previous gas chromatography with flame ionization detection method (GC-FID) for tributyrin due to lack of sensitivity of the latter method.

R-16

STRUCTURAL RELATIONSHIP IN THE MECHANISM EFFECTED ON CYP450

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Objective: As one of the mechanisms for drug interactions is by making a formation of Metabolic Intermediate Complex (MIC) which is complex of CYP and drug metabolites. It is said that those inhibitors must have the secondary and tertiary amines. However there is another report stating that primary amine also form such complex. Fluoxetine (secondary amine) and fluvoxamine (primary amine) from SSRI group, known to inhibit the CYP activities, were selected to investigate differences in enzyme inhibition.

Method: Incubate theophylline in human liver microsome added media. Of the three theophylline metabolites, 1-methylxanthine (1-MX) was closely examined because of its importance as a 1A2, 2D6 metabolite. Fluoxetine or fluvoxamine was added to media together with or 1 hour before theophylline is added. Theophylline metabolites were identified via high performance liquid chromatography (HPLC).

Result Discussion: With the pre-administration of fluoxetine the product of theophylline metabolites decreased, while simultaneous administration increased the yields of metabolites. It is estimated that pre-administration caused the MIC formation before theophylline was metabolized. On the other hand, pre-administration and simultaneous administration of fluvoxamine decreased theophylline metabolism, so that MIC was not formed.

Conclusion: It is suggested that CYP inhibitors which have the secondary amines in their structures can form metabolic intermediate complex with CYP enzymes, but not the primary amines.

R-17

EVALUATION OF GENETIC CONTRIBUTION TO VARIABILITY IN CYP3a-MEDIATED DRUG DISPOSITION

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The Repeated Drug Application (RDA) method has been recently proposed as an alternative to twin studies for measuring the contribution of heredity in drug response. We evaluated the genetic contribution to variability in CYP3A activity, by applying the RDA method and using "clean" data from bioequivalence studies. Five CYP3A substrates were selected: diltiazem, nifedipine, nimodipine, sibutramine and zopiclone. Each drug was administered orally twice (using bioequivalent formulations) to healthy subject with sample size ranging from 12 to 40. Apparent oral clearance (CL/F) and terminal elimination half-life ($t_{1/2}$) for each substrate were determined. The genetic factor (r_{GC}) to disposition of each CYP3A substrate based on CL/F and $t_{1/2}$ were estimated using the formula $(\delta_{inter} - \delta_{intra})/\delta_{inter}$, where inter- ($\delta_{inter}$) and intra-subject ($\delta_{intra}$) variances were obtained from analysis of variance (ANOVA). The point estimate of rGC for CL/F of diltiazem, nifedipine, nimodipine, sibutramine and zopiclone, ranged from 0.74 to 0.96, and for $t_{1/2}$ r_{GC} ranged from 0.63 to 0.81. Our analyses suggest that considerable genetic factors contributed to the variability in CYP3A activity and CYP3A-mediated drug disposition.

R-18

SIMULTANEOUS LIQUID CHROMATOGRAPHIC DETERMINATION OF TIZANIDINE AND ROFECOXIB IN FORMULATION

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A reverse phase high performance liquid chromatographic method to determine tizanidine and rofecoxib in combination is proposed and applied to the pharmaceuticals. This method allows the determination of 0.1 to 0.5 μg/ml of tizanidine and 1.2 to 6.0 μg/ml of rofecoxib, alongwith 10 μg/ml of nimesulide (internal standard), in a mobile phase consisting of 1% v/v triethylamine (pH adjusted to 2.5 using dilute orthophosphoric acid) : acetonitrile in the ratio 55 : 45 % v/v. Detection wavelength of 303nm and flow rate of 0.8ml/min were fixed for the study. The limit of detection for tizanidine and rofecoxib were found to be 10 ng and 1 ng respectively. The limit of quantification for tizanidine and rofecoxib were found to be 80 ng and 12 ng respectively. The amount of drug present in the tablet and the recovery studies were also carried out. The %RSD of recovery studies for tizanidine and rofecoxib were found to be 0.0673 and 0.0146 respectively. The method is validated for accuracy, precision, ruggedness and robustness.

R-19

A PROSPECTIVE POPULATION PHARMACOKINETIC STUDY OF TACROLIMUS IN ASIAN LIVER TRANSPLANT PATINETS

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Objectives: A population pharmacokinetic model of tacrolimus in an Asian population with whole blood drug concentration data was developed to compare the variability of the pharmacokinetic parameters, and to search for the main patient characteristics that explain the variability in the pharmacokinetic parameters.

Materials and Methods: Concentrations of tacrolimus in whole blood were determined by an electrospray high-performance liquid chromatography tandem mass spectrometric assay. 213 whole blood tacrolimus concentrations were used for building a nonlinear mixed-effects (NONMEM) population model to describe the disposition of tacrolimus in whole blood. Covariates including demographic characteristics, biological markers of liver and renal functions, and haematological parameter were investigated.

Results: A one-compartment model was used to describe the whole blood concentration-time data of tacrolimus after oral administration. The population estimates of the first-order absorption rate constant (k_a), apparent whole blood clearance (CL_b/F) and volume of distribution (V_b/F) were 2.08 hr^{-1}, 14.1 L/hr and 217 L, respectively. Weight and liver function influenced CL_b/F, while height and haematocrit influenced V_b/F.

Conclusions: A whole blood population model of tacrolimus in Asian adult and paediatric liver transplant patients was developed using prospective data in a clinical setting. It has identified and quantified sources of interindividual variability in CL_b/F and V_b/F of tacrolimus in Asian liver transplant patients.

R-20

STUDY ON DETERMINATION OF NIACIN IN PLASMA AND ABSORPTION IN RAT BY RP-HPLC WITH ION PAIR REAGENT

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Objective: To determine the concentration of niacin in rat plasma and investigate its absorption in rats following bred with niacin of feed additives.

Methods: The rats were divided into 2 groups in a randomized way: the control group and the niacin group.8 rats in each group were killed at 1d, 3d, 7d, 14d, 21d and 28d for collected plasma. Plasma samples were processed by liquid-liquid extraction and a reverse phase ion pair chromatography was developed for the determination of niacin in rat plasma.

Results: Assay linearity was obtained in the of 0.22~42.6μg·mL^{-1} (r=0.9999). The recovery of niacin from rat plasma was 96.9%. The inter-day and intra-day relative standard deviations (RSD) for 0.44μg·mL^{-1} were 3.95 % and 6.23 %, respectively. The absorption of niacin was rise over 8μg·mL^{-1} at 1d, the concentration of niacin was about 20μg·mL^{-1} in 3d~14d, and the concentration is similar to the 1d level after 21d in niacin groups.

Conclusion: The method described in this report was high sensitive and selectivity for accurate determination of the plasma concentration of niacin in rat. The absorption of niacin was very good in rats supplementing niacin. The plasma concentration of niacin in rat was maintained highly for a long time.

Key words: niacin; absorption; reverse phase ion pair chromatography; ion-pair reagent

R-21

THE ANTIMALARIAL AND ANTILEISHMANIAL ACTIVITY OF FERROCENYL CHALCONES

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A series of ferrocenyl chalcones was synthesized to investigate their antimalarial and antileishmanial activity. The antimalarial activity of ferrocenyl chalcones was determined by measuring their inhibition of [H^3] hypoxanthine uptake into a chloroquine resistant strain *P. falciparum* (K1). The antileishmanial activity of the compounds was tested against *L. donovani* promastigotes and amastigotes by the Mauël assay. MTT assay on KB-31 and MDCK cell lines was also carried out to evaluate the toxicity of the compounds. More than 1/3rd of the compounds showed antimalarial activity with IC_{50} less than 20 μM. 8 out of 45 compounds also demonstrated antileishmanial activity against promastigote with IC_{50} below 10 μM, but have limited activity against amastigotes. In the MTT assay, ferrocenyl chalcones showed little toxicity to KB-31 and MDCK cell lines. 1-Ferrocenyl-3-(4-nitorphenyl)-2-propen-1-one is a promising compound that has good antiplasmodial (IC_{50} 12.6 μM) and antileishmanial (IC_{50} amastigotes 31 μM) activities, and low toxicity against macrophages (IC_{50} 112 μM) , KB-31 and MDCK cells.

R-22

TRANSPORT PROPERTIES OF ANGIOTENSIN PEPTIDES

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Objectives: To investigate the influence of physicochemical properties on the transport properties of des-Asp-Angiotensin I (DAAI) and its potential break down products (Ang III, Ang IV) across the Caco-2 monolayer.

Materials & Methods: The transport of the peptides was investigated by reported methods at different concentrations, temperatures and in the presence of various inhibitors. Hydrophobicity, hydrogen bonding, size, volume parameters were determined by experimental and *in silico* methods. Solution conformation was determined by circular dichroism and 2D-^{1}HNMR methods.

Results: DAAI was transported by a passive diffusion route while Ang III, Ang IV were transported by an energy-requiring/carrier-mediated pathway. The hydrophobic character of DAAI favors its transport by passive diffusion but its random solution conformation, high hydrogen bonding potential suggests that it is not optimized for this process.

Conclusions: DAAI is reasonably stable to enzymatic hydrolysis and is not a substrate of the efflux protein in the Caco-2 monolayer. These factors enhance its therapeutic potential as a drug against cardiovascular pathologies. Peptidomimetic design to introduce conformational restraint or a β-turn should be attempted to improve the permeability of DAAI across the monolayer and hence, its pharmacokinetic profile.

R-23

DEVELOPMENT OF CATIONIC DNA VACCINE MICROPARTICLES FOR PULMONARY DRUG DELIVERY

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Cationic microspheres were developed to adsorb DNA on their surface. DNA adsorbed microspheres have the potential to promote the immune responses of the antigen presenting cells (APC`s) and to enhance the transfection properties of the delivery system through the complex formed between cationic polymer and pDNA - polyplexes. The polyplexes were based on polymeric microparticles prepared with PLGA with different cationic polymers in the surface: PEI 25000, PEI2000, LPEI, PLL, DMA and TMC.

The physicochemical properties of the delivery systems were studied in terms of their size; morphology; zeta potential; DNA loading by fluorimetry. DNA binding to microspheres was estimated by an indirect method and finally the effect of DNA adsorption on agglomeration analysed through the measurement of the particle size. TMA and PEI cationic polymers in concentration of 0.1% afford DNA loading ranging from 1.3-2.3 μgDNA/ mg microparticles, which has been reported to be high enough to achieve immunization.

R-24

QUANTITATION OF FERULIC ACID IN DERMATOLOGICAL PREPARATIONS BY HPLC

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Ferulic acid, an ubiquitous plant constituent, possesses a powerful antioxidant potential and an ultraviolet absorption characteristic. With a photo-protective activity, ferulic acid is used as whitening and sun screening agent in dermatological applications. To control the quality of these preparations, a validated analysis method is needed. In this study, a simple and sensitive HPLC method was modified from others for use in the determination of ferulic acid in dermatological preparations. The mobile phase composed of acetonitrile, deionized water and phosphoric acid at a volume ratio of 25:76:0.5 with a pH of 3. The detection wavelength was 330 nms. A peak of ferulic acid could be observed at approximately 7 mins (6.8-7.4 mins). The limit of detection was 28.5 ng/ml and that of quantitation being 71.2 ng/ml. The concentration range that illustrated linear correlation (r^2 of 0.9999) was ranging from 0.07 to 110 μg/ml. Intraday and interday observations indicated good validation with a percentage of coefficient of variations of less than 5. Dermatological preparations were extracted with methanol, and separated by centrifugation. The supernatant were diluted with the HPLC mobile phase and used for injection. The recovery of the extraction was approximately 100%. The method is rapid, easily reproduced, selective and sensitive. The modification made possible to increase the pH and decrease the amount of the acid of the mobile phase used. The application to determine ferulic acid in dermatological preparations showed good separation with little or no substantial interference from other inactive ingredients.

R-25

CURCUMIN CONTENT DETERMINATION IN TURMERIC OIL LOTION

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Curcumin, one of the turmeric constituents found in rhizome of the plant *Curcuma longa*, family Zingiberaceae, has been traditionally used as a skin care ingredient in various Asian countries. Currently, 2 forms of turmeric raw materials oil and powder, are commercially available for incorporate in skin preparations. Turmeric oil is easy to handle when formulating as a cream or a lotion. This study aims at using turmeric oil as a source of curcumin in skin lotion preparations and quantifying the content of curcumin when turmeric oil was the added to the preparations. The content of curcumin in the formulation prepared could be used to qualify and assure the products. Freshly prepared skin lotions that incorporated turmeric oil were subjected to an HPLC analysis of curcumin. A reverse-phase HPLC was used; the system of which being, as follows: stationary phase, HIQ Sil C_{18}; a 4.6 x 150 mm column contained 5 μm with a column guard; a pH controlled mobile phase consisted in methanol : water : glacial acetic acid at the volume ratio of = 41 : 23 : 36 : 1; a flow rate of 1.0 ml/min; wavelength of 420 nms. A major peak of curcumin was observed at 6.87 mins and a minor peak at 5.84 mins. Intra-day and inter-day validations performed showed good acceptance for determinations of curcumin from preparations. 10% of turmeric oil was used in a lotion using triethanolamine stearate as the emulsifier and its pH was determined at 8.03 (SD 0.25, n = 3). By adding 10% the turmeric oil into the lotion base prior to assay, the content of curcumin was found to be 0.01% w/w. Comparisons of lotion ingredients suggested some incompatibility with curcumin.

R-26

AN HPLC METHOD DEVELOPED FOR APPLYING IN QUALITY CONTROL OF *ANDROGRAPHIS PANICULATA* PRODUCTS

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Andrographolide is the main active constituent in *Andrographis paniculata*. This plant is used as the folk remedy medicine in many Asian countries to treat gastrointestinal tract and upper respiratory infections. The quality control of *A.paniculata* products is important to ensure the consistency and effectiveness of its activities. Four *A.paniculata* products commercially in Thailand were used in this study. The criterias set up for quality control in this study were assay of andrographolide content, the uniformity of dosage unit and dissolution testing. A Hewlett-Packard LC-1100 gradient liquid chromatography instrument equipped with autosampler system and a photodiode array detector were used for andrographolide determination. The analysis was performed on a Hypersil ODS column (5 μm, 250x4 mm). A good resolution of andrographolide from other component was achieved in the conditions of acetonitrile:10mM phosphate buffer pH 2.0 (50:50, v/v), flow rate of 1ml/min and the optimum detection wavelength at 230 nm. The medium used in dissolution testing were water, 0.1 N hydrochloric acid solution and phosphate buffer solution pH 6.8. The absolute recovery of andrographolide in this validated method ranged between 95.5% and 102.6%. The inter-day coefficient of variation was 0.3% to 1.9% and intra-day coefficient of variation was 0.4% to 1.4%. This HPLC method for determination of andrographolide in *A.paniculata* product is sensitive, reliable and accurate which could be applied for the quality control of these *A.paniculata* products. The percent of andrographolide content in dry powder of these *A.paniculata* products ranged between 1.44 % and 2.67% (%RSD 0.98 to 7.74). The uniformity of dosage unit in thirty capsules could be calculated in the term of the amount of andrographolide per one capsule unit which ranged between 4.73 mg to 9.34 mg (%RSD 5.95 to 13.73). From dissolution testing, the amount of andrographolide dissolved in 60 min were 3.00 mg to 7.77 mg (%RSD 7.60 to 11.83) in water, 0.40 mg to 1.15 mg (%RSD 5.16 to 16.72) in 0.1 N hydrochloric acid solution and 1.03 mg to 7.28 mg (%RSD 4.94 to 19.71) in phosphate buffer solution pH 6.8.

Key words: andrographolide, *Andrographis paniculata*, quality control and HPLC

R-27

PROTECTIVE EFFECT OF *INDIGOFERA APALATHOIDES* AGAINST CCl_4 - INDUCED HEPATIC DAMAGE IN RATS

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The alcoholic extract of stem of *Indigofera aspalathoides* was evaluated for its antihepatotoxic activity against CCl_4 -induced hepatic damage in rats. The activity was evaluated by using biochemical parameters, such as serum glutamate pyruvate transaminase, serum glutamate oxaloacetate transaminase, alkaline phosphatase, total bilirubin and gama glutamate transpeptidase. The histopathological changes of liver sample were compared with respective control. The extract showed remarkable hepatoprotective effect.

R-28

THE SKIN PERMEATION STUDY OF HALOPERIDOL AND (r)-(-)-CARVONE

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Objectives: To examine potential relationship between the skin permeation profile of a drug haloperidol and an enhancer (r)-(-)-carvone

Materials & Methods: Haloperidol solutions (3mg/ml) with and without (r)-(-)-carvone were prepared with pure propylene glycol. The concentration of (r)-(-)-carvone is 50mg/ml. Flow-though diffusion cells and human epidermis were used for the in vitro permeation study. The concentrations of haloperidol and (r)-(-)-carvone were determined by a reversed phase HPLC method with a diode array detector at 254nm and 240nm, respectively. Parameters were estimated with a nonlinear regression method.

Results[a]: Compared with the control, (r)-(-)-carvone increased the steady-state permeation of haloperidol by more than 3 times while the increase of lag time not significant. The permeation profile of the enhancer and the drug are similar with respect to their lag time and permeability coefficient. The flux of (r)-(-)-carvone, however, are 19 times that of the haloperidol in the same solution.

	Lag time(h)	Permeability coefficient (cm/h) x 10^4	Flux(μg/mc^2/h)
Control	18.06 ± 1.35	1.18 ± 0.204	0.355 ± 0.061
Haloperidol	34.56 ± 9.49	3.86 ± 0.726[b]	1.158 ± 0.218[b]
(r)-(-)-carvone	22.48 ± 8.32	4.40 ± 0.220	21.98 ± 1.102

[a] Mean ± SD(n = 3)

[b] One-way ANOVA Tukey's method with control (P<0.05)

Conclusions: (r)-(-)-carvone significantly increased the permeation of the hydrophobic drug haloperidol. The amount of the enhancer passing through skin is much higher than the drug due to its higher concentration gradient although they share similar permeation profiles.

R-29

SKIN PERMEATION OF HALOPERIDOL IN TWO ORGANOGELS

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Objective: To study the performance of two SMGA organogels for the transdermal delivery of an antipsychotic drug, haloperidol.

Methods: The organogel was prepared with the gelator, GP-1; the solvent, propylene glycol (PG) or isostearyl alcohol (ISA); a permeation enhancer and the drug, haloperidol (3mg/ml) by heating the mixture to 120ºC and then cooling down to room temperature. Flow-through type diffusion cells and human epidermis were used for the *in vitro* permeation study. Sampling of the receptor solution is at every 6 hours during the whole 48-hour experiment. Drug concentrations were determined by a reversed phase HPLC method.

Results: Both PG and ISA yielded stable thermoreversible organogels, which delivered haloperidol through the skin at rates of $1.51 \times 10^{-3} \pm 9.79 \times 10^{-4}$ (cm/h) and $4.71 \times 10^{-4} \pm 6.6 \times 10^{-5}$ (cm/h) respectively. Though PG gel increased the permeability coefficient compared with the ISA gel but it is not significant ($n = 4$, $p<0.05$). The permeation lag time of the PG gel, which is 73.52 ± 9.79 h, increased significantly compared to the lag time of ISA gel, 9.45 ± 0.64 h ($n = 4$, $p<0.05$).

Conclusions: PG and ISA in the organogel yielded similar drug permeation coefficient. The permeation lag time, however, is significantly prolonged by PG. The ISA gel is preferred for transdermal delivery of haloperidol over PG gel because the lag time was shorter and there was less variability of the permeability coefficient.

R-30

SUBCHRONIC TOXICITY OF PLANT EXTRACT OF *APOROSA LINDLEYANA* ON RATS

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Toxicological study was performed on albino rats with alcoholic extract of root of *Aporosa lindleyana* and rats were orally administered 100, 200 and 300 mg/kg of extract once daily for 28 days. Symptoms were observed mainly with 300 mg/kg and no mortality was observed. The effect of alcoholic extract of *A. lindleyana* on certain biochemical, haemotological parameters and histology of rats were studied after 28 days of exposure. The results suggest that alcoholic extract of *A. lindleyana* did not produce any toxicity at the doses tested.

R-31

SILMULTANEOUS DETERMINAITON OF ENALAPRIL AND ITS ACTIVE METABOLITE ENALAPRILAT IN HUMAN PLASMA BY LC-MS METHOD: APPLICATION TO CLINICAL PHARMACOKINETIC STUDY

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The existing published analytical methods for enalapril and enalaprilat are inadequate for clinical pharmacokinetic studies due to lack of sensitivity or inefficient sample preparation. We developed an improved LC-MS method which allowed simultaneous determination of enalapril and enalaprilat in human plasma suitable for general pharmacokinetic studies. The assay involved solid phase extraction with the analytes separated and determined using reversed-phase HPLC coupled with mass spectrometry (operated in the positive ion multiple-reaction monitoring mode). The total run time was 4.0 min for each sample. The method was linear over 1-200 ng/ml, with the limit of quantification of 1 ng/ml. The intra-day coefficients of variation (CVs) were 0.4-9.0% and 2.4-9.5% for enalapril and enalaprilat respectively; whereas the inter-day CVs were 3.7-7.6% and 5.1-9.9% for enalapril and enalaprilat respectively. The accuracy ranged from 87.8 to 110.4% for enalapril and 91.9 to 109.6% for enalaprilat. This assay method is relatively convenient and has short turnover time and good sensitivity. The method has also been successfully applied to a clinical pharmacokinetic study of enalapril in healthy subjects.

R-32

VARIATION IN CONTENT OF FLAVONOIDS THAT CAUSE DRUG INTERACTION: ANALYSIS OF GRAPEFRUIT JUICE PRODUCTS

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The amount of flavonoids and furanocoumarins ingested is an important factor in determining the overall grapefruit juice-drug interaction. The aim of the present study was to determine the content of naringin, naringenin and bergapten in different brands of grapefruit juice (GFJ) products sold in California, USA. Twenty commercial products of GFJ were randomly sampled (N = 3 each) from grocery stores in California. The concentrations of naringin, naringenin and bergapten in GFJ were assayed by HPLC methods. Naringin was found to be the most abundant flavonoid in GFJ products, followed by naringenin and bergapten. There was a 6-fold variation in the content of naringin ranging from 104 mg/L (Tropicana ruby red) to 628 mg/L (Ralph's white frozen concentrate). The average contents of naringin in ruby red (174 ± 66 mg/L) and pink (279 ± 123 mg/L) GFJ products were significantly lower than white (481 ± 94 mg/L). Content of naringenin was also varied from brand to brand and ranged from 3.9 mg/L (Von's white frozen concentrate) to 31.2 mg/L (Tree Sweet Pink). Bergapten content was very low in GFJ products ranging from 0 (not detectable) to 1.3 mg/L. There were no significant differences in naringenin and bergapten contents among ruby red, pink and white GFJ products.

R-33

EFFECT OF *LEUCAENA LEUCOCEPHALA* L SEMEN EXTRACT ON BLOOD SUGAR LEVELS, REGENERATION OF PANCREATIC ISLETS AND SERUM LIPIDS IN STREPTOZOTOCIN DIABETIC RATS

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Diabetes mellitus is a syndrome characterized by chronic hyperglycaemia and disturbance of carbohydrate, fat, and protein metabolism associated with absolute or relative deficiencies in insulin secretion and or insulin action. One component in management of the diabetes especially for the Non-Insulin Dependent Diabetes (NIDDM) is oral hypoglycaemic agents. In Indonesia, traditional medicines are fairly popular among the people at large. One of the alternatives of oral hypoglycemic agents in Indonesia is a medicinal pl *National University of Singapore, 18 Science Drive 4, Singapore 117543*ant called lamtoro (*Leucaena leucocephala* L). Aqueous extract of *Leucaena leucocephala* L semen was administered orally and the effect of different doses of the extract on blood glucose, regeneration of pancreatic islets, serum lipids in streptozotocin-induced diabetic rats were studied. Chlorpropamide was used as standard reference drug. *Leucaena leucocephala* L semen extract, at doses of 0.25 g/kg, 0.5 g/kg, 1 g/kg body weight for 14 days supressed the elevated blood glucose, lipids levels and the number of pancreatic islets per unit area was also significantly increased ($p<0.05$). It is proposed that the extract of *Leucaena leucocephala* L semen acts as hypoglycaemic agent by a selective regeneration of beta-cells of streptozotocin-damaged pancreas and that its presence can protect the beta-cells against the necrotic effect of subsequently administered streptozotocin.

Key words: diabetes mellitus, islet of langerhans, rats, *Leucaena leucocephala* L, lipids, Streptozotocin, rats.

R-34

COMPARISON OF THE CHARACTERISTICS OF RANITIDINE HYDROCHLORIDE EFFERVESCENT GRANULES MADE BY DRY AND WET GRANULATION METHODS

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Objectives: Dry and wet methods can be applied for granulation. It is said that the final use of prepared granules as tablets or granules dictates the preparation method. At the present study the formulation of effervescent granules of Ranitidine hydrochloride was performed by use of Citric acid, Tartaric acid and Sodium bicarbonate as effervescent base of formulation using dry and wet methods and compared in respect to characteristics like clarity, PH, taste compressibility and other properties.

Materials & Methods: Ranitidine hydrochloride (AARTI DRUGS LTD, India), Citric acid, Tartaric acid, Sodium bicarbonate, Ethyl alcohol, Sorbitol, Sodium saccharin and Polyvinyl pyrolidone all from Merck company was used.
To find the best formulation of each of these compounds, tertiary diagram was applied. Sixty-six different mixtures obtained from diagram was prepared and compared in characteristics like clarity, PH, taste and other physical properties. The best mixtures was selected and granulated with wet and dry granulation methods.

Results & Conclusions: Results showed that granules made with wet method had better characteristics in respect to uniformity of particle size of granules, its time of effervescency and especially in compressibility. It was concluded that it is better to use wet method for granulation if final aim is to produce tablets of the granules. Otherwise if the granules will be used as such and there is no need for compression, dry method can be used because of the advantages of this method in respect to low cost of production course, no need to use organic solvents and feasibility in industrial scale production.

R-35

HERBAL-DRUG INTERACTION: *IN-VITRO* EFFECT OF SPIRULINA ON RAT LIVER METABOLISM

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Spirulina are blue-green algae rich in vitamins, minerals, antioxidants and other nutrients and has been used as a food supplement for more than 20 years. Animal studies have shown that spirulina to be an effective immunomodulator; has therapeutic effects on hyperlipidemia and obesity and has antioxidant and anticancer activities. The objectives of this study are to study the *in-vitro* effect of spirulina on the hepatic metabolism of a model drug, aminopyrine, in rat liver and also to determine the influences of age, gender and disease (diabetes) on the *in-vitro* effect of the studied spirulina. Isolated hepatocytes from normal and streptozotocin-induced diabetic rats (male and female; young, adult and old) were prepared by using the collagenase perfusion technique. Aminopyrine metabolism is mainly metabolized in the liver by aminopyrine N-demethylase. Aminopyrine-N-demethylase activity was determined by measuring the quantity of formaldehyde according to the colorimetric method of Nash (1953). Our results showed that spirulina significantly decreased hepatic aminopyrine metabolism in old male normal rats at 45 ng/ml - 4.5 mg/ml concentrations. Spirulina increased aminopyrine metabolism at high concentrations (45 mg/ml) in other normal and diabetic rat groups. In conclusion, spirulina is capable of decreasing aminopyrine metabolism in rat liver and the effect seen is age-, gender- and disease-dependent.

R-36

EFFECT OF PARTICLE SIZE OF SODIUM ALGINATE ON DRUG RELEASE FROM SODIUM ALGINATE MATRICES

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Preliminary studies performed using 14 commercial grades of sodium alginate differing in their particle sizes, viscosities and chemical compositions showed the dominant influence of particle size on drug release from sodium alginate matrices. Viscosity was found not to significantly influence drug release. Hence, further investigations into particle size effect were necessary. The comminution of sodium alginate particles were investigated using Manucol LB with a median particle size of 164 μm. Cryogenic milling was carried out using an impact pulverizer mill with a 0.3 mm mesh (Goblin, Nara, Japan) at temperatures of about -60°C. Four different milling speeds were used and milling was performed in duplicates for each milling speed. The particle size distribution of the milled and unmilled particles was determined by laser diffractometry (Coulter LS 230, USA) and the median particle size obtained from the results.

It was found that cryogenic milling reduced the median particle size of sodium alginate in a speed-dependent manner; milling speeds of 7500, 10000, 12500 and 15000 rpm produced particles with median sizes of 88, 60, 44 and 41 μm, respectively. The extent of particle size reduction increased linearly with milling speed up to 12500 rpm, beyond which the particle size leveled off. Dissolution studies of matrices containing each milled fraction showed differences in release and these were affected by the alginate particle sizes. It was concluded that particle size of sodium alginate played a significant role in modulating drug release.

R-37

IMPACT OF POVIDONE AND COPOLYVIDONE ON THE COMPACTIBILITY OF PARACETAMOL AND THE PROPERTIES OF RESULTANT ROLLER COMPACTS AND TABLETS

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The impact of povidone and copolyvidone, as binders, on the flowability and compactibility of paracetamol powder and the properties of resultant roller compacts and tablets were investigated. Povidone or copolyvidone was mixed with paracetamol in various concentrations (5, 10 and 15% w/w). Hausner ratios and Kawakita constants of the paracetamol powder and blends were determined before subjecting them to roller compaction at two different roller speeds. The roller compacts were comminuted and the size, size distribution and friablility of the granules obtained were evaluated. Granules with 5, 10 % w/w and without binder were compressed into tablets and the tablet hardness was evaluated. The compactibility of the paracetamol powder was found to increase with the addition of the binder. Generally, powder flow was improved with the addition of the binder except at 15% w/w. Both powder flow and cohesiveness affected the formation of roller compacts when a higher roller speed was employed. The influence of binder concentration was more apparent when a lower roller speed was used. Higher yields of roller compacts and finer granules with wider size distribution were obtained with higher binder concentrations used. Povidone and copolyvidone exerted varying impact on granule friability. The tablets compressed from granules with binder were harder than those without binder. Harder tablets were produced with increasing copolyvidone concentration whereas the effect of povidone was less marked. In conclusion, povidone and copolyvidone affected paracetamol powder compactibility, roller compaction and tablet properties to different extents despite similarity in their molecular weights.

R-38

NOVEL THERMO-SENSITIVE POLYMER MICELLE AS A CARRIER FOR DRUG CONTROLLED RELEASE

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A novel amphiphilic graft polyphosphazene (PNIPAm-g-PPP) comprising NIPAm oligomers and glycine ethyl side groups (1:5.25 molar ratio of PNIPAm to glycine ethyl) was synthesized by co-substitute reaction. IR, NMR and elemental analyses were used to characterize the chemical structure of PNIPAm-g-PPP. And turbidimetry test indicated that PNIPAm-g-PPP had a lower critical solution temperature (LCST) near 30ºC. Dynamic light scattering and transmission electron microscopy measurements of PNIPAm-g-PPP aqueous solutions revealed that the thermo-sensitive change from polymeric micelles to nanoparticles occurred as the temperature increased over LCST. Encapsulation of a model drug, pyrene, was also found when the concentration of the polymer reached its CMC. These results suggest the potential application of PNIPAm-g-PPP as a carrier for drug controlled release.

Keywords: polymeric micelles; poly(N-isopropylacrylamide); polyphosphazenes; thermo-sensitivity

R-39

GEA-NUS: TRAINING FUTURE LEADERS FOR PHARMACEUTICAL PRODUCT AND PROCESS DEVELOPMENT

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GEA-NUS Pharmaceutical Processing Research Laboratory was established in April 1997 as an initiative for research and development in pharmaceutical formulation and processing technology. It aims to create and transfer innovative formulation sciences and advanced technology from the academia to the pharmaceutical and allied industries. In addition, GEA-NUS also provides specialised manpower training. Currently, there is a shortage of trained manpower for industrial R & D in the area of pharmaceutical technology, notably in drug delivery systems and process technology. The wide range of pharmaceutical processing and analytical equipment in GEA-NUS enables students to have "hands-on" experience for acquiring practical skills essential for undertaking R & D and manufacturing. Areas of research and training include i) particle technology (material characterisation and particle development); ii) pharmaceutical processes (melt pelletisation, spheronisation, spray drying and coating, fluid bed granulation and coating, microencapsulation and tabletting); iii) drug delivery systems (oral, buccal, transdermal and aerosol delivery) and iv) preparation of herbal medicines using modern technology (extraction, concentration and final product development).

R-40

NOVEL ANTIDIABETIC INSULIN-SENSITIZER

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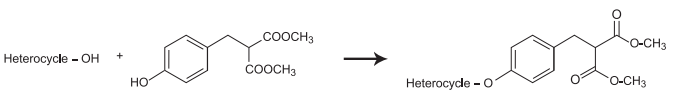
Type 2 diabetes is a life-threatening disease that features metabolic disorder. Insulin resistance and the relative absence of insulin secretion developed from insulin resistance, are the predominant underlying factors in Type 2 diabetes. Early therapeutic agents for Type 2 diabetes were some insulin-released stimulators and α-glucosidase inhibitors. The first availability of thiazolidinedione insulin-sensitizer was in 1997. However, their hepatic toxicity of thiazolidinediones has transferred the study emphasis of insulin-sensitizer to the development of non-thiazolidinedione compounds.

In order to search more potent and low toxicity of insulin-sensitizers, several aspects of work have been accomplished:

1. Forty-seven 1,3-dicarboxyl derivatives were designed and synthesized. Compounds were screened for insulin-sensitizing activity in 3T3-L1 cells. The results suggested that one of compounds showed a similar activity with control compound rosiglitazone



2. Twenty-three new α-nitrogen substituted phenylpropionic acid derivatives were designed and synthesized, in which ten S-configuration compounds were screened for insulin-sensitizing activity. One of the synthesized compounds showed satisfactory insulin-sensitizing activity and higher PPARγ activating potency than control compound rosiglitazone.
3. Twenty-two benzopyran derivatives were designed and synthesized, and twenty of them were reported first-time. In which compound **69** exhibited higher PPARγ-activating potency than control compound rosiglitazone.

R-41

SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL ACTIVITY OF 3-METHOXY-4-HYDROXYBENZALDEHYDE 4-(P-CHLOROPHENYL) THIOSEMICARBAZONE AND ITS METAL(II) COMPLEXES

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Thiosemicarbazones have extensive biological activity. The synthesis, characterization and the antimicrobial activity of these compounds have received considerable attention. It has been found that many thiosemmicarbazones have significant antimicrobial activity. Because some transition metals play a role in a vast number of widely differing biological process, it is possible to improve the antimicrobial activity of some thiosemicarbazones by forming their complexes with some metal ions. Thus, 3-methoxy-4-hydroxybenzadehyde 4-(p-chlorophenyl)thiosemicarbazone (MCTS-H)and four of its new transition metal(II)complexes M(MCTS-H)Cl_2 (M=Cu, Cd) or M' $(MCTS)_2$ (M' =Ni, Zn) have been prepared and characterized by elemental analyses, molar conductance, IR, ^1H NMR and electronic spectral data. The antimicrobial activity of the ligand (MCTS-H) and its four complexes were tested *in vitro*. The smallest lethal concentrations are listed in Table 1 and 2. From the results it may be seen that the ligand exhibits no activity but its four complexes exhibit significant activity against the four fungi. Also, it has been observed that the Ni$(MCTS)_2$ complex is highly active against *Aspergillus niger, Penicillium chrysogenum* and *Verticillium dahliae kleb*. In addition, we can see that the ligand exhibits almost no inhibitory effect on bacteria and the complexes exhibit inhibitory activity only in high concentrations. In fact, there is no report on an inhibitory effect of this kind of ligands and their metal complexes against bacteria, except Chough found that some N(4)-substituted salicyladehyde thiosemicarbazones and their Cu (II) and Co (II) complexes exhibited inhibitory effects against *Staphylococcus aureus* and *E. Coli*. By comparing Chough's experimental results with ours, the o-hydroxyl group on the aromatic ring may play an important part in the antibacterial activity for this kind of compounds.

Table 1. Antifungal Activity of MCTS-H and its Complexes (μg/mL)

Compound	Aspergillus niger	Penicillium chrysogenum	Verticillium dahliae kleb	Fusarium vasinfectum Atk
MCTS-H	>1000	>1000	>1000	>1000
Cu (MCTS-H) Cl_2	>1000	125-250	150-200	450-500
Cd (MCTS-H) Cl_2	50-75	300-350	100-150	300-350
Ni $(MCTS)_2$	50-75	50-75	< 50	150-200
Zn $(MCTS)_2$	300-350	350-400	250-300	1000-500

Table 2. Antifungal Activity of MCTS-H and its Complexes (μg/mL)

Compound	Bacillus Subtilis	Staphylococcus aureus	Escherichia coli
MCTS-H	>1000	500-1000	>1000
Cu (MCTS-H)Cl_2	500-1000	500-1000	500-1000
Cd (MCTS-H)Cl_2	300-350	500-1000	400-450
Ni$(MCTS)_2$	350-400	>1000	>1000
Zn$(MCTS)_2$	500-1000	300-350	>1000

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DEVELOP THE ORAL LIQUID OF "TIAN YE SHUNG QI"

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Objective: prepare the oral liquid of "Tian Ye Shuang Qi" and establish the standard of its quantity.

Method: Adopt the chemistry appraisal to carry on the qualitative analysis of the main compositions; Adopt the "TLC" method to research all kinds of compositions and to make sure the standard of its quantity.

Result: It is available to apply above method to carry on the qualitative analysis and to establish the standard of its quantity between sample and standard sample.

Conclusion: the oral liquid of "Tian Ye Shuang Qi" and the standard of its quantity is match the provision of pharmacopoeia£ The "TLC" method can conduct the qualitative analysis acurative and quickly to all kinds of the oral liquid of compositions£ So the method can be used as the standard of quantity.

Keyword: the oral liquid of "Tian Ye Shuang Qi"; TLC qualitative analysis; the standard of quantity

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ABBREVIATED PRESCRIBING INFORMATION
Nexium IV (esomeprazole)
See local Prescribing Information for full details, as Prescribing Information may vary from country to country. Presentation: Each vial contains esomeprazole sodium 42.5 mg, equivalent to esomeprazole 40 mg. **Indications:** Nexium is indicated for gastroesophageal reflux disease in patients with oesophagitis and/or severe symptoms of reflux as an alternative to oral therapy in patients when oral intake is not appropriate. **Dosage:** Patients who cannot take oral medication may be treated parenterally with 20-40 mg once daily. Patients with reflux oesophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily. Usually the iv treatment duration is short and transfer to oral treatment should be made as soon as possible. *Injection:*40 mg dose -The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes. 20 mg dose - Half of the reconstituted solution should be given as an intravenous injection over a period of approximately 3 minutes. *Infusion:*40 mg dose - The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. 20 mg dose - Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes. Nexium should not be used in children since no data is available. Dose adjustment is not required in patients with impaired renal function or mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20 mg Nexium should not be exceeded. Dose adjustment is not required in the elderly. Any unused solution should be discarded. **Contraindications:** Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other excipients of this medicinal product. **Warnings and Precautions:** In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Nexium may alleviate symptoms and delay diagnosis. **Pregnancy and lactation:** Caution should be exercised when prescribing Nexium to pregnant women. Nexium should not be used during breast-feeding. **Undesirable Effects:** The following adverse drug reactions have been identified or suspected in the clinical trials programme. Common: nausea/vomiting, diarrhoea, constipation, abdominal pain, flatulence and headache. Uncommonly the following were reported or suspected: dermatitis, pruritus, urticaria, dizziness, blurred vision and dry mouth. Rarely, Stevens Johnson syndrome, erythema multiforme, myalgia and hypersensitivity reactions e.g. angioedema, anaphylactic reaction, increased liver enzymes. **Interactions:** Due to the decreased intragastric acidity, the absorption of ketoconazole and itraconazole can decrease during esomeprazole treatment. Esomeprazole inhibits CYP2C19 so when Nexium is combined with diazepam, citalopram, imipramine, clomipramine and phenytoin the plasma concentrations of these drugs may be increased and a dose reduction could be needed. Concomitant administration of esomeprazole resulted in a 45% decrease in clearance of diazepam. Concomitant administration of esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. The plasma concentrations of phenytoin should be monitored when treatment with esomeprazole is introduced or withdrawn. In healthy volunteers, combined therapy with esomeprazole and cisapride resulted in a 32% increase in AUC and a 31% prolongation of elimination half-life but no significant increase in peak plasma levels of cisapride. A few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment with esomeprazole and warfarin. Monitoring is recommended when initiating and ending concomitant treatment. Date: May 2004
Based on PLT 01/JD/GI.000-039-784.3.0
References: 1. Wilder-Smith C, et al. Gut 2003; 52 C Suppl V12 A129 and associated poster. 2. Keating GM, et al. Drugs 2004; 64: 875-882.

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Xenical : 4-Year Landmark Study

XENDOS (XENical in the prevention of Diabetes in Obese Subjects)

L. Sjöström[1], J.S. Torgerson[1], J. Hauptman[2], M. Boldrin[2]

[1] Sahlgrenska University Hospital, Gothenburg, Sweden;
[2] F. Hoffmann-La Roche, Nutley, NJ, USA

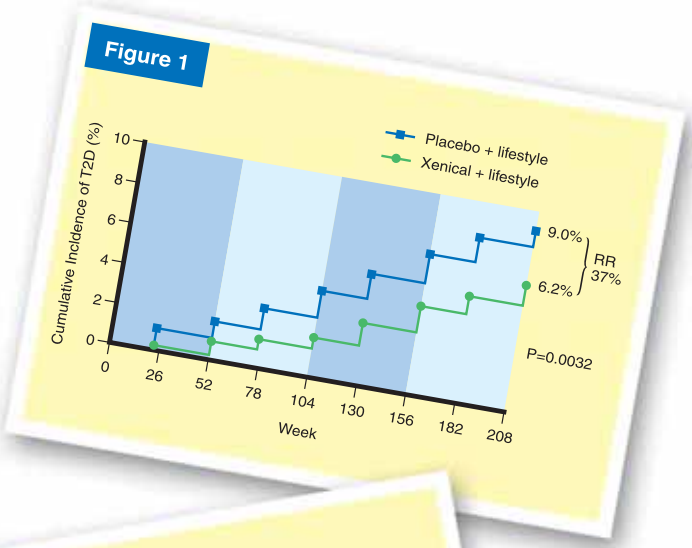
Figure 1. Cumulative incidence of type 2 diabetes (T2D) in all patients receiving Xenical 120 mg tid + lifestyle changes vs placebo tid + lifestyle changes. Based on 2-hour oral glucose tolerance test; RR = reduction in risk of progressing to type 2 diabetes vs placebo.

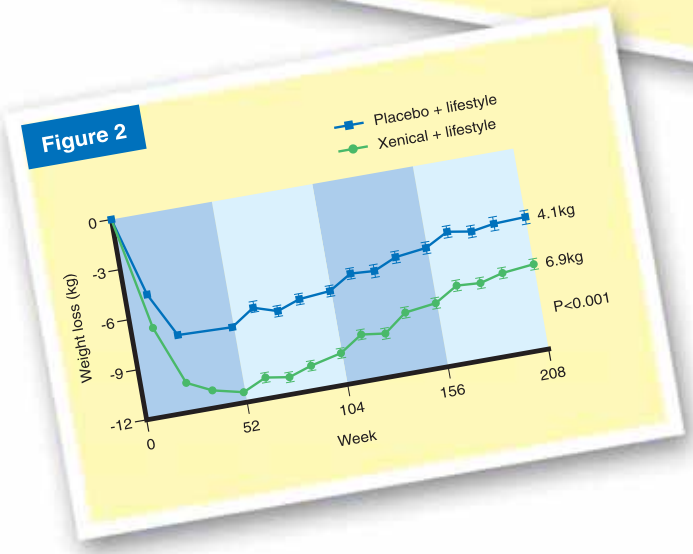
Figure 2. Weight loss in patients receiving Xenical 120 mg tid + lifestyle changes vs placebo tid + lifestyle changes.

* Source of information.
Torgerson J. S. et al. "XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study". Diabetes Care, 2004; 27 (1): 155-161.

The XENDOS Study which involved 3304 patients showed:

- After 4 years of treatment, **Xenical had significantly decreased the development of type 2 diabetes** compared with placebo. The hazard ratio showed a **37.3% decrease** with Xenical compared with placebo (Figure 1).
- Mean weight loss was significantly greater in Xenical than placebo patients at 1 year and remained significant at the end of the 4-year study (Figure 2). Approximately 50% more Xenical than placebo patients achieved weight loss of ≥ 5% and ≥ 10% at both 1 and 4 years.
- This study **confirms the efficacy and safety** of long-term Xenical treatment for **up to 4 years**.
- Xenical plus lifestyle changes results in **significant and sustained reductions in cardiovascular risk factors** such as blood pressure and lipid levels.





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