

# HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 15 NO 1 Jan - Jun 2008 ISSN 1727-2874

## *An Encounter with the Pioneers*

*Experience in the Drug Information Centre, the Oncology Outpatient Clinic and the Oncology Ward in the University of Illinois Medical Center at Chicago*

## *Common Oral Problems*

*Interactions Between Drugs and Herbal Supplements*

*Pharmacogenetics: one drug doesn't fit all (2 CE Units)*

*Exenatide: A Novel Therapy for Type 2 Diabetes*

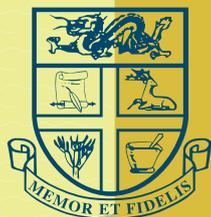
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*Hong Kong Pharmacy Conference 2008*

*Januvia/Cervarix/Isentress*



*The Pharmaceutical Society of Hong Kong  
The Practising Pharmacists Association of Hong Kong  
The Society of Hospital Pharmacists of Hong Kong*



The new issue of Hong Kong Pharmaceutical Journal (HKPJ) is finally released. I am in deep apology for the delay in the publication of the new issue. The main reason for such a long delay is that we are lacking resources in both manpower and finance. We have been struggling for a long time and with a lot of effort the problems are now resolved.

Regarding the manpower issue, more editorial members are recruited. Thanks to the Society of Hospital Pharmacists of Hong Kong. They have sent 3 experienced pharmacists to help HKPJ. Thanks to Johnny Wong, Bobby Pang and Ken Lee for their willingness to contribute to HKPJ. My thanks also goes to Ivy Chan, she rejoins HKPJ and becomes one of our Business Managers. With her more than 10 years experience in HKPJ, she will definitely bring a lot to HKPJ. Special thanks also goes to Mary Cheng from the Pharmaceutical Society of Hong Kong. With her organizing power, HKPJ will be nourished to become a reputable journal with good contents. We intend to recruit more editorial members. If you are interested in publication and is willing to help our HKPJ, please contact any one of our editorial board members. HKPJ belongs to the pharmacists and works for the pharmacists.

Regarding the financial issue, HKPJ need 5 to 6 advertisements to cover the printing, postage and packaging costs. In the current adverse situation in Hong Kong, HKPJ has difficulty in obtaining the funding for printing. It is fortunate that the three professional Societies/Associations agreed to set aside some funds to sponsor HKPJ. This will definitely ease off the situation.

HKPJ will be published quarterly a year (every 3 months). The focus of the journal is still on the practice of pharmacy. Pharmacy practice covers a wide range of pharmacy activities, among them and not being comprehensive, pharmaceutical care, social pharmacy, pharmacy education and policy, process and outcome research, health promotion and education, health informatics, pharmacoepidemiology, etc. With your active submission of articles to HKPJ, HKPJ can attract more readers and have a wider circulation such as extending our arm to Mainland China. All of us would like to see HKPJ to become a reputable journal in the future.

Managing Editor

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Pharmacy Practice	Drug & Therapeutics
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Comments on any aspects of the profession are also welcome as Letters to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

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For any queries on submission, please feel free to contact the Editorial Committee through mail or by the e-mail address.

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## An Encounter with the Pioneers

Regina Chan, Pharmacist, Tuen Mun Hospital

### A Bitter Start

**Journey** home is joyful, but leaving the beloved ones is painful. With the luggage in my arms and my daughter's angelic voice in my heart, I arrived at Chicago downtown in a Saturday afternoon. Chicago was almost my second hometown. Having lived in her neighbor city for many years, I was longing to come back. However, at this very moment, she became such a strange place to me while I was wandering in the streets of the "Magnificent Area". The mellow Mid-Fall afternoon was chilly despite of being sunny. The busy downtown was lonely despite of being crowded. I comforted myself that it was just because I was still in the Hong Kong state of mind and things would definitely get better when my training in the University of Illinois at Chicago ("UIC") had begun. Therefore, I looked forward to starting my attachment even more enthusiastically.

### New Roles of Pharmacist -- Days in the Neurosurgery Unit

During the first week, I was assigned to the neurosurgery units. I was very impressed by the newly developed pharmacist's roles in the clinical settings. The pharmacists were addressed as pharmacotherapists in the UIC because their roles were quite broadened from those of the traditional clinical pharmacists. Besides assuming the traditional clinical pharmacists' role, such as reviewing medical charts, monitoring therapeutic results, providing recommendations of drug selections, carrying out patient education and counseling, the pharmacotherapists were actively involved in prescribing processes.

The neurosurgery unit was comprised of two floors, the intensive care floor and the step-down floor. In the intensive care floor, the pharmacotherapists usually started their days by reviewing the overnight medical notes and charts at 6 a.m., half an hour before ward round.

They interviewed the patients or/and the nurses to ensure the regimens were appropriate. They might alternate the regimens if needed. The medication orders were entered into computer system called "Gemini" by the pharmacotherapists directly and then countersigned by the physicians before the medications were administrated to the patients. At about 630 a.m., the attending physician would lead discussions about patient's progress while everyone gathered around the X-ray/CT compute rand interpreting the radiograms of each patient. Then the whole group, which usually included the attending physician, medical residents, pharmacotherapists, pharmacy students, would march to the patient's bedside to evaluate the patient and perform necessary interventions. Because most patients admitted to the intensive care floor were suffered from cerebral ischemia or intracerebral hemorrhage and planning for intracranial arterial bypass surgery, appropriate blood pressure was vital to achieve successful treatment. Usually, after the attending physician discussed with the group on what the patient's blood pressure should be, the pharmacotherapists would select appropriate hypertensive agents and enter medication orders into the computer and then communicated such information to the nurses. Moreover, for the pre-operation patients, the pharmacotherapists would select the appropriate pre-operation medications such as antimicrobial agents for prophylaxis, anti-emetics for post-operation GI disturbances, analgesics for post-operational pain control, based on the patient's status, like hepatic and renal functions, concurrent chronic drugs, etc. This would enable the patient to receive the most effective treatment before and after surgery. After ward-round, which finished at about 830 a.m., the pharmacy team would be occupied with entering prescribing orders, both new and amended orders, decided in the round.

The step-down floor was quite different

from the intensive care floor, where everything was rush and intensive. In the step-down floor, the patients were relatively stable; some of them were ready to be discharged. After the ward-round in the intensive floor, I started to work in the step-down floor. Like their pharmacy students, two patients were assigned to me for management at a time. It was my responsibility to obtain their medical histories, assess their admission notes, evaluate their medication regimens, and monitor their progress. If a patient was planning to be discharged, I would also become responsible for preparing the pharmacy discharge summary, medications chart, calling community pharmacies for prescriptions to be filled and counseling patient about medication usage before he/she left the hospital. Although I was trained to perform these duties in the pharmacy school, it was still a bit challenging for me to pick up all these again, specially after having practised for ten years in Hong Kong, where similar clinical activities were quite minimal. I had to grasp this golden opportunity to refresh my professional knowledge and clinical skills.

### More than Professional - Oncology Out-patient Clinic and In-patient Services

I have been fascinated by hematology and oncology for years and to acquire the updated professional knowledge and skills in oncology was my primary objective of this attachment. The five-week hand-on experiences in oncology services of UIC not only enhanced my professional knowledge, but also enabled me to acquire an extra skill-set that often could not be taught -- empathy.

The out-patient oncology clinic was operated by a multidisciplinary term of oncologists, hematologists, an oncology-specialist pharmacist and the chief medical oncologist. Oncology residents were rotated on a monthly basis and were responsible for the care of patients

in both in-patient and out-patient. Because of the potentially serious toxicities of cytotoxics, the oncology services developed an effective system to ensure the safe use of these agents. After evaluating the patient and determining appropriate chemotherapy regimen, the oncologist would refer the patient to the oncology pharmacist for consultation regarding ancillary treatments, evaluating the current medications and possible dosage adjustment. When such a referral was received, the oncology pharmacist would review the patient's medical histories and health status and then complete a prescribed "Chemotherapy Order Form", which required information including the title of the protocol, the types of cancer for which regimen was indicated, the specific sequence of drugs, the dose per body surface (or area under curve), route of administration and infusion rate, compatible solutions, dosing schedules and the pre- and post- treatments, the pertinent laboratory reports and the clinical monitoring parameters, anticipated cycles, etc. Serving as a prescription for the chemotherapy, this "Form" would be kept with medical charts for subsequent cycles and further references. When the "Form" was completed, it would be checked and countersigned by an oncology fellow. Before the patient received the treatment, the oncology pharmacist would check the patient's lab results to ensure that the patient's condition was suitable to receive the previously agreed protocol and the dosage was appropriate. Then the dispensing pharmacist would check the completed order form again before the cytotoxics were reconstituted and dispensed. Finally, the oncology nurses would check the product before administration of the drug. Patient education about the chemotherapy was carried out by the oncology pharmacist while the drug was being administered. The oncology pharmacist and the nurses would monitor the patients periodically. Any

unusual signs and symptoms, Grade III or Grade IV side effects, together with interventions and recommendations made were recorded in the patient's profile by the oncology pharmacist.

I was much honored to have a chance to work with Dr. Sandra Cuellar to learn how to apply my knowledge and skills on oncology in the out-patient setting. Though started slowly, I learned how to complete the "Chemotherapy Order Form", how to monitor the toxicities of different cytotoxic agents, how to handle these toxicities, and finally how to use pre- and post-medications for various agents. To digest what I had learned, I reviewed the previously developed "Chemotherapy Order Forms" and patient records being kept in the out-patient clinic. I seized every chance to discuss with Dr. Cuellar when questions arose. By this process, I developed skills to complete the "Chemotherapy Order Forms" for different protocols, and gained knowledge of the most frequently encountered drug-related problems and toxicities.

In-patient oncology services were similar to those of out-patient, besides the chemotherapy was more intensive and the patient's conditions were more complicated. Rounding with the attending hematologist and the oncology-specialist pharmacist Dr. Rakesh Beri also enhanced my knowledge of hematological disorders. Since the patient load was low in the in-patient oncology unit, the oncology team had the luxury to discuss treatment details of each case before ward-round. I gained the most valuable experience of providing supportive cares to the post-chemotherapy patients, such as management of febrile neutropenia, severe mucositis and GI disturbance through those discussions. I had spent lots of time to memorize all the adverse drug reactions associated with cytotoxic agents. However, during this in-patient rotation, I found that the best way to learn them was by 'doing' and 'seeing'.

For example, when I observed the skin reactions associated with high dose cytarabine in a patient, I finally understood what 'skin freckling' was and would never forget such drug reaction.

When serving oncology patients, I realized that the already demanding role of a pharmacist is an amalgamation of pharmacology and human emotions. Dr. Cuellar and Dr. Beri, two distinguished oncology pharmacists showed me how a pharmacist would contribute to the care of cancer patients, especially those were overwhelmed by the pain of grief. The ways they interacted with the cancer patients demonstrated excellent examples on how to communicate with cancer patients, how to express our genuine concerns and how to alleviate the concerns of cancer patients.

### **A Sweet Ending**

Time flew and six weeks passed like a flash. The educational and yet enjoyable journey had come to an end. The fruit from this attachment was that my competency in oncology had been enhanced and my clinical knowledge had been enriched. However, I knew this greenish fruit had to be ripened by ample hard work. The inspiration of pharmacotherapists in UIC had showed me how to prepare myself to be an oncology pharmacist, and most importantly, how to treat my patients with care and love.

### **Acknowledge**

I would like to express my great gratitude to my department manager, Ms Pauline Chu for her ongoing professional and personal support. I would like to thank Dr. Alan Lau for organizing such a marvelous program, Mr. Winham Lok and the Chief Pharmacist's Office for their efforts on establishing this program; Dr. Sandra Cuellar and Dr. Rakesh Beri for their inspiring training.

*Miss Regina Chan* is a pharmacist working in Tuen Mun Hospital.

## **How Can I Receive A copy of the Hong Kong Pharmaceutical Journal Regularly?**

If you are a member of any one of the following societies, you will be on the HKPJ mailing list:

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# Experience in the Drug Information Centre, the Oncology Outpatient Clinic and the Oncology Ward in the University of Illinois Medical Center at Chicago

Leone Wong, Pharmacist, Princess Margaret Hospital



Figure 1. Flag of Chicago.



Figure 2. The entrance to the Drug Information Center

## Introduction

One week in the Drug Information Centre, three weeks in the Oncology Ward and two weeks in the Oncology Outpatient Clinic was my schedule. I did not like oncology in particular but after the trip, I started to gain interest in it. I can feel the uniqueness of helping cancer patients. Oncology is an area that involves many new treatments. You may come across new therapies every month. Pentostatin, Aprepitant, Avastin, Aranesp, Erbitux, Aloxi..... how many drug names that you may know? And we can foresee that there would be even more and more new drugs coming. Pharmacists had an important role in helping the rational use of new treatments and explaining the mechanism of action of new drugs to the patients. For more, chemotherapy is a class that may induce very extensive types of adverse drug reactions, regardless of whether it is used for the first time or for a long time. So, tackling the adverse drug reactions is another big issue for pharmacists. For cancer patients who had already been tortured by the disease itself, would it be cruel to let them suffer more by the adverse drug reactions that are manageable or avoidable?

In this article, I would focus on the training in the Drug Information Center since another colleague from Tuen Mun Hospital, Ms Regina Chan, would tell you more on oncology clinical attachment. In fact, I had learnt much from Regina who is a board certified oncology pharmacist in the United States. After a brief paragraph describing the Drug Information Center, it will follow by two examples of using the knowledge learnt in the Drug Information Center during my clinical attachment.

## Description of the Drug Information Center

Established in 1965, the UIC Drug Information Center is operated by clinical faculty from the College of Pharmacy who has advanced training and experience in clinical practice, literature evaluation and medical writing. I am so glad that I had the chance to learn in this unit for a week.

I am so impressed that this Drug Information Center employs six full time pharmacists and two part time pharmacists, assisted by one pharmacy practice and drug information specialty resident and six student assistants who work ten hours a week. You may wonder what kind of services they provide in order to accommodate so many pharmacists. I am curious too. Ms Mary Lynn Moody, clinical assistant professor, explained that the tasks are so extensive that they really need many staff to handle the jobs. The Drug Information Center offers a wide variety of services from consumer education to professional support, for example, developing continuing education materials for healthcare providers, providing drug information support to 400 hospitals, supporting the herbal line for patients and customers, drafting drug reviews for the University of Illinois Medical Center at Chicago in the process of formulary management, etc. I will elaborate further in the following paragraphs.

### a. Consumer Education

It offers a series of custom brochures and fact sheets organized around relevant consumer health topics and self

management of several disease states. It also runs a toll-free consumer hotline and "Ask the Pharmacist" website.

### b. Professional Support

Services include disease-state management reviews, therapeutic class reviews, individual drug monographs and pharmacoeconomic evaluations. This center gives a strong support to the University of Illinois Medical Center at Chicago in formulary management. Evidence based medicine is important for the formulary management especially in a country with private-run insurance scheme. It also brings its expertise to different parties in the form of workshop and seminars. Besides the healthcare professionals, commercial pharmaceutical companies, such as Baxter, Cigna, Owen, are also the parties to which they provide professional support. They also offer a one-year specialized residency program for those who pursue their career as a drug information pharmacy practitioner.

### c. E-commerce

They would assist in the information credibility and update for the electronic access in the commercial website. Consumers and the healthcare professionals can access to correct and timely drug and herbal information.

If you are interested to know more about the Drug Information Center, please click on the link.

<<http://www.uic.edu/pharmacy/services/di/index.html>>



Figure 3. Dr Sandra Cuellar, a phenomenal oncology pharmacist who works in the outpatient clinic.



Figure 4. An award for the devotion of caring patients by oncology outpatient pharmacy

**Example 1: Familiarize yourself with the features of each reference available**

After learning in the Drug Information Center, I spent two weeks in the oncology outpatient clinic. On one day, the oncology pharmacy practitioner discussed a case with us and asked if we could figure out a solution. She told us that a patient, who suffered from estrogen-dependent breast cancer, had named two herbal products and asked if she could take any of them for her libido which is very common side effect from the treatment of breast cancer. Our concern was whether the herbs would have estrogenic or steroidal characteristics that might affect the disease state. I remembered that I had come across quite a number of references on herbal products in the Drug Information Center. With the 1-week orientation in Drug Information Center, I could easily locate references on pharmacology of herbs, namely, Review of Natural Products, WHO monographs, PDR for Herbal Medicines, Natural Medicines: A Comprehensive Database, Complementary and Alternative Medicines. After looking up the references, we figured out that one of them was a good choice for the patient because of its local irritating effect on vagina, being free of estrogenic or steroidal activities. The patient was so thankful for our advice.

**Example 2: Search Strategy for researching a clinical question**



Figure 5. Left to right: Leone, Dr Christina Mactal Haaf, Dr Rakash Beri. My tutors in oncology ward.

I spent three weeks in the oncology ward and they had given me assignment on the cancer prevention trial: SELECT, Selenium and Vitamin E Chemoprevention Trial. My task was simply reviewing the articles and sharing the information with other pharmacy staff during the journal club. Before searching through the web-based Medline, I decided to look up some background information in tertiary references first and the book I choose was "Cancer: Principles and Practices of Oncology (DeVita)". Tertiary reference, then secondary one, followed by finally the primary one is the proper sequence of search strategy for researching a clinical question. This is a key step to avoid making careless mistakes in handling drug information enquiries. With the knowledge learnt in drug information center, the quality and the speed of extracting information had been improved.

**Conclusion**

When answering a drug information enquiry, the question should be researched systematically, from tertiary reference to primary ones. Secondly, we had to familiarize with the references available and identify the strength and weakness of each reference. Are the text referenced? How is the text indexed or organized? What type of information does it include? Finally, we should pay attention to develop our skill in literature evaluation.

Wouldn't you agree that the experience in handling drug information enquiry is valuable for daily tasks?

**Acknowledgement**

Thanks to Dr Alan Lau and his wife, Shirley for everything which ranges from driving me to the Chinese Christian Union Church every Sunday to caring me on a great variety of ways. I will never forget the dinner after his tiring 5-hour driving because they would like to farewell me on my last day in Chicago.



Figure 6. Having dinner in the Cheese Cake Factory with Dr Alan Lau, Shirley, their family and friends.

Thanks to Dr Andrew Donnelly and other associate directors, Dr Christina Mactal Haaf, Dr Rakash Beri, Ms Vanessa Caparros, Dr Sandra Cuellar, Dr Hashimoto, Dr Mary Lynn Moody, Ms Priscilla How, Ms Eunice Addy, Ms Regina Chan, Ms Kathy Mak, Mr Winham Lok, Ms Rosa Yao and my colleagues in the Princess Margaret Hospital. Special thanks also to Dr Rakash Beri for giving me lectures every day and Sandy for inspiring my interest in caring cancer patients.

Mr. Leone Wong can be contacted at wongkml@ha.org.hk. She is currently working at the Princess Margaret Hospital.



Figure 7. I had brought along some Western Ginseng from Hong Kong to remove "hot air"



Figure 8. Walking along Magnificent Mile, it made me think of Tsim Sha Tsui.



Figure 9. What kind of Chinese culture is this in the Field Museum of Chicago?

# Common Oral Problems

Yung, Maxwell

**Oral problems such as canker sores and sensitive teeth are commonly presented in the retail pharmacy. This article will review and provide recommendations for the prevention and management of these common problems in the mouth. Some commonly available commercial products available for these conditions will also be reviewed. Community pharmacists should be familiar with these conditions to provide their professional advice and referral if necessary.**

## I GENERAL ORAL HYGIENE

**Maintaining** a good oral hygiene is essential for prevention of many dental and oral infections. Oral bacteria in the dental cavities mix with the saliva and food debris to form a plaque attaching to the teeth. These bacteria produce acids in the plaque and corrode the teeth, creating a hole, or cavities, in the teeth. Once the enamel has been corroded, pain may occur as the dentine is exposed and irritated. Filling is necessary if a sizeable cavity has developed. Figure 1 provides some

<b>Figure 1. General recommendations for maintaining good oral hygiene</b>
• brush teeth at least twice daily
• drinking fluorinated water
• floss at least daily
• use fluoride toothpaste or mouthwash
• rinse the mouth after food
• avoid acidic/sugary drinks, candies
• regular dental visit (at least 2 times/yr)

general recommendations to maintain oral hygiene.

## II GUM DISEASES

Gum disease is caused primarily by oral bacteria, or secondarily by drugs (e.g. oral contraceptives) or other medical conditions (e.g. diseases affecting the immune system). The bacteria form a plaque and produce gum-irritating chemicals.

### i) Gingivitis

Gingivitis (inflammation of the gum) is a reversible early stage gum disease causing reddening, swelling and bleeding when brushed. Pain is not usually present.

### ii) Periodontitis

Periodontitis is a late stage gum

disease affecting more on the gums. It can spread to the periodontal ligament and bony socket. Teeth may become loose, fall out, and may eventually require removal (figure 2). Figure 3 lists some risk factors for the above gum diseases.

#### Counseling tips:

Patients should be advised to observe general dental hygiene. Chlorhexidine or fluoride mouthwash may be used. For periodontitis, dental visit should not be delayed.

## III OTHER DENTAL PROBLEMS

### i) Teeth Discoloration

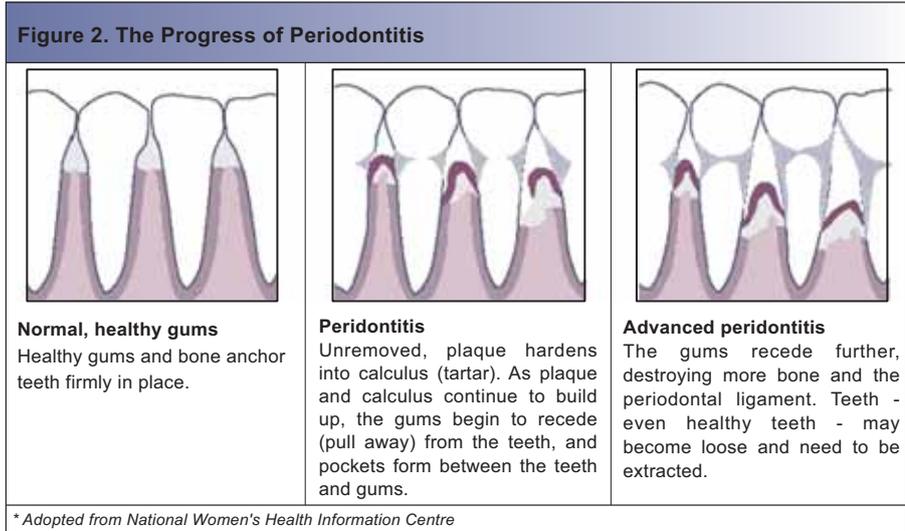
Teeth discoloration can be caused by staining, aging, or chemical damage to the teeth. Medications, coffee, tea or cigarettes can cause teeth staining. People who drink large amounts of caffeinated drinks can also experience similar staining. Table 1 provides a list of commonly available teeth whitening products over the counter.

### ii) Sensitive teeth

Sensitive teeth refer to a sudden pain or tingling sensation that is triggered by hot, cold, sweet or sour food or drinks. Pain from sensitive teeth is not always present; it can come and go away. Normally, the dentine is protected by the gum and enamel. When this protection is lost, either due to gum diseases or enamel erosion, dentine tubules allow heat, cold and other irritants to irritate the nerve and trigger pain.

#### Counseling tips:

Advise the patient to switch to a softer toothbrush and use a de-sensitizing toothpaste containing potassium nitrate or strontium chloride to block the



<b>Figure 3. Risk factors for gum diseases</b>	
• Smoking	• Use of oral contraceptives, antidepressants
• Poor nutrition	• Genetic predisposition
• Pregnancy	• Condition that affects the immune system
• Stress	

Table 1. Commonly available Teeth Whitening Products		
Product Name	Active Ingredients	Instructions for Use
Natural White 5 Minute Tooth Whitening System	Hydrogen Peroxide	Step 1: Apply a thin line of gel in the mouth-tray, leave on teeth for 5-15 minutes twice daily. Step 2: Use oral rinse solution to rinse the mouth, then rinse with water.
Colgate Simply White Advanced	Colgate 7 days Formula	After each brushing, apply the solution up and down to each teeth, do not rinse mouth
Crest White-strips Premium	Hydrogen Peroxide	For upper and lower teeth, apply one strip t twice daily for 7 days

Table 2. Examples of de-sensitizing toothpastes		
Product Name	Active ingredients	Instructions for Use
Sensodyne Fresh Mint/ Fresh Impact	Potassium Nitrate, Fluoride	Brush teeth twice daily.
Sensodyne Original	Strontium Chloride	

dentine tubules. Table 2 provides examples of some de-sensitizing toothpastes.

#### IV OTHER ORAL PROBLEMS

##### i) Halitosis

Halitosis refers to a bad smell in the breath. It can be short termed or chronic. It may indicate a tooth or gum disease, intestinal disorders or other serious disorder (e.g. diabetes, liver and kidney failure). The condition is usually

caused by oral bacteria that produce volatile sulfur compounds such as hydrogen sulfide, methyl mercaptan and dimethyl sulfide which gives the bad breath.

##### Counseling tips:

Oral hygiene is a must to prevent halitosis. Treat the underlying causes (e.g. periodontal disease) if applicable. Commercial mouthwashes may be recommended to improve the breath by masking the bad smell but can last for only several hours. Table 3 provides examples of some commonly available mouthwashes.

##### General Advice for mouthwash use:

- If relief is not obtained or if symptoms persist or spread, discontinue and see the doctor.
- Nausea, vomiting, headache and fever indicates severe infection and referral to doctor is necessary
- Mouthwash is not for use in children under 6 years old
- Do not swallow the mouthwash

##### ii) Dry Mouth

Dry mouth is caused by a reduced salivary production. It may cause pain, difficulties in chewing, swallowing, speaking, and increase the risk of gum disease and tooth decay. Causes for dry mouth may include salivary glands disease, medications (e.g. sedating antihistamine), other medical conditions (e.g. RA, Sjogren syndrome) or radiation to the neck or head.

##### Counseling tips:

Dry mouth can be relieved by sipping cool water, chewing sugar free gum, sucking ice or sugar free candies, avoiding smoking and caffeinated drinks which can dry out the mouth. Table 4 provides some examples of commercial products to help relieve dry mouth.

Table 3. Commercial mouthwashes for tooth decay, gum disease and halitosis			
Product Name	Active Ingredients	Dosage	Indication
Amosan Mouthwash Powder	Sodium Perborate Monohydrate, Sodium Bitartrate	One sachet in 30ml warm water QID, after meal and before bedtime for 30 secs	Gingivitis, Vincents infection, Denture infection, Minor oral infection
Bactidol	Hexetidine, Ethanol	15-30ml undiluted for 30 secs BD - TID	General oral hygiene, Sore throat, Tooth decay
Corsodyl	Chlorhexidine Gluconate	10ml undiluted for 1 min BD	General oral hygiene, Gingivitis, Recurrent oral ulceration, Thrush, Denture stomatitis
Colgate Plax Fresh	Triclosan, Methylvinylether/maleic Acid Co-polymer	15ml undiluted for 1 min BD	General oral hygiene, Anti-cavities
Gengigel	Hyaluronic Acid	10ml undiluted for 1-2 min after brushing teeth 3-4 times per day for 3-4 weeks	Gingivitis, Mouth and gum discomfort after tooth distraction or surgery
Listerine Teeth and Gum Defence	Menthol, Thymol, Methyl Salicylate, Eucalyptol, Benzoic acid, Sodium Fluoride	20 ml undiluted for 30 secs BD	Gingivitis, General oral hygiene, Tooth decay
Listerine Fresh Burst			
Listerine Original			
Listerine Cool Mint	Menthol, Thymol, Methyl Salicylate, Eucalyptol, Benzoic acid, Ethanol		
Listerine Tartar Control	Zinc Chloride, Menthol, Thymol, Methyl Salicylate, Eucalyptol, Benzoic acid, Ethanol		
Oral B Tooth and Gum Care	Cetylpyridium Chloride, Sodium Fluoride	15ml undiluted for 30secs BD	General oral hygiene, tooth decay
Oral B Gingivitis Mouth rinse	Chlorhexidine Gluconate		General oral hygiene, gum inflammation
Sensodyne Gentle Mouthwash	Sodium Fluoride, KCl, Triclosan	Half cap-full undiluted for 30secs BD	Gingivitis, anti-cavities

Table 4. Products for Dry Mouth		
Product Name	Active ingredients	Dosage
Biotene Mouthwash	Lysozyme, Lactoferrin, Glucose Oxidase, Lactoperoxidase	Use 15ml and swish mouth thoroughly for 30 seconds and spit out.
Biotene Toothpaste for Dry Mouth		Use in place of your regular toothpaste. Rinse toothbrush in water before applying. Brush for 2 minutes, including the tongue, and rinse lightly. For best results, use in the morning, after eating, and at bedtime.

### iii) Oral Thrush

Oral Thrush is a candida overgrowth in the mouth and throat. Symptoms include white, cottage cheese-like patches on the tongue or other oral surfaces. When scraped or rubbed, the patches may come off, leaving tissue underneath with a red and raw-looking appearance and bleeding may occur. For more severe thrush, the throat may be affected, causing pain and difficulty swallowing. Treatment includes Nystatin or Amphotericin lozenges, and Miconazole gel.

### iv) Canker Sores (Aphthous Ulcer)

Canker sore (aphthous ulcer) is a non-contagious painful ulcer in the mouth. They appear most often on the non-keratinized oral mucosa including the tongue, lips, buccal mucosa, and the soft palate. Preceding the ulcer, patients may experience prodromal symptoms

like burning or tingling of the mouth. It can be classified into minor, major and hepetiform ulcer according to the factors listed in Table 5. Table 6 lists examples of products that can be used for canker sores.

### v) Cold sore

Cold sore (Herpes Simplex Labialis) is a recurrent infection caused by Herpes Simplex Virus-I (HSV-I) (less commonly HSV-II) around the mouth and lips. Prodromal symptoms appear up to 24 hours before the visible sign noticed, including itching, tingling or burning sensation. Painful blisters appear once the prodromal phase passed. The skin around the blisters is often red and inflamed. The blisters can break up, weep with a clear fluid and ulcer, and then scarred. Healing may take 7 - 10 days. Treatment includes acyclovir cream and povidone-iodine paint. Examples of these products are provided in Table 7.

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**Table 5. Classification of Canker sore**

Types of Canker Sore	Number of Ulcers	Size of Ulcer (cm)	Time for remission (days)
Minor	1-5	<1	7-10
Major	1-10	>1	Up to 6 weeks
Hepetiform	10-100	1-3	7-10 days

**Table 6. Products for Canker Sore**

Product Name	Active Ingredient	Dosage	Precaution
Ad-Muc Ointment	Extr. Chamomillae fld., Myrrhae tinct., Ment. Pip. aetherol	Apply BD, after teeth brushing or after food; Dry the mucus from saliva before use, massage well in the affected area.	Continue to apply once daily for some time after disappearance of symptoms
Betadine Antiseptic Paint	PVP Iodine	Apply undiluted BD prn, allow to dry	Rinse the brush thoroughly after use
Bonjela	Choline Salicylate, Cetalkonium Chloride	Apply not more than once every 3 hrs	Not for infants < 4 months
Diffiam Mouth Gel	Benzydamine HCl, Cetylpyridium Chloride	Apply approx. 1cm of gel with a clean finger with gentle massage Q2-3h (Max: 12 times/day). Do not eat or drink for 15 min thereafter.	Treatment should not exceed 7 days without medical supervision. Avoid contact with eyes. Not for children < 6 years old.
Diffiam Anti-inflammatory Lozenge	Benzydamine HCl, Cetylpyridium Chloride	Suck 1 loz Q1-2h (Max: 12 loz daily)	Treatment should not exceed 7 days without medical supervision. Not for children < 6 years old.
Diffiam Lozenge (Mint)	Benzydamine HCl		
Diffiam-C Solution	Benzydamine HCl, Chlorhexidine Gluconate	Rinse 15ml undiluted Q1.5-3hr for 30secs	Treatment should not exceed 7 days without medical supervision. Not for children < 6 years old. Do not swallow solution.
Herpesan	Carbenoxolone	Apply QDS	-Not for children < 3yo
Medijel	Lignocaine, Aminacrine	Apply directly to painful area, Q20min prn	Treatment should not exceed 7 days without medical supervision.
Orased	Choline salicylate	Apply Q3h, before meal and at bedtime	Not for children < 4 months. Wipe surface free of mucus before application. Not for prolonged use in infants.
Solcoseryl	Solcoseryl, Polidocanol	Apply 3-5 times daily	

**Table 7. Products for Cold Sore**

Product Name	Active Ingredient	Dosage	Precaution
Zovirax Cream	Acyclovir	Apply 5 times/day (4 hr interval) for 5 days	Apply as soon as possible to lesion or impending lesion once symptoms start. If healing not occur, treatment can be extended to 10 days). Avoid contact with mucous membrane (oral cavity, eye, vagina)
Entir Cold Sore Cream			
Acyclovir Stada Cold Sore Cream			
Betadine Antiseptic Paint	PVP Iodine	Apply undiluted BD prn, allow to dry	Rinse the brush thoroughly after use

# Interactions Between Drugs and Herbal Supplements

Law, Jasmine

## I INTRODUCTION

**Natural** products and herbal supplements are widely available in the market nowadays. The so-called "slimming" and "detoxifying" products are also increasingly popular. They are claimed to contain ingredients that are "herbal" or derived from "natural sources". In addition, traditional Chinese medicines (TCM) are also taking up a large proportion in the health supplement market. Some health product companies may even add TCM into some vitamin and mineral supplements. Generally, people call them "health products" or "health supplements". More and more people rely on these products to keep themselves "fit" and "healthy".

Health product companies usually use "natural" and "no side effects" as gimmicks when they promote their products. Advertisements are deeply affecting customers' impression on health supplements. They think natural products are safer than "western" medicines.

In many occasions, it may be true that these health supplements do not cause harmful effects. However, many people have neglected the importance of potential drug interactions between these health supplements and the drugs they are taking. Community pharmacists are, therefore, playing a very important role in providing appropriate public education on the safety of these products. This article will focus on the drug and health product interactions. Health products include all herbal medicines, traditional Chinese medicines (TCM) or products that are derived from natural sources in this article.

## II MECHANISMS OF INTERACTIONS

Health products interact with drugs or other health products with similar mechanisms as drugs. It is based on the same pharmacokinetic and pharmacodynamic principles. First of all, some health products affect the absorption of drugs. Product with laxative effect is an example. For instance, herbs like Aloe vera, senna, Psyllium seed and Rhubarb contain hydroxyanthracene constituents which have laxative properties. They can reduce the intestinal transit time and hence affect the absorption of other food and drugs. These herbs are common

ingredients in "detoxifying" and "slimming" products. They are popular especially among Asian women who want to keep fit and improve their body shapes. They think that the laxative effect helps them remove the "toxic wastes" in their bodies. Besides, St. John's Wort (*Hypericum perforatum*), which is a herbal supplement for depression, may decrease the absorption of common P-glycoprotein substrates such as digoxin and cyclosporin by inducing P-glycoprotein which is a membrane-bound protein in the gut wall to reduce influx of these drugs<sup>1</sup>.

Actually, there is not much evidence to confirm that these herbs significantly affect the serum level of the concurrent drugs that patients are taking. However, until further larger trials to support that the use of these products do not significantly affect the serum level of other drugs are available, it is better to avoid taking any health supplements if patients are already taking concurrent drugs with narrow therapeutic index such as digoxin. Community pharmacists are responsible for educating their customers on the possibility of drug-herb interactions.

In addition, health supplements that affect the enzyme systems for drug metabolism may interact with the drugs that share the same enzyme systems for metabolism. In fact, there is growing evidence for this. Many studies that investigate these metabolic interactions involve St. John's Wort.

## III SOME CLASSIC EXAMPLES OF DRUG-HERB INTERACTIONS

### i) St. John's Wort



In Germany, St. John's Wort is commonly prescribed for different conditions involving depression and anxiety. In Hong Kong, it is a common over-the-counter herbal supplement for treating mild to moderate depression and relieving some anxiety symptoms. However, the safety and efficacy of St. John's Wort are not evaluated in the appropriately designed studies that the FDA requires for antidepressant drugs.

St. John's Wort contains naphthodianthrone components such as hypericin which are potent cytochrome P-450 isoenzymes 3A4, 2C9, 1A2 inducers. It can increase the metabolism of drugs that are metabolized by these isoenzymes and hence reduce their serum levels. For example, it reduces the serum level and thus the therapeutic activity of anticonvulsants such as carbamazepine and phenytoin, protease inhibitors such as indinavir, non-nucleoside reverse transcriptase inhibitors such as efavirenz, oral contraceptives, theophylline, cyclosporin and digoxin. Patients should avoid St. John's Wort when they are taking these drugs.

Besides pharmacokinetic interaction, health supplement may also interact with drugs through pharmacodynamic mechanisms. There is evidence which shows that St. John's Wort extract can inhibit serotonin, dopamine and noradrenaline reuptake in vitro<sup>2</sup>. Therefore, it may have additive effect with anti-depressant drugs. Increased serotonergic effects in patients taking St. John's Wort and selective serotonin reuptake inhibitors (SSRIs) like paroxetine and sertraline have been reported<sup>3</sup>. Since St. John's Wort may increase the serotonin level, it can potentially cause serotonin syndrome with SSRIs if used in high doses. Serotonin syndrome is dangerous and can be fatal. The symptoms include euphoria, drowsiness, restlessness, rapid muscle contraction and relaxation in the ankle causing abnormal movements of the foot, muscle twitching and rigidity, sweating, high body temperature, confusion or even loss of consciousness. Therefore, it is not recommended for patients who are already on anti-depressive drugs to take St. John's Wort although they may think that this herb can help them relieve depressive symptoms.

### ii) Coenzyme Q10

Moreover, there are more and more studies concerning the interactions between health products and anticoagulants such as warfarin. For example, coenzyme Q10 (ubiquinone or ubidecarenone), a health supplement for treating congestive heart failure and cardiovascular disorders and protecting gum and immune system, may interact with warfarin because it is structurally related to vitamin K which may decrease the effect of warfarin.

### iii) Danshen (丹参)



Several traditional Chinese medicines are found to have interactions with anticoagulants. Danshen (*Salvia miltiorrhiza*) is a traditional Chinese medicine. It is commonly used for treating atherosclerosis-related disorders such as cardiovascular and cerebrovascular diseases. It is also indicated for internal blood stagnation manifested as irregular menstruation, amenorrhea, abdominal pain or postpartum abdominal pain. It can inhibit platelet aggregation and interfere with extrinsic blood coagulation. It is antithrombin III-like and promotes fibrinolytic activity. It will increase the risk of bleeding with anticoagulants such as warfarin<sup>4</sup>. In another study, Danshen was found to potentiate anticoagulation in three patients stabilized on warfarin. The International normalized ratio (INR) was increased from around 2.0-3.0 to over 5.5 after taking danshen for 2-4 weeks<sup>5-6</sup>.

### iv) Dong Quai (当归)



Dong Quai (*Angelica sinensis*) is also a traditional Chinese medicine. It is indicated for stimulating central nervous system (CNS) and used as a mild energizer. It is also used for treating menopausal symptoms, menstrual cramping and irregular menses of women. Phytochemical analyses found that Dong Quai consists of natural coumarin derivatives such as sodium ferulate that inhibit cyclooxygenase

activity and platelet aggregation<sup>7</sup>. A case report suggested that Dong Quai had resulted in an increase in the INR in a woman who took warfarin concurrently. One animal study has also shown a pharmacodynamic interaction between Dong Quai and warfarin. Yet, the exact mechanism remains unknown<sup>8</sup>. Doctors and pharmacists should be aware of the potential interaction between warfarin and Dong Quai and advise patients to avoid using them together.

### v) Garlic



Garlic (*Allium sativum*) contains allicin and scordinin which are antioxidants. They can reduce low-density lipoprotein (LDL / so called "bad cholesterol") and increase high-density lipoprotein (HDL or so called "good cholesterol") and prevent hyperlipidemia, hypertension and cardiovascular diseases. It also boosts immunity to prevent cold and flu. Garlic is found to inhibit platelet aggregation in vitro. A few case reports have shown an increased hemorrhagic risk when warfarin and garlic are used concurrently<sup>9</sup>. Heavy use of garlic supplement was associated with one case of spontaneous spinal epidural hematoma and two cases of prolonged clotting time with increased post-operative bleeding. Garlic supplement should be stopped for at least 10-14 days before surgery<sup>9</sup>.

### vi) Ginger



Another herb, ginger, which is used as an antispasmodic and antiemetic agent, has also been shown to increase bleeding risk when used together with warfarin. However, the true risks of these interactions and effects are difficult to characterize because of limited evidence and studies currently<sup>9</sup>.

### vii) Ginkgo



Ginkgo (*Ginkgo biloba*) is another common herbal supplement which is found to interact with warfarin. Ginkgo contains flavanoid constituents. These substances improve blood circulation in brain and other tissues by directly dilating the micro-capillaries. Ginkgo also prevents platelet aggregation or clumping inside the arterial walls. This increases arterial wall strength and flexibility and also decreases the chance of atherosclerotic plaque formation. Since ginkgo improves oxygen supply to the brain, it enhances the brains' uptake and utilization of glucose. Therefore, it improves memory, alertness, headaches and symptoms of Alzheimer's disease. However, Ginkgo at a daily dose of 80-160 mg was associated with a few cases of hemorrhage. Although only one hemorrhage case actually involved concurrent warfarin and another involved aspirin, patients taking warfarin and aspirin should avoid Ginkgo supplement to avoid possible increased risk of hemorrhage<sup>8</sup>.

### viii) Fish oil

Besides herbs, fish oil is a very popular health supplement nowadays. Fish oil, an omega-3 polyunsaturated fatty acid, consists of eicosapentaenoic acid and docosahexaenoic acid. According to the American Heart Association (AHA), omega-3 fatty acids may have beneficial effects on the cardiovascular system such as decreased of cardiac arrhythmias, decreased risk of blood clot formation which leads to stroke or heart attack, decreased level of blood triglyceride (TG) and also lowered blood pressure<sup>10-12</sup>.

Fish oil may affect the platelet aggregation and/or vitamin K-dependent coagulation factors. It may also lower the thromboxane A2 supplies within the platelet and also decrease factor VII levels<sup>13</sup>. Therefore, it may increase the anticoagulation effect with warfarin. It has also been reported to increase the bleeding risk of warfarin, although the result is still controversial. A case report reveals a significant rise in INR after doubling the dose of concomitant fish oil in patients taking warfarin<sup>13</sup>.

Although the significance of the increased INR and bleeding risk needs to be confirmed in larger randomized and controlled trial, patient should be warned about the potential interaction between warfarin and fish oil. Pharmacists should be aware that a patient who wants to start fish oil supplement is most likely the one who is already taking warfarin or other anticoagulant or antiplatelet drugs. The reason is simple. Patients with atherosclerotic diseases probably also have dyslipidemia. They need to take anticoagulants or antiplatelets for the atherosclerotic diseases. It is understandable that these patients may sometimes want to find some health supplements that help them lower their blood cholesterol levels and improve the health of their cardiovascular systems. They are not aware of any potential interactions between fish oil and the drugs they are taking. Therefore, patients should better consult their doctors or pharmacists first when they want to start fish oil supplement.

#### IV TIPS TO PHARMACISTS

So, how should community pharmacists consult their customers on these health products? Here are the tips.

- Community pharmacists should consult more reliable and independent sources of information on natural products rather than just rely on literature provided by manufacturers of the health supplements. Always have a critical mind and make professional judgment when reading these materials.
- Be aware of the differences in regulatory control and labeling requirements between drugs and natural products. Do not forget the "Undesirable Medical Advertisements Ordinance" which contains regulations on the claims and wordings on promotion materials and advertisement of health products. Do not sell any products that violate the law.
- Be aware that natural products have variable qualities and potencies,

unidentified and inconsistent components, unproven efficacy, interactions and side effects. Recommend products from trustworthy manufacturers with high quality control standards. Herbal products are derived from plants. Pesticides, heavy metals and impurities may not be completely removed in the manufacturing process of the herbal supplement. A quality manufacturer should be able to produce a certificate that shows that the levels of these pesticides, heavy metals and impurities are within safety limits.

- The general public may have a common myth that separating the time of taking health products and drugs can solve all problems. This method is useful in some cases only but does not apply to all situations. For example, calcium supplements should be separated with antibiotics like tetracycline as calcium will bind to tetracycline and reduce its absorption. This is a simple chemical reaction. Yet, drugs and herbs or natural supplements do not always interact by simple mechanisms. Furthermore, for drugs with long half-lives, it is meaningless to separate the dosing time of health supplement and the drugs. A sufficient drug level retains in the body for the whole day. It can interact with the health supplement no matter when the patient takes it. Pharmacists must educate their patients on this important issue.
- Pharmacists should encourage the patients to tell their doctors or pharmacists before starting any health supplements including any TCM if they have underlying diseases or taking other concurrent medicines.
- So, next time when a customer comes to your pharmacy counter to ask for your advice on health products, ask them for more information. You will probably discover that many customers are unaware of the danger of drug-herb interactions. You are here to provide them with correct information on these health supplements and improve the safe use of them.

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**Table 1. Summary table of health product & drug interactions**

Health products	Possible drug interactions	Results of interactions
Aloe vera, senna, Psyllium seed and Rhubarb	Contain hydroxyanthracene constituents which have laxative properties	May reduce absorption of other food & drugs
St. John's Wort	Induce P-glycoprotein	May reduce absorption of some drugs
	Contains naphthodianthrone components such as hypericin which are potent cytochrome P-450 isoenzymes 3A4, 2C9, 1A2 inducers Inhibits serotonin, dopamine and noradrenaline reuptake	Increase metabolism of some drugs, reduce their serum levels Enhance effect of antidepressants
Coenzyme Q10	Structurally related to vitamin K	May reduce effect of warfarin
Danshen	Anti-thrombin III-like and promotes fibrinolytic activity	May increase bleeding with anticoagulants
Dong quai	Consists of natural coumarin derivatives that inhibit cyclooxygenase activity and platelet aggregation	
Ginkgo biloba	Prevents platelet aggregation or clumping inside the arterial walls	
Fish oil	Lowers the thromboxane A2 supplies within the platelet and also decrease factor VII levels	

## Pharmacogenetics: one drug doesn't fit all

Wong, Sammas



### INTRODUCTION

The response to drug therapy varies with individuals. With the same drug and dosage, some patients obtain the desired therapeutic effect while some may not or even experience adverse drug reactions (ADRs). A number of factors contribute to variable drug response, including gender, age, race, co-morbidities, drug-food /drug-drug / drug-disease interactions, and renal and hepatic function. However, these factors are not adequate to explain some of these unexpected ADRs. A meta-analysis conducted by Lazarou et al showed that among those hospitalised patients, the incidence of ADRs was 6.7% and of them, 0.32% was fatal.<sup>1</sup> The incidence rate had excluded errors in drug administration, overdose, drug abuse, therapeutic failure and non-compliance. ADRs had been ranked between the fourth and sixth leading cause of death in the United States.

### What is pharmacogenetics?

Pharmacologically speaking, the therapeutic effect of drugs is influenced by pharmacokinetics (PK) and

pharmacodynamics (PD). At molecular level, PK is influenced partly by metabolising enzymes and transporter proteins while PD is affected by various drug target receptor proteins. The genetic makeup determines the molecular structures of these proteins and hence variation in genes would affect the therapeutic effect of drugs. (see Figure 1)

Pharmacogenetics (PGx) is the study of inter-individual variations in deoxyribonucleic acids (DNA) sequence related to drug response. It focuses on the difference in drug response due to heredity and identifies genetic polymorphisms (see below) that lead to the altered therapeutic outcomes. Historically speaking, as early as in 510BC, Pythagoras had noticed ADRs in some individuals who took fava bean (which was due to haemolytic anaemia in people with glucose-6-phosphate deficiency). The idea that genes had bearings on drug response was proposed in 1950s, and the term "pharmacogenetics" was coined by Friedrich Vogel in Heidelberg, Germany.<sup>2</sup> PGx was further extended by biochemical studies in the 1970s and 80s when

genetic polymorphism influencing drug metabolism was discovered. During the past decade genes encoding drug targets and transporters were also sequentially identified.

### Genetic polymorphism

Genetic polymorphism refers to the variation in the structure of a gene or an allele (loci on gene) for which the frequency of variation is not less than 1%. The most common variation is single nucleotide polymorphism (SNP) in which one nucleotide base of a gene at a given location on a chromosome is altered in some way, resulting in formation of non-functional or supra-functional proteins. There are four nucleotide bases in human DNA, namely adenosine, guanine, thymine and cytosine. Since each person has a pair of each chromosome, he or she has two alleles for each gene, hence a person could be homozygous (two identical alleles) or heterozygous (two different alleles) for a particular inherited feature. The difference in genotypic inheritance leads to different phenotypes. As discussion of molecular science is beyond the scope of the present article, we will focus on the practical issues instead.

### PGx affecting drug metabolising enzymes (Typical examples: cytochrome(CY) P450s, NAT2, TPMT)

Drug metabolism is basically divided into phase I (functionalization reactions that produce chemically reactive groups on drugs); and phase II (conjugative reactions that give the inactive, excreted metabolites).

Genetic polymorphisms of drug metabolising enzymes lead to four different phenotypes in general: poor metabolizers (PMs), who bear only defective alleles and lack functional enzymes; intermediate metabolizers (IMs), who are heterozygous with one

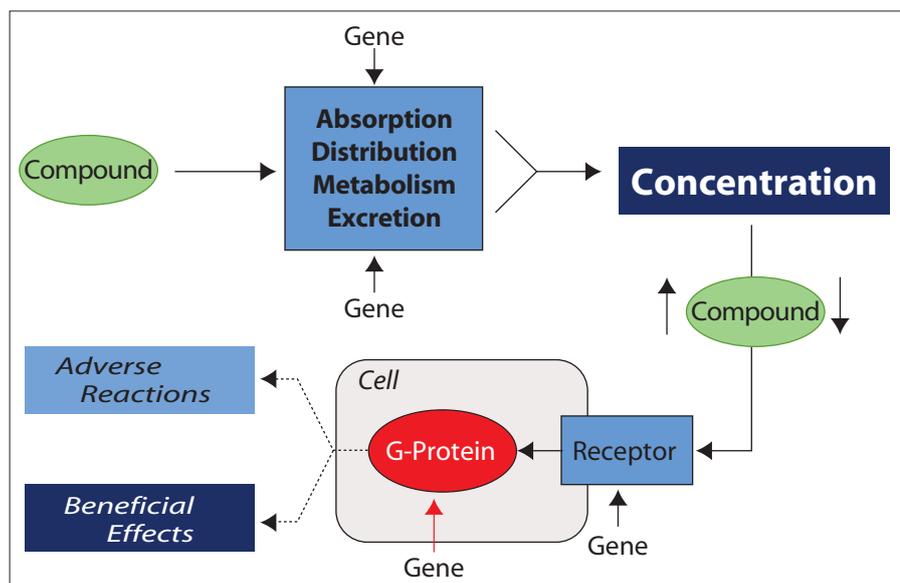


Figure 1. A schematic diagram showing the effects of genes on drug response.

defective allele or having two alleles with decreased activities; extensive metabolizers (EMs) or wild traits, who bear two functioning alleles; and ultra-rapid metabolizers (UMs), who may have duplicated or multiple functioning alleles.

The CYP450s family, an example of phase I drug metabolising enzyme, has been extensively studied in the field of PGx. It began with the discovery of the debrisoquine (sympathocolytic anti-hypertensive drug) and sparteine (anti-arrhythmic and oxytocic drug) polymorphisms of drug oxidation in 1970s. Some subjects who had participated in a PK study developed severe orthostatic hypotension after ingesting debrisoquine which was found to be due to deficient mono-oxygenase enzyme and later designated as CYP2D6 isoenzyme.<sup>3</sup> With the advance of molecular technology, other polymorphic forms of CYP450s enzymes were subsequently identified in the years that followed: notably the mephenytoin and phenytoin / warfarin polymorphisms due to mutations of CYP2C19 and CYP2C9 genes respectively. It is noteworthy that the frequencies and types of alleles vary among different population and ethnic groups; thus the prevalence of each phenotype would differ. For instance, PMs of CYP2D6 are more common in Caucasians (7%) than in Asians (1%) whereas PMs of CYP2C19 are more frequent in Asians (15-18%) than in Caucasians (2%).<sup>4,8</sup>

On the other hand, CYP3A4 is another isoenzyme that attracts researchers' interest since it is responsible for phase I metabolism of around 45% of existing drugs.<sup>5</sup> Allelic variant forms of this isoenzyme, however, had not been observed in both Caucasians and Orientals and therefore the clinical effects of its polymorphism are not yet concluded.

CYP450s polymorphisms are responsible for the development of a number of ADRs. Phillips et al estimated that 48% of drugs that had been cited in studies of ADRs were metabolised by CYP450s.<sup>6</sup> In particular, polymorphic isoenzymes (including CYP2D6, CYP2C9 and CYP2C19) account for over 40% of CYP450s mediated drug metabolisms.

N-acetyltransferase-2 (NAT2), and thiopurine S-methyltransferase (TPMT) are examples of phase II drug metabolising enzymes that exhibit polymorphisms. Genetic defect of NAT2 leads to two phenotypes: slow and fast acetylators. It was first observed after the advent of isoniazid (NAT2 substrate) for tuberculosis treatment in 1950s. Slow acetylators have a higher risk of experiencing drug toxicity due to reduced metabolism and are more common in Caucasians than in Chinese. For TPMT, it affects metabolism of thiopurine drugs such as mercaptopurine and azathioprine. In patients who are inherited with non-functional TPMT alleles, these drugs could potentially cause severe or even life-threatening haematopoietic toxicity. Fortunately clinical diagnostic tests are now available for detecting SNPs in human TPMT gene. This is done by determining the level of TPMT in red blood cells and the PMs could be managed with appropriate drug dosage reduction.

To date, a number of other human drug metabolising enzymes are well-known to demonstrate genetic variations that could affect an individual's response to drug. To facilitate understanding, Table 1 summarizes the polymorphisms of some selected examples which are clinically important.

It should be remembered that both UMs and PMs could suffer from ADRs depending on whether the drug toxicity originates from the drug or its metabolite. Some drugs could also induce or inhibit various CYP450s isoenzymes and influence drug metabolisms. However, only when the polymorphic enzymes account for a large proportion of the metabolism of the drug or when the therapeutic window of the drug is narrow will the risk of developing ADRs or treatment failure be attributed to PGx. Moreover, environmental factors including diets could also alter drug metabolism. Grapefruit juice, for example, is a typical inhibitor of intestinal CYP3A4 isoenzyme. Concomitant administration with substrate drugs such as cyclosporin and felodipine would result in a substantial increase in bioavailability of the drugs and produce ADRs and toxicities.

## **PGx affecting transporter proteins / receptor proteins**

**(Typical examples: p-glycoprotein, beta-receptors, Bradykinin receptor B2)**

Besides drug metabolizing enzymes, polymorphisms of genes encoding transporter proteins and drug target receptor proteins also influence drug responses. Perhaps the most famous discovery is the ABCB1 (ATP-binding-cassette sub-family B member 1) gene, also called MDR-1 (Multiple drug resistant -1) gene. ABCB1 controls the expression of ATP-driven drug efflux transporter pump: p-glycoprotein (PgP) in human. PgP distributes in various normal tissues as well as in tumour cells. In general, PgP protects the body from xenobiotics (foreign objects including drugs). It is expressed at intestines, blood-brain-barrier (BBB), liver, kidney and reproductive organs. Since a number of drugs are transported through PgP, their PK and PD would be affected by inhibitors and inducers of PgP as well as the extent of its expression (see Table 2). Depending on their locations, PgP reduces uptake and promotes excretion of xenobiotics. For instance, the accumulation of various drugs (cyclosporin, vinblastine, digoxin, loperamide and dexamethasone) in brain is limited by the PgP at the BBB.<sup>9</sup>

One of the SNPs of PgP occurs at the gene position C3435T (cytosine replaced by thymine). Individuals who are homozygous for the mutation at this position (TT) have significantly lower PgP level in the small intestine than people with (CC) or (CT) genotypes. Consequently, individuals who carry the TT genotype have enhanced oral bioavailability of digoxin as reflected by a higher  $C_{max}$ . In people with TT polymorphism, the plasma concentrations of fexofenadine and nelfinavir were found to be consistently lower compared to those who expressed the CT or CC genotypes. Better recovery of CD4 cells after initiation of anti-retroviral therapy was observed in TT individuals.<sup>16</sup>

Geographically, significant ethnic differences exist in the frequency of

Table 1: Examples of genetic polymorphisms on drug metabolising enzymes <sup>4, 7, 8</sup>				
Gene that codes for drug metabolizing enzymes	Polymorphic alleles in PMs	Percentages of major variants for the PMs phenotype	Medications involved (Examples)	Clinical consequences
Phase I enzymatic metabolism				
Dihydropyrimidine dehydrogenase (DPYD)	DPYD*2A	Unclear, but 1% of population is heterozygous	Fluorouracil	↑ Central nervous system toxicity in PMs
CYP2D6	Multiple inactive alleles exist: *3, *4, *5, etc	7% of Caucasians 1% of Chinese	Nortriptyline; Codeine Beta-blockers; Anti-depressants Anti-psychotics	↑ Drug effect and possibly toxicity in PMs Lack of analgesic effect of codeine in PMs
CYP2C9	*2 and *3	1% of Caucasians 0.04% in Asians	Phenytoin; Warfarin Tolbutamide; Glipizide, Losartan; NSAIDs <sup>a</sup>	↑ Risk of bleeding from standard dose warfarin in PMs ↑ Risk of hypoglycaemia in PMs
CYP2C19	*2 and *3	2% of Caucasians 15% of Chinese and 18% of Japanese	Omeprazole; Diazepam Amitriptyline; Imipramine	↑ AUC <sup>b</sup> of omeprazole and higher H. pylori eradication in PMs ↑ Risk of diazepam toxicity in Asians due to prolonged t <sub>1/2</sub>
Phase II enzymatic metabolism				
Thiopurine-S-methyltransferase (TPMT)	TPMT*2, TPMT*3, TPMT*4	0.3% of Caucasians 0.04% of Asians	Mercaptopurine Azathioprine	Homozygous for polymorphic alleles ↑ risk of hematopoietic toxicity and secondary cancer
N-acetyltransferase 2 (NAT2)	Slow acetylators: NAT2 (*2A, *6A, *7A or B, *14A or B)	52% of Caucasians 17% of Japanese	Isoniazid; Hydralazine; Procainamide	↑ Drug toxicity in slow acetylators
Uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1)	UGT1A1*28	11% of Caucasians 4% of Chinese 1% of Japanese	Irinotecan Bilirubin (endogenous)	*28 ↑ Gastrointestinal toxicity (diarrhea and leucopenia) to irinotecan Gilbert's syndrome due to bilirubin
Cetachol O-methyltransferase	Val108/135Met	25% of Caucasians Unclear for Asians	Levodopa	Met alleles associated with higher neuroleptic daily dose and poor response
<sup>a</sup> NSAIDs: nonsteroidal anti-inflammatory drugs <sup>b</sup> AUC: area under the concentration-time curve <sup>c</sup> For isoniazid, liver toxicity and peripheral neuropathy may result PMs: poor metabolizers				

Table 2. List of substrates, inhibitors and inducers of human p-glycoprotein determined by clinical studies	
PgP substrates <sup>9</sup>	<b>Antibiotics:</b> erythromycin; levofloxacin; sparfloxacin <b>Anti-emetics:</b> domperidone; ondansetron <b>Anti-cancer agents:</b> etoposide; doxorubicin; irinotecan; mitomycin C; paclitaxel; vinblastine; vincristine <b>Anti-diarrhoeal agents:</b> loperamide <b>Beta-adrenergic blockers:</b> celiprolol; talinolol <b>Calcium channel blockers:</b> diltiazem; verapamil <b>Cardiac drugs:</b> digoxin, digitoxin, quinidine <b>H1 antihistamines:</b> fexofenadine; terfenadine <b>H2 antihistamines:</b> cimetidine; ranitidine <b>Protease inhibitors:</b> amprenavir; indinavir; nelfinavir; saquinavir; ritonavir <b>Immunosuppressants:</b> cyclosporin ; tacrolimus <b>Lipid lowering drugs:</b> atorvastatin; lovastatin <b>Steroid:</b> dexamethasone <b>Others:</b> losartan; phenytoin; rifampicin; morphine; debrisoquine
PgP inhibitors <sup>10,11,12,13,14</sup>	<b>Polyethylene glycol</b> (excipient): enhance intestinal absorption of amprenavir <b>Erythromycin:</b> increase nimodipine level in brain; increase oral bioavailability of digoxin, cyclosporin, talinolol <b>Fluoroquinolone</b> (especially sparfloxacin): enhanced gastrointestinal uptake of erythromycin <b>Quinidine:</b> significantly increase digoxin serum concentration and result in toxicity
PgP inducer <sup>15</sup>	<b>St. John's Wort:</b> lower plasma concentration / pharmacological effects of alprazolam, amitriptyline, cyclosporin, digoxin, fexofenadine, indinavir, irinotecan, tacrolimus
The above list is based on the references available and is not meant to be exhaustive	

C3435T polymorphism. The prevalence of the CC, CT, TT genotypes in Chinese are 32%, 42% and 26%, respectively. For African American, the prevalence is 61-68% for CC, 31-34% for CT and only 1-5% for the TT genotype.<sup>17</sup>

Genetic variation in drug receptor proteins also influences the PD of drugs. Beta-receptors, for instance, determine the clinical response to the bronchodilating effect of beta<sub>2</sub>-adrenergic agonist in asthmatic patients. On the other hand, the chance of developing angiotensin converting enzyme inhibitors (ACEIs) induced cough, a common but annoying side effect, is affected by the PGx variants of bradykinin receptor B2. Listed in Table 3 are examples of human drug transporter / receptor proteins for which drug responses have been shown to be significantly affected by polymorphisms. The numerous proteins involved in transducing drug effects explain the difficulties in elucidating the gene-drug response relationship for receptor proteins compared to that for drug metabolising enzymes.

### Translating PGx into clinical practice

With the completion of human genome project a couple of years ago,<sup>18</sup> the "phenotype to genotype" approach in exploring the field of PGx may eventually be replaced by the "genotype to phenotype" method. This also explains the term "pharmacogenomics" that refers to the determination of drug response through genetics.

Currently patients having the same empirical diagnosis would receive similar pharmacological treatments despite the fact that their responses to therapy are likely to be different. With advancing PGx the treatment approach could be tailor made. Patients could use different drugs if their genes have predicted poor response, and for those expected to have an increased risk of toxicity, lower drug dosage or other alternatives could be sought. The followings are some examples illustrating such potentials of PGx.

As mentioned at the very beginning, ADRs is one of the major reasons for hospitalization and even death. With the introduction of PGx diagnostic tools that enable prospective genotyping of TPMT,

CYP2D6 and CYP2C9 isoforms,<sup>19,20</sup> undesirable drug response could be prevented in susceptible individuals (PMs). Findings from clinical studies on PGx in CYP450s also help to guide appropriate treatments. Nortriptyline is almost entirely metabolized by CYP2D6. Its daily dosage ranges from 30-50mg in PMs to as much as 500mg in UMs.<sup>21</sup> Codeine requires activation by CYP2D6 to morphine and thus the analgesic effect of codeine could be diminished in PMs. Sertraline, a CYP2C19 substrate, produces toxicities in PMs that warrant dosage reduction up to 60%.<sup>22</sup> Patients who are heterozygous for the \*2 or \*3 alleles of CYP2C9 require 30% dose reduction of warfarin compared to the wild traits, and those who are homozygous for \*2 or \*3 alleles need up to 70% dose reduction of the drug.<sup>23</sup>

PGx also has its pharmaco-economic implications. An example is the use of omeprazole in eradicating H. pylori. It is metabolized by CYP2C19 and therefore lower dosage (20mg daily, hence lower cost) may be used in PMs while nearly 100% eradication rate could be achieved.<sup>24</sup> Genotyping for CYP2C19

**Table 3. Examples of genetic polymorphisms that affect drug transporter / receptor protein in human<sup>7</sup>**

Gene codes for drug transporters / targets	Alleles	Medications involved (examples)	Clinical effects of recessive traits
Drug transporter <sup>a</sup>			
ABCB1 (ATP-binding-cassette sub-family B member 1) or MDR-1(Multiple drug resistant -1)	C3435T	ABCB1 affects the expression of p-glycoprotein Numerous drugs affected: e.g. Digoxin, Protease inhibitors (PIs), anti-epileptics	TT individuals have ↑ Digoxin oral bioavailability, less drug resistant epilepsy, and better immune recovery after initiating PIs treatment
Drug receptors			
ADRB1 (beta-1 adrenergic receptor)	Arg389Gly	Beta-1 antagonist	Gly/Gly homozygotes have reduced blood pressure lowering effect by beta-adrenergic receptor antagonists
ADRB2 (beta-2 adrenergic receptor)	Arg16Gly	Beta-2 agonists: Salbutamol; Terbutaline	Gly allele patients have poorer bronchodilation response to the drugs
BDKRB2 (Bradykinin receptor B2)	C-58T	Angiotensin converting enzyme inhibitors (ACEIs)	T allele associated with ACEIs-related cough
HTR2A (Serotonin receptor 2A)	His452Tyr	Anti-psychotics (Clozapine)	Tyr allele associated with less response to clozapine and more susceptible to drug-induced tardive dyskinesia
Miscellaneous			
ADD1 (alpha-adducin)	Gly460Trp	Diuretics (Hydrochlorothiazide)	Trp allele patients have less myocardial infarction and stroke risk relative to Gly traits
APOE (apolipoprotein E)	E4	Statins	E4 leads to poorer response to statins
LIPC (hepatic lipase)			

<sup>a</sup>see text for more details

has been estimated to save US\$5000 per 100 Asian patients for anti-ulcer drug treatment using omeprazole.<sup>25</sup>

In the field of cancer chemotherapy, the expression of HER-2 gene, which occurs in 25% of breast cancer patients, predicts favourable response to a humanized monoclonal antibody, Trastuzumab (Herceptin®).<sup>26</sup> To the pharmaceutical industry, novel compounds with high affinity for polymorphic CYP450s enzymes would be undesirable and structural modification is preferred in order to bypass such metabolic pathway.

So what are the key messages to pharmacists? The landmark on PGx falls on the selection of right drug at a suitable individualized dose in order to optimize treatment outcome and prevent ADRs from happening. The

major obstacles that hinder PGx from application in clinical settings are the lack of large, prospective and conclusive studies to definitely demonstrate the improvement in drug efficacy through genetic differentiations, and the fact that most prescribers are not familiar with the clinical relevance of PGx. Being regarded as knowledgeable professionals on drugs, it is our role to maximize the benefits of drug therapy while minimizing risk and avoiding unsuccessful treatment. Experts predict that one future vision of PGx is the development of metabolic gene panel. The panel is performed once in a lifetime to document each person's metabolic pathway profile. Drugs are then designed to target a specific pathway and marketed together with a diagnostic tool which predicts efficacy.<sup>27</sup>

## Concluding highlights

The clinical relevance of PGx on drug response is well established for genetic polymorphism that alters drug metabolisms. The forthcoming era of pharmacogenomics and possible development of gene metabolic panel in future would enable individualisation of drug therapy and allow pharmacists to screen for gene-drug interactions. The impacts on social, economical and ethical aspects should never be overlooked in the future pharmacy practice. There is a complex interplay between genes and the environment that determines most drug effects and treatment outcomes.

### Author information

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# Questions for Pharmacy Central Continuing Education Committee Program

( Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

**1. Genetic polymorphism is defined as the variation in the structure of a gene or an allele (loci on gene) with frequency of variation:**

- A. Not less than 1 in 10 of a population
- B. Not less than 1 in 100 of a population
- C. Not less than 1 in 1000 of a population
- D. Not less than 1 in 10,000 of a population
- E. Not less than 1 in 100,000 of a population

**2. Which of the following statement(s) is / are correct?**

- A. PMs of CYP2D6 is more common in Caucasian than in Chinese
- B. PMs of CYP2C19 is more common in Chinese than in Caucasian
- C. PMs of CYP3A4 occurs at similar frequency in Chinese and Caucasian
- D. A and B
- E. All of the above

**3. Which of the following statements regarding CYP3A4 isoenzyme is/are correct?**

- A. It accounts for over 40% of phase I drug metabolism in human
- B. Genetic polymorphism of CYP3A4 is not yet clearly defined
- C. It exists at our intestinal wall and is responsible for drug metabolism in G.I. tract
- D. A and B
- E. All of the above

**4. CA, 56yo White male was put on irinotecan chemotherapy for his metastatic colon cancer. He subsequently developed severe diarrhea with low white cell counts. Which of the following factors could have contributed to the adverse outcomes?**

- A. CA may be a PM of TPMT
- B. CA may be an EM of TPMT
- C. CA may be a PM of UGT1A1
- D. CA may be an EM of UGT1A1
- E. None of the above



**5. HW, 62yo American female with history of hypertension and non small cell lung cancer (inoperable), he had also experienced adverse drug reaction of excessive drop in blood pressure after taking standard dose of metoprolol. Recently her oncology specialist had prescribed codeine phosphate to her for pain management. HW, however, did not respond to codeine even with high dose. Her pain control responded well to just a minimal dose of morphine. From the point of PGx, what may have explained for such a phenomenon?**

- A. HW is a PM of CYP2C9
- B. HW is a PM of CYP2C19
- C. HW is a PM of CYP2D6
- D. HW is a PM of CYP3A4
- E. HW is a PM of DPYD

**6. Omeprazole, a proton pump inhibitor (PPI), has been commonly used as part of PPI based triple therapy for eradicating H. pylori. Literature data showed that Asians report a higher eradication rate than Caucasians with the same regimen and dosage. Why?**

- A. Asians are usually colonised with H.pylori that have less drug resistance
- B. Asians have better drug tolerance and compliance to the regimen
- C. PMs for CYP2C9 is more common in Asians than Caucasians
- D. PMs for CYP2C19 is more common in Asians than Caucasians
- E. None of the above

**7. Angiotensin converting enzyme inhibitor (ACEI) induced cough is a common side effect leading to discontinuation of treatment. Literature showed that the frequency of such problem in Chinese is around 12%. Which drug receptor polymorphism is known to be associated with this problem?**

- A. Bradykinin receptor B3
- B. Bradykinin receptor B2
- C. Bradykinin receptor B1
- D. Angiotensin receptor A2
- E. Angiotensin receptor A1

**8. What is being used for genotypic testing for the polymorphism of human TPMT gene?**

- A. Erythrocytes
- B. Leucocytes
- C. Platelet
- D. Skin cells
- E. DNA

**9. PgP protects the body from xenobiotics by reducing their uptake or promoting excretion; which of the following statements is incorrect?**

- A. It expresses at ileum, kidney, liver and blood brain barrier
- B. Quinidine decreases the serum concentration of digoxin due to inhibition of PgP expression at intestines
- C. Polyethylene glycol may enhance the intestinal absorption of some protease inhibitors
- D. Erythromycin may inhibit PgP and lead to cyclosporine toxicity but itself is also a substrate of PgP
- E. St John's Wort should not be used with amitriptyline since it reduces the uptake of the amitriptyline into systemic circulation

**10. Slow acetylators are more susceptible to which of the following adverse drug reactions?**

- A. Bradycardia due to atenolol
- B. Bleeding due to accumulation of warfarin
- C. Haemolytic anaemia due to quinolone antibiotics
- D. Myelosuppression due to azathioprine
- E. Peripheral neuropathy due to isoniazid

**Answers will be released in the next issue of HKPJ.**

Answers for the past issue (Oct-Dec2005)

Suggested answers:  
1)B 2)D 3)E 4)C 5)C 6)D 7)B 8)A 9)B 10)E

# Exenatide: A Novel Therapy for Type 2 Diabetes

Grace Tang

## INTRODUCTION

**Type 2** diabetes is a progressive disease characterized by a continuous loss of pancreatic  $\beta$  cells functions. (1,2) Realizing that sulphonylureas-type treatment in type 2 diabetes will eventually lead to  $\beta$  cells exhaustion and sulphonylureas therapy failure, new pharmacological agents for management of type 2 diabetes have been shifted to preserving or enhancing  $\beta$  cells functions in order to slow the disease progression.

In April 2005, FDA approved Exenatide (Byetta<sup>®</sup> by Amylin Pharmaceuticals and Eli Lilly) as a new class of treatment option for diabetes. The drug is approved as adjunctive therapy to improve blood glucose control in patients with type 2 diabetes who fail to achieve adequate control with conventional therapy. (3)

## PHARMACOLOGY

Glucagon-like peptide 1 (GLP-1) is a naturally occurring incretin hormone. It is produced by the proglucagon gene in L-cells of the small intestine in response to food intake. (4) Following the findings that patients with type 2 diabetes have decreased GLP-1 secretion, research has focused on this area to design novel treatment for type 2 diabetes. (5)

Exenatide belongs to a new drug class called incretin mimetics (GLP-1 analogs). Exenatide is a synthetic form of the 39-amino acid peptide exendin-4. Exendin-4 is a naturally occurring component of the saliva of the Gila monster lizard (*Heloderma suspectum*). It has 53% homology with the mammalian GLP-1. (6) GLP-1 produces desirable glucoregulatory actions via its receptors found in the pancreatic periductal cells and beta cells, kidney, heart, stomach and brain. (4) Exenatide shares similar pharmacological effects as GLP-1 including glucose-dependent insulin release, glucose-dependent inhibition of inappropriately high glucagon secretion, (7) reduction in food intake (8) and promotion of  $\beta$  cell proliferation and neogenesis. (9) It also modulates gastric emptying to slow the entry of ingested sugars into the blood stream. (10, 11)

One remarkable feature of exenatide

is its ability to restore first-phase insulin response, an activity of the insulin-producing cells in the pancreas that is lost in patients who have type 2 diabetes. (3, 12) It means that the drug enhances  $\beta$ -cell insulin release only when the plasma glucose level is above the normal range (i.e. glucose-dependent). This is compared to other hypoglycemic agents which only increase insulin secretion regardless of the glucose level and therefore may make the patients prone to hypoglycemia. (13)

## PHARMACOKINETICS AND PHARMACODYNAMICS

Glucagon-like peptide 1 has a short half-life of less than 2 minutes and is subjected to rapid degradation by the proteolytic enzyme dipeptidyl peptidase IV (DPP-IV). (15) Exenatide is an agonist at the GLP-1 receptor with a longer duration of action, partially attributable to the extended absorption of the drug into the blood from the subcutaneous injection site. Compared with native GLP-1, exenatide has >1000-fold in vivo potency for glucose lowering, probably due to its resistance to DPP-IV mediated inactivation. (4, 16)

From pharmacokinetics studies, administration of a single injection of exenatide resulted in a dose-dependent increase in circulating concentration of exenatide. Exenatide was detectable in plasma as early as 10-15 minutes post-dose reflecting its rapid absorption after subcutaneous injection. Also, it was still detectable 15 hours post-dose after a single injection of dose greater than 2mcg/kg. (17) Bioavailability study showed that the pharmacokinetic profiles were similar after subcutaneous injection into the arm, thigh or abdomen. (18)

## CLINICAL STUDIES

### 1. Effect on HbA<sub>1c</sub>

Exenatide has shown promising results in phase III trials in lowering HbA<sub>1c</sub> without causing significant hypoglycemia or weight gain. (19)

A study was conducted to evaluate the effect of exenatide on blood glucose control in sulphonylurea-treated type 2 diabetes patients. In a triple-blind, placebo-controlled, 30-week study conducted at 101 sites in the U.S.,

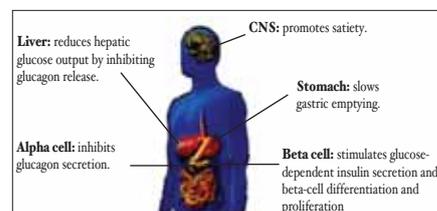


Figure 1. Multiple sites of action for GLP-1 (14)

377 subjects (age 55±11year, HbA<sub>1c</sub> 8.6±1.2%) were randomized to receive 5mcg subcutaneous exenatide twice daily (arms A and B) and placebo. The dose in arm B patients was subsequently escalated to 10mcg twice daily. All subjects continued their sulphonylurea therapy. After the study period, the changes in HbA<sub>1c</sub> from baseline were -0.9±0.1, -0.5±0.1 and 0.1±0.1% in the 10mcg, 5mcg and placebo arms, respectively (P<0.001). For patients with HbA<sub>1c</sub> >7% at baseline (n=237), 41% in 10mcg arm, 33% in 5mcg arm and 9% in placebo arm achieved HbA<sub>1c</sub> of ≤7% at study end (P<0.001). (20)

In a study looking into the effect of exenatide on metformin-treated patients in type 2 diabetes, 272 patients (age 53±10year, HbA<sub>1c</sub> 8.2±1.1%) were randomized to 5mcg exenatide or placebo given subcutaneously twice daily for 4 weeks. This was followed by 5mcg or 10mcg exenatide, or placebo given subcutaneously twice daily for 26 weeks. All patients continued metformin therapy. After 30 weeks, the changes from baseline HbA<sub>1c</sub> were -0.8±0.1%, -0.4±0.1% and 0.1±0.1% in the 10mcg arm, 5mcg arm and placebo arm, respectively (adjusted P<0.002). Forty-six percent of patients in the 10mcg arm, 32% in the 5mcg arm and 10% in the placebo arm achieved HbA<sub>1c</sub> ≤7% after the study period (P<0.001). (21)

A study was performed in type 2 diabetes patients treated with metformin and sulphonylurea. Seven hundred and thirty-three patients were enrolled in a double-blind, placebo-controlled trial. Subjects (age 55±10year, HbA<sub>1c</sub> 8.5±1.0%) were randomized to 5mcg exenatide twice daily (arm A and B) or placebo for 4 weeks. The dose in arm B patients was escalated to 10mcg twice daily thereafter. Patients continued their dose of metformin and sulphonylurea throughout the study. After 30 weeks, the changes in HbA<sub>1c</sub> were -0.8%±0.1%,

-0.6%±0.1% and 0.2±0.1% in the 10mcg arm, 5mcg arm and placebo arm, respectively (P<0.001). Exenatide-treated patients were more likely to achieve HbA<sub>1c</sub> goal. Thirty-four percents in the 10mcg group and 27% in the 5mcg group achieved HbA<sub>1c</sub> of ≤7% after 30 weeks, compared with 9% in the placebo group (P<0.0001).<sup>(22)</sup>

## 2. Effect on Body Weight

In clinical studies, patients in the exenatide arms were found to have significant weight loss compared with the placebo group. For those who entered the open-label extension studies, 35 patients who had completed 52 weeks of treatment with exenatide and sulphonylureas experienced a mean weight loss of 2.9kg. Among the 51 patients who had completed 52 weeks of treatment with exenatide and metformin, the mean weight loss was 4.5kg. For those treated with combination of exenatide, metformin and sulphonylurea, the mean weight loss was 3.3kg. The significant reduction in blood glucose and associated weight loss brought about by exenatide would be favorable in the management of type 2 diabetes.<sup>(19-22)</sup>

## 3. Effect on Beta-cell Function

Exenatide administration was associated with beta-cell proliferation and islet neogenesis from precursor cells in both in vitro and in vivo models.<sup>(12)</sup> In a triple-blind, placebo-controlled study involving 109 patients treated with a sulphonylurea and / or metformin, patients were given exenatide 0.08mcg/kg/injection twice to thrice daily or placebo. Homeostasis model assessment (HOMA) was conducted to assess β-cell function at baseline and after 4 weeks. It was found that the β-cell index for all regimens was 50 to 100% greater at day 28 of exenatide treatment compared with baseline (day 1), while there was no change in placebo-treated patients. HOMA analysis revealed improved β-cell secretory function following exenatide therapy.<sup>(23)</sup>

The ability of exenatide to promote β-cell proliferation and neogenesis may help to combat the progressive β-cell failure in type 2 diabetes patients.

## 4. Effect on Lipids

Some studies of exenatide included lipid profiles as one of the study parameters. Apart from HbA<sub>1c</sub> lowering effect, the aforementioned triple-blind study also found that the postprandial triglyceride concentrations tended to decrease after 4 weeks of exenatide

therapy (change from day 1 to day 28, range -0.25 to -0.35mmol/l) as compared with that of placebo (change from day 1 to day 28, 0.14mmol/l).<sup>(23)</sup>

In another open-label study involving 265 patients receiving exenatide 10mcg twice daily, treatment with exenatide was associated with improvements in HDL-cholesterol levels, triglyceride levels and BP as well.<sup>(24)</sup>

## SIDE EFFECTS

Side effects of exenatide were generally well tolerated. The most commonly reported side effects were mild to moderate nausea and vomiting, which usually occurred at the beginning of the therapy.<sup>(19-22)</sup> Slowly titrating the dose upwards over several weeks may decrease the risk.<sup>(25)</sup> Some patients experienced hypoglycemia when taking exenatide with sulphonylureas.<sup>(20,26)</sup> Lowering the dose of sulphonylurea may be required in combination therapy. Other side effects include diarrhea, dizziness, headache and acid stomach.<sup>(27)</sup>

Exenatide does not appear to carry the adverse effects associated with current agents. It is associated with no or low risk of hypoglycemia, no weight gain or even weight loss, and no edema. The side effect profile seems to be favorable.

## CAUTIONS AND CONTRAINDICATIONS

Since exenatide requires β cells to function, it should not be used in patients with type 1 diabetes. Also, exenatide is not a substitute for insulin in insulin-requiring patients. It is not recommended in patients with end-stage renal disease or severe renal impairment, or in patients with severe gastrointestinal disorders. Lastly, since exenatide delays gastric emptying, caution should be exercised when it is used in patients taking oral medications that require rapid gastrointestinal absorption.<sup>(3)</sup>

## USE AND ADMINISTRATION

Exenatide is given in form of fixed dose by subcutaneous injection prior to morning and evening meals. It is available in form of 5mcg and 10mcg per dose in prefilled pen-injector device.<sup>(3)</sup>

## DRUG INTERACTIONS

As mentioned, exenatide will slow gastric emptying. It may reduce the rate and extent of absorption of oral drugs. For medications such as oral

Exenatide Drug Interactions		
Precipitant drug	Object drug*	Description
Exenatide	Acetaminophen	↓ When given concomitantly acetaminophen AUC and C <sub>max</sub> decreased and T <sub>max</sub> increased. Give acetaminophen 1 hour before exenatide injection.
Exenatide	Digoxin	↓ Coadministration of repeated doses of exenatide decreased C <sub>max</sub> 17% and delayed T <sub>max</sub> ~ 2.5 hours. AUC was not changed.
Exenatide	Lisinopril	↓ Lisinopril AUC and T <sub>max</sub> was delayed 2 hours.
Exenatide	Lovastatin	↓ Lovastatin AUC and C <sub>max</sub> were decreased ~ 40% and 28%, respectively, and T <sub>max</sub> was delayed ~ 4 hours when administered concomitantly with exenatide.
Exenatide	Oral antibiotics	↓ Advise patients to take oral antibiotics at least 1 hour before exenatide injection.
Exenatide	Oral contraceptives	↓ Advise patients to take oral contraceptives at least 1 hour before exenatide injection.

\* ↓ Object drug decrease.

Figure 2. Adapted from reference <sup>(29)</sup>.

contraceptives and antibiotics, the efficacy of which is dose-dependent, patients should be advised to take those drugs at least 1 hour before exenatide.<sup>(28)</sup>

Studies also found that exenatide interacted with digoxin, lovastatin and paracetamol, leading to a reduction in C<sub>max</sub> and / or AUC of the latter drugs.<sup>(28-30)</sup>

## FUTURE DEVELOPMENT

Long-acting preparations of exenatide are being developed, including daily, weekly and monthly <sup>(10)</sup> injections. An intravenous GLP-1 formulation is also being studied. A new formulation made by genetic fusion of human albumin and GLP-1 (albumin-glucagon-like peptide-1) is being researched. Preliminary data showed that the new formulation resulted in decreased clearance and prolonged half-life of GLP-1. Non-injectable delivery method, e.g. transdermal formulation of GLP-1 analog is also under development.<sup>(31)</sup>

## CONCLUSIONS

Exenatide is a novel drug in a new class of medication called incretin mimetics. It improves glycemic control through a variety of complementary mechanisms. Since its actions mediating insulin secretion and inhibiting glucagon release are glucose-dependent, it has a lower risk of hypoglycemia as compared with the conventional anti-diabetic agents. Its blood glucose-lowering action and side effect profile may make the drug a favorable option in the management of type 2 diabetes. Longer-term studies are needed to determine the long-term efficacy and safety of the drug.

### Author information

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## Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee, led by the Managing Editor, will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80].

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

## Applications of a Database System for the Formulation of Eye Drops Preparations

Hui, KW; Tsang, YW

*In recent years, there has been growth in the global ophthalmic pharmaceutical market. If formulation scientists can shorten the time from designing the formulation of eye drops to selling in the market, it would be a great benefit to the pharmaceutical companies. However, formulation design used to be a trial and error practice that is time-consuming. Setting up a database system can speed up the formulation design. A database system, called 'Eye Drops Database System to Assist Formulator' (Eye-SAF) has been designed by the FDA to help the formulation scientists who do not have enough eye drops formulation experience, to choose suitable excipients such as buffers and preservatives to design a stable formulation with better bioavailability. In this article, improvement of formulation design using the Eye-SAF is introduced. A couple of formulations according to the guide of Eye-SAF are described. Through this approach, the preparation successfully passed the specific requirements for eye drops.*

**Keywords:** Database system; Formulation; Eye drops preparation; Eye-SAF; Ophthalmic solutions; Ophthalmic suspensions

### I INTRODUCTION

#### i) Background

There is an interesting and mystical history of ophthalmic formulations. An informative historical chronicle indicated that the remarkable development of ophthalmic preparations has undergone changes over the course of many years remarkably. In the Mesopotamian (the ancient name of Iraq) era, circa 3000-4000 B.C., the earliest ocular treatment was used for prophylaxis to prevent demons from entering the eyes through various rituals. Until the seventh century B.C., vegetable drugs became common when washes, powders or ointments mixed with water, oil, milk or urine were used. At that time, the powders were administered pically into the eyes through tubes or reeds. Between 20 B.C. to A.D. 50, one of the first therapeutic delivery systems was noted in the writings of Celsus. It was the collyrium introduced by the Romans. However, it was not a lotion. It was a small bar of soap in which the drug was incorporated. When using it, a small piece was taken and dissolved in a solvent such as water, oil or other available liquids. Then, the solution was applied to the eyes [18]. Now, most topical ophthalmic dosage forms are simplistic. Usually, the water-soluble drugs are administered through an aqueous solution topically, and water-insoluble drugs are delivered through an aqueous suspension or administered topically as an ointment [7].

#### ii) The Ophthalmic Market

The diversity of conventional ophthalmic formulations has gradually evolved over the last few decades because of the invention of potent entities. Most ocular diseases are treated with eye-drops topically, so nearly 90% of the currently accessible marketed formulations are these conventional dosage forms. Figure 1 summarizes the ophthalmic medications available in the U.S.A [14,15]. Generally, the reasons for choosing solutions are the favorable costs and the greater simplicity of formulation development and production [15].

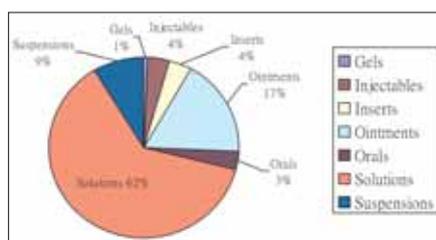


Figure 1. The Ophthalmic Medications Market in USA<sup>[14,15]</sup>

In the market, there are societal pressures to reduce healthcare costs with the costs of new drug development in the pharmaceutical industry. Thus, it needs to increase the rate of drug discovery and formulation design to the market with reduction in the number of failures and the cost of development. Although drug delivery system development is the rate-limiting step, formulation scientists still use the trial-and-error approach to formulation development based on individual traditional experiences traditionally. Therefore, accelerating the development

of cost-effective formulations to be manufacturable is very important [10]. Nowadays, some systems such as the "Expert System" for formulation of hard gelatin capsules from CAPSUGEL [11] and "FormRules" software from Intelligensys [5] are developed to design formulations easily and quickly. Intelligensys states that it can provide time and cost advantage over traditional statistical techniques in formulation development [4].

In the global ophthalmic market, there were has been growth in ophthalmic pharmaceuticals and it is slightly ahead of total pharmaceuticals in 2001 and in 2002 (Figure 2 & 3). A few years ago, Stevenson reported that the ophthalmic market was a vibrant one and did have a significant amount of upside potential. His study lead to a conclusion that the growth of ophthalmic products would continue to be driven positively by technology, demographics and geographic expansion as the economies in various third-world countries improve [20, 21].

In the next five years, there will be over US\$10 billion worth of drugs

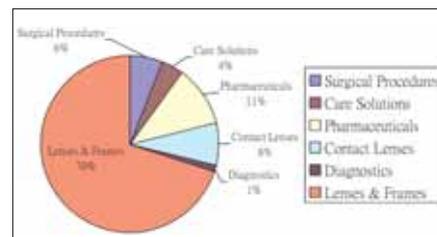


Figure 2. The Global Ophthalmic Market in 2001<sup>[20]</sup>

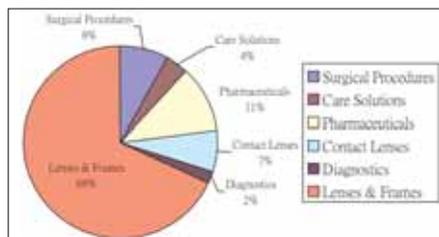


Figure 3. The Global Ophthalmic Market in 2002<sup>[21]</sup>

coming-off patent, so not only enhancements of efficacy and new indications of products are necessary, new dosage forms or new drug delivery systems and speedy formulation strategies are required to extend the life cycle of a drug product after the patent life<sup>[22]</sup>. These problems are also applied to ophthalmic products. Therefore, rapid formulation development is needed.

## II ANATOMY AND BIOAVAILABILITY OF THE EYE

Before proceeding to formulation design, pharmacist should know about the basic structure of an eye. Since drug penetration can be affected by the different tissues of an eye, the formulator should choose the right components in the formulae of eye drop to improve the effectiveness of medication. The structure of the eye is shown in Figure 4.

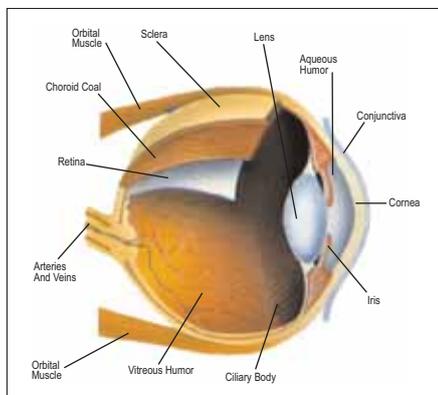


Figure 4. Structure of human eye<sup>[13]</sup>

The outermost layer of the eyeball is a tough, pliable but non-stretchable structure that is maintained in its shape by the internal pressure exerted by the vitreous and aqueous humours. The cornea is a clear and colorless layer containing no blood vessels but is richly supplied with nerve endings. In fact, the cornea consists of three layers, which are the corneal epithelium, the substantia propria (stroma) and the corneal endothelium. Both the epithelium and the endothelium are lipid-rich layers. However, the stroma is an aqueous barrier. The other part of the boundary layer of the eyeball is the

sclera that is opaque and white in color and contains most of the blood vessels nourishing the anterior tissues of the eye. The outermost surface of the sclera is loosely covered by the conjunctiva, which is continuous with the lining of the inner surface of the eyelids. In Figure 5, the conjunctival and corneal surfaces are continually lubricated by the lacrimal glands that secrete tears, a clear watery fluid containing mineral salts, glucose, protein and enzymes<sup>[1, 16]</sup>.

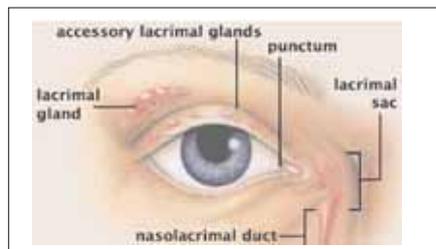


Figure 5. The lacrimal system<sup>[19]</sup>

Nowadays, topical ophthalmic applications such as eye drops are considered the preferred way to achieve therapeutic levels of active pharmaceutical ingredients (API) used to treat ocular diseases. However, from a biopharmaceutical point of view, eye drops have considerable drawback as a dosage form for ocular medication because ocular bioavailability is a significant factor in the effectiveness of an applied medication. Particularly for ophthalmic solutions, it ranges from 1 to 10% of the total administered dose to be absorbed across the cornea and thus enter the anterior chamber of the eye<sup>[7, 15, 16, 18, 25]</sup>. There are physiologic factors, physicochemical characteristics of API and product formulation that mainly affect ocular bioavailability.

For physiologic factors, protein binding, drug metabolism and lacrimal drainage affect ocular bioavailability. Normally, tears contain between 0.6 and 2.0% of protein, including globulins and albumin, but disease states such as uveitis can raise these protein levels. Protein-bound drugs are incapable of penetrating the corneal epithelium due to the size of the protein-drug complex. Also, tears contain enzymes such as lysozyme, capable of the destruction of saprophytic organisms for sterility of the eye, but the metabolic degradation of drug substance may occur in the eye<sup>[1, 6]</sup>. In the lacrimal drainage system shown in Figure 5, the tear film is constantly being replenished in the eye by blinking which spreads the film evenly over the surface of the eye and sweeps any excess fluid into the triangular lacrimal lake, which lies at the angle of the inner junction of the eyelids.

Excess tears are drained from the lacrimal lake into the lacrimal sac that is activated as a pump by blinking to drain the tears through the nasolacrimal duct into the nasal cavity and finally down the back of the throat into the gastrointestinal tract (GIT)<sup>[16]</sup>. Although ocular protein binding is reversible, tear turnover causes the loss of bound and unbound drug by washing away<sup>[1]</sup>. After topical administration of an ophthalmic solution, the drug is first mixed with the lacrimal fluid. The contact time of the drug with ocular tissues is about 1 to 2 minutes because of the permanent production of lacrimal fluid. Then, approximately half of the drug flows into the lacrimal sac and elimination of drug via the nasolacrimal duct to the GIT<sup>[15]</sup>. Next, systemic side effects may happen. For potent drugs such as timolol, the systemic exposure through nasolacrimal drainage after topical administration can be sufficiently high to cause systemic toxicity, i.e. distribution of timolol<sup>[7]</sup>.

The administration of drugs by instillation figure and which must penetrate into the eye enter primarily through the cornea because it is a much more effective route into the eye than the conjunctiva and underlying sclera, even though the cornea lacks vascularity that limits diffusion of drugs from the blood into the aqueous and vitreous humours<sup>[6, 16]</sup>. Moreover, both the corneal epithelium and endothelium are lipid-rich layers and represent significant barriers to water-soluble drugs, but allow lipid-soluble drugs to pass through easily. In the stroma, it is an aqueous barrier, which is permeable to water-soluble drugs such as tetrahydrozoline hydrochloride but not to lipid-soluble drugs such as prednisolone acetate<sup>[15, 16]</sup>. In fact, drugs penetrate across the corneal epithelium through the paracellular or transcellular pathway. Lipid-soluble drugs prefer the transcellular route while water-soluble drugs penetrate primarily via the paracellular pathway, which involves passive or altered diffusion through intercellular spaces. The transcorneal penetration appears to be hindered by the binding of the drug to the corneal tissues. Then the cornea may act as a drug reservoir and finally the drug is released into aqueous humour slowly<sup>[15]</sup>.

For the physicochemical characteristics of API and product formulation, the pH of eye drops can affect bioavailability because absorption is faster when a weak acid or weak base is in the unionized form. However, the diminished absorption of weak bases

from acidic solutions may be partly due to increased lacrimation caused by the low pH of the solution. The rate of lacrimation is lower at slightly alkaline pH values but poor stability may preclude the presentation of eye drops in solution of pH 8 [16]. Apart from pH value, large particle size, sharp particle shape and improper isotonicity also induce lacrimation to drain the drug into nasolacrimal duct shown in Figure 5<sup>[18, 24]</sup>.

In addition, drop size affects bioavailability. A decrease in drop size, to between 5  $\mu$ l and 15  $\mu$ l, would reduce the amount of overflow, the rate of drug loss through drainage, the cost of therapy, and the incidence of systemic side effects [16, 24, 25].

To improve the low ocular bioavailability, the formulator can add viscosity enhancers such as various celluloses, formulate in situ-forming gel or suspension to prolong the ocular contact time<sup>[1, 3, 7, 8]</sup>. Also, adding penetration enhancers such as chelating agents (e.g. sodium edetate), preservatives (e.g. benzalkonium chloride), surfactants (e.g. Tween 20 & 80) and bile salts can increase corneal drug penetration<sup>[7, 9, 12]</sup>.

### III FORMULATION OF EYE DROPS

The British Pharmacopoeia (BP) defines eye drops as sterile aqueous or oily solutions or suspensions of one or more active substances intended for instillation into the eye. Eye drop solutions examined under suitable conditions of visibility are practically clear and free from particles. For eye drop suspensions, they may show sediment that is readily redispersed on shaking to give a suspension which remains sufficiently stable to enable the correct dose to be delivered<sup>[2]</sup>. In the eye drop formulation, it can be regarded as a system comprising API along with some inactive ingredients.

The preparation of ophthalmic solutions and suspensions requires special consideration with regard to sterility, preservation, isotonicity, buffering, viscosity, surface activity, clarity, ocular bioavailability and packaging because these factors influence the stability of the eye drops, and the comfort and safety of the patient. Therefore, the usefulness of the excipients in eye drops is to adjust the tonicity or the viscosity of the preparation, to adjust or stabilize the pH, to increase the solubility of the active substance, or to stabilize the preparation. These substances do not

adversely affect the intended medicinal action or, at the concentrations used, may cause local irritation<sup>[2]</sup>.

The FDA provides a new formulation tool for the pharmaceutical industry to help with the formulation of new drug products. The Inactive Ingredients Database including more than 102,000 listings of inactive ingredients present in FDA-approved drug products was finalized and used in late December 2002<sup>[17]</sup>. In the Eye Drops Database System to Assist Formulation (Eye-SAF) set up by the FDA, maximum potency for each excipient mostly comes from the Inactive Ingredient Database. The common formulation components in eye drops are listed in Table 1.

### IV EYE-SAF

Designing a formulation of eye drops in a quicker and easier way is a benefit to the ophthalmic drug market, so a database system for the formulation of eye drops preparations is set up and aims for formulation scientists to develop an eye drops formulation more quickly and conveniently. This database system is called, "Eye-SAF" which stands for "Eye Drops Database System to Assist Formulator". Selection of the type and amount of excipients to design

a stable formulation with better bioavailability and patient compliance is a large challenge for formulation scientists. In Figure 6, the users and experts input the scientific data and knowledge into the computer. Eye-SAF is a computer program with artificial intelligence that can work just like a person with experience in a specific area of knowledge that is like an expert. Finally, the eye drops formulation is designed.

#### i) Design and Architecture

Fundamentally, the Eye-SAF is constructed by some formulation concepts and information from references. In Figure 7, three databases provide all information from the marketplace, references and expert to form some facts and rules. Then, a decision tree is constructed based on these facts and rules. Next, the users just need to input some basic information of active pharmaceutical ingredient (API) such as solubility and particle size to the Eye-SAF (input package). The decision tree acts as a brain to select all suitable excipients with concentration for users (output package). Finally, the formulation is evaluated and some experience is gained to improve the core of facts and rules.

#### ii) Prototype Eye-SAF Guide

Table 1. Formulation Components in Ophthalmic Solutions & Suspensions		
Component	Ophthalmic Solutions	Ophthalmic Suspensions
API		
Buffer		
Preservative		
Antioxidant	O	O
Viscosity Enhancer	O	
Wetting & Spreading Agent	O	
Tonicity Adjusting Agent	O	O
pH Adjusting Agent	O	O
Vehicle		

"N/A" = not applicable; "|" = component is included or generally included; "O" = optional

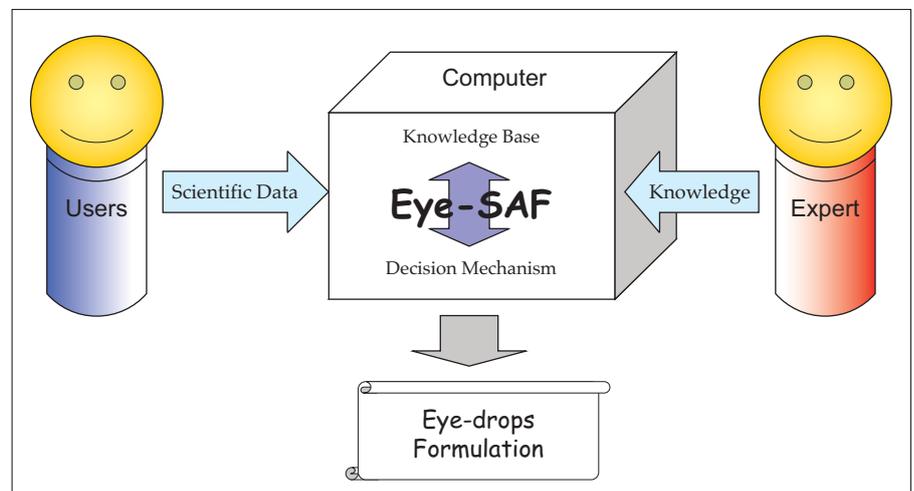


Figure 6. Concept of FDA's Eye-SAF

Before setting up software, a prototype Eye-SAF guide is designed and tried as a pilot scheme. In the guide, the structure is the same as in Figure 7. Three databases are grouped and divided into eleven chapters as follows:

- Chapter 1: Active Pharmaceutical Ingredient
- Chapter 2: pH & Buffer
- Chapter 3: Preservatives
- Chapter 4: Antioxidants
- Chapter 5: Viscosity Enhancers
- Chapter 6: Wetting & Spreading Agents
- Chapter 7: pH Adjusting Agents
- Chapter 8: Tonicity Adjusting Agents
- Chapter 9: Vehicle & Solvent
- Chapter 10: Packaging
- Chapter 11: Sterilization & Clarification

These eleven chapters form the facts and rules. Then, the decision tree is constructed and its concept map is shown in Figure 8 which is come from the prototype Eye-SAF guide.

Basically, the prototype Eye-SAF guide is divided into two parts, which are the database and the Formulation Record Form (FRF). In the database, there are many formulation factors needed to be considered. It is necessary that the formulator should use the guide from the first chapter to the last chapter in order. Thus, when designing a new formulation, it should be started by reading the first chapter of Active Pharmaceutical Ingredient (API) to the last chapter of Sterilization. Also, there is a criterion that the formulators design a formulation with only one API.

In every chapter, there is some information of formulation factor and inactive ingredient tables. Moreover, there is some interesting and updated information discussed in some related chapters in the database. According to the database, the formulator can choose some information and fill in the FRF. Finally, an eye drop formulation is designed after only doing some simple calculations.

### iii) Formulation of Timolol Maleate Eye Drops 0.5%w/v

In the study, the formulation of Timolol Maleate Eye Drops 0.5%w/v was designed by using the prototype Eye-SAF guide for demonstration.

Timolol Maleate Eye Drops is used for the treatment of glaucoma. From Martindale 32 ed., Timolol Maleate is soluble in water and the molecular weight is 432.5. From the specification in

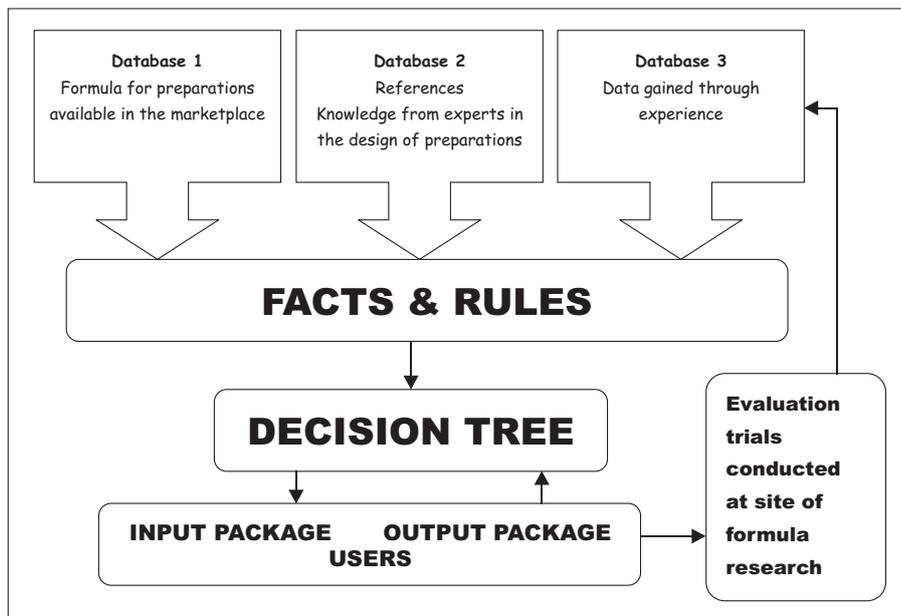


Figure 7. Structure of Eye-SAF

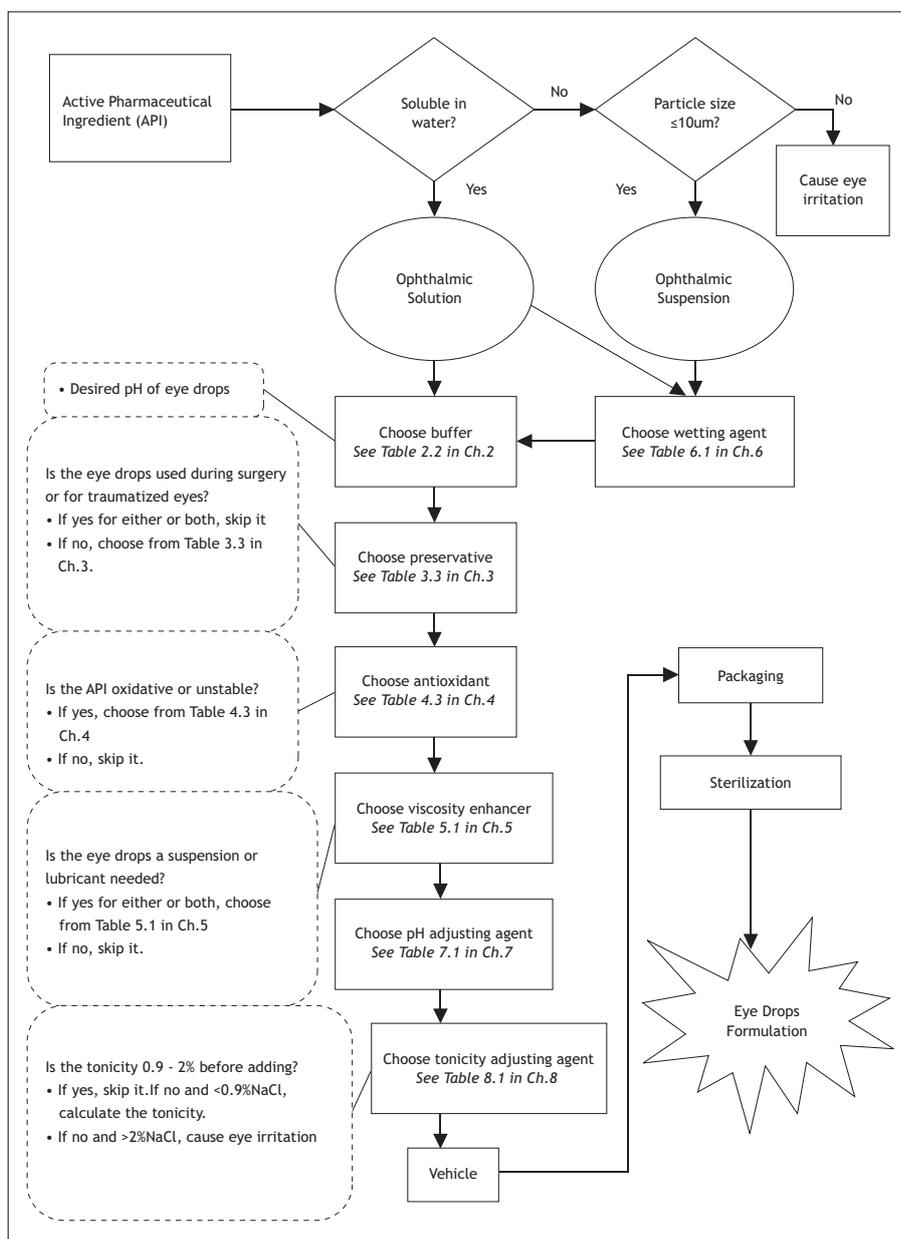


Figure 8. Decision Tree in Prototype Eye-SAF Guide

**Table 2. Formulation of Timolol Maleate 0.5%w/v**

Formula	Type	%w/v	NaCl Equivalent	Contribution to NaCl
Timolol maleate	API	0.5	0.14	0.07
Anhydrous monobasic sodium phosphate	Buffer	0.16	0.46	0.0736
Dibasic sodium phosphate dodecahydrate	Buffer	1.91	0.22	0.4202
Benzalkonium chloride	Preservative	0.01	0.16	0.0016
Sodium chloride	Tonicity	0.33	1	0.33
Sodium hydroxide/Hydrochloric acid	pH adjust	q.s.		
WFI	Vehicle	q.s. 100mL		

USP 24, Timolol Maleate Eye Drops formulation is a sterile, aqueous solution of Timolol Maleate. It contains an amount of Timolol Maleate equivalent to not less than 90%w/v and not more than 110%w/v of the labeled amount of Timolol. The pH is between 6.5 and 7.5 [23].

The formulation components generally included in ophthalmic solutions are API, buffer, preservative and solvent. From the related chapters from prototype Eye-SAF guide, phosphate buffer, benzalkonium chloride and Water For Injections (WFI) were selected. Then, tonicity was calculated by sodium chloride equivalent method and adjusted by sodium chloride. The formulation is shown in Table 2.

After recording FRF, Timolol Maleate Eye Drops can be compounded and given to Quality Control (QC) Laboratory for accelerated stability testing including assay and pH for 6 months. Initially, the assay was 100% and the pH was recorded as 7.0 that passed its specification stated in USP 24. After 6 months, the results still complied with

the specifications with an assay of 99.2% and the pH was unchanged. The formulation of Timolol Maleate Eye Drops 0.5%w/v was designed successfully by using Eye-SAF

## V CONCLUSION

In conclusion, although the formulators had spent some time to calculate the tonicity and sodium chloride equivalents of some substances which were not found in the prototype Eye-SAF guide, the basic eye drop formulation could still be designed through Eye-SAF in a more scientific, systematic, easier, quicker way than traditional trial and error method.

For suggestions of future work, the three databases should be reviewed frequently to update and extend the information. Furthermore, the formulators should challenge the prototype Eye-SAF guide with more commercially available formulations and then test the products for their stability,

assay, pH, clinical efficacy etc. Moreover, Eye-SAF can be computerized for automatic data processing in the future. This piece of software will help the formulators to choose the right excipients by simply clicking a few buttons. Meanwhile, it can also prompt the users with useful information stored in the databases such as the physical and chemical properties of the excipients, the reason why you cannot use some particular excipients, etc. This will certainly form a useful teaching tool. Computerized Eye-SAF may become a milestone in the field of eye formulation design in the future.

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# Simultaneous Determination of Nicotinic Acid, Nicotinamide and 3-cyanopyridine Using High Performance Liquid Chromatography

Chan, LW; Lam SL

*A rapid and reliable high performance liquid chromatographic method for the simultaneous determination of heterocyclic compounds, namely nicotinic acid, nicotinamide and 3-cyanopyridine, in industrial effluent is described. A 4.6 mm x 150 mm, 5 μm C-18 reversed phase stationary phase and a methanol-acetonitrile-water tertiary mobile phase (20:20:60 v/v) were used for the separation. The detection wavelength of a diode array (DAD) was set at 216 nm with a bandwidth 16 nm. Phenol was used as an internal standard. Regression equations revealed a linear relationship between the concentration of the analytes injected and the peak area detected by DAD. The limits of detection (S/N=3) ranged from 0.70 to 1.18 mg L<sup>-1</sup>, the recoveries ranged from 87 % to 102 % and the precision expressed as % RSD intra-day and inter-day varied from 0.9 to 3.9 and 1.2 to 5.6, respectively. This method is rapid, sensitive and suitable for the monitoring of nicotinic acid, nicotinamide and 3-cyanopyridine in effluent of related pharmaceutical manufacturing plants.*

## I INTRODUCTION

Vitamin B<sub>3</sub> (or PP) which is part of the B complex group, namely nicotinic acid (or niacin) and nicotinamide (or niacinamide), structurally contain a carboxylic or a carboxamide functional groups, respectively, bound on a pyridine ring. The conjugated π system of its heterocyclic aromatic structure allows detection by ultra-violet light. These compounds are soluble in water and generally very stable. Vitamin B<sub>3</sub> is a well-known precursor in the synthesis of the coenzymes NAD<sup>+</sup> and NADP (nicotinamide adenine dinucleotide phosphate) involved in cell metabolism. A deficiency of which causes inflammation of mucus membranes and an illness known as pellagra.

A pharmaceutical manufacturing plant in Guangzhou, China synthesizes this vitamin B<sub>3</sub> with 3-cyanopyridine as one of the intermediates. Residual amounts of nicotinic acid, nicotinamide and 3-cyanopyridine are the major waste products in the effluent that constitute a high measured biochemical oxygen demand<sup>1</sup> causing environmental concern. A number of methods have been developed for the quantification of vitamin B<sub>3</sub> and its metabolites in areas other than the environment, such as pharmaceutical formulations<sup>3,4</sup>, biological fluids<sup>5,6</sup> and food<sup>7,8</sup>. However, the analysis of vitamin B<sub>3</sub> and its synthetic intermediates in industrial effluent has not been reported elsewhere. To our knowledge, this report is the first of its kind to describe the simultaneous quantification of nicotinic acid, nicotinamide and 3-cyanopyridine in environmental monitoring. The main objectives of this study are to assess their initial level present in the effluent and to apply this method for the monitoring of the subsequent levels after biological

treatment via bacterial degradation to be developed in future work. The level of all of the three compounds was found to be in excess of the maximum permissible level stipulated in the integrated wastewater discharge standard GB8978-1996<sup>2</sup> in China, bringing to public attention the issue of environmental pollutants.

In this work, an isocratic elution HPLC method with a methanol-acetonitrile-water tertiary mobile phase and the most common stationary phase (RP-C18) was developed, and it is suitable for the analysis of the residual vitamin B<sub>3</sub> and its synthetic intermediates in related environmental samples.

## II EXPERIMENTAL

### i) Apparatus and chemicals

The HPLC method was carried out on a HP1100 high performance liquid chromatographic system (Hewlett-Packard), equipped with an auto-injector, a vacuum degas module, a quaternary pump and a diode array detector. The data were collected using a HP with ChemStation. A reverse-osmosis system (Orion) and resin columns (Aries) were used to purify and to deionise water of 18 MΩ-cm resistivity.

All of the chemicals used in this study were of analytical-reagent grade, deionised water was used to prepare a mobile phase and other solutions. Nicotinic acid, nicotinamide, 3-cyanopyridine and phenol were purchased from Fluka, methanol was from Fisher Scientific and acetonitrile was from Labscan. The effluent was collected from a pharmaceutical manufacturing plant in Guangzhou, China. Stock solutions of nicotinic acid,

nicotinamide and 3-cyanopyridine were prepared in deionised water with a concentration of 1000 mg L<sup>-1</sup>. The standard mixtures were diluted to 1, 5, 10, 20, 30 and 40 mg L<sup>-1</sup>, respectively, using the described mobile phase, and a constant amount of the internal standard was dispensed into each of the standard mixtures.

### ii) Preparation of samples

The samples of effluent were stored in a refrigerator at 4°C, and they were warmed at 23°C for about 30 min before use. A constant amount of the internal standard was dispensed into each sample. They were filtered through a 0.45 μm membrane filter and then diluted 200 times by the mobile phase prior to the HPLC run.

### iii) HPLC Conditions

A separation column of 4.6 mm x 150 mm, 5 μm C-18 reversed phase and a guard column of the same material (Alltech) were used. The column temperature was operated at 23°C in a controlled laboratory environment. The mobile phase used was methanol-acetonitrile-water (20:20:60 v/v) at a flow rate of 1.5 mL min<sup>-1</sup> isocratic. The detection wavelength was set at 216 nm, and the injection volume of samples was 20 μL by an auto-injector.

## III RESULTS AND DISCUSSION

### i) Resolution of nicotinic acid, nicotinamide and 3-cyanopyridine

The content of methanol in the mobile phase exerted a greater influence on the capacity factor of 3-cyanopyridine and phenol than that of nicotinic acid and nicotinamide. When the content of methanol was increased, 3-cyanopyridine

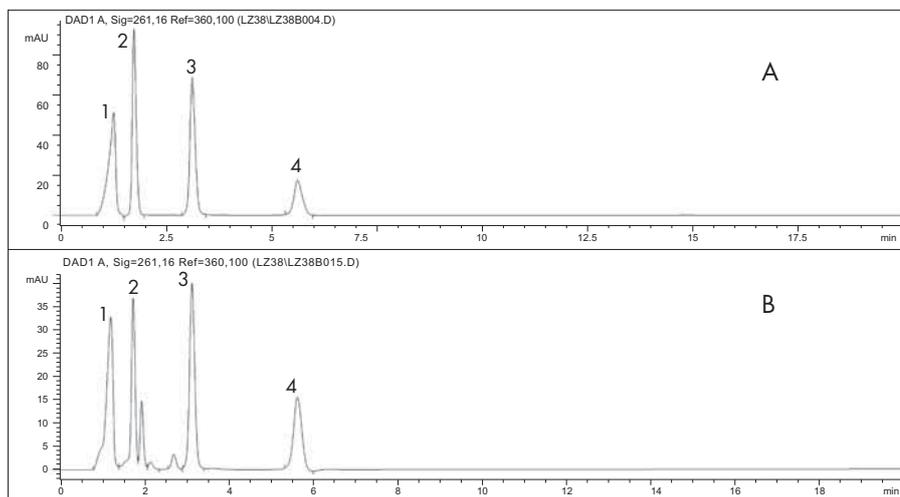


Fig. 1 HPLC chromatographs of standards (A) and effluent samples (B). Analytes: 1, nicotinic acid; 2, nicotinamide; 3, 3-cyanopyridine; 4, phenol.

Table 1. Calibration curves, calibration Ranges and detection limits for the three analytes

Compound	Regression Equation	Calibration Range (mg L <sup>-1</sup> )	Correlation Coefficient (r)	Detection Limit <sup>a</sup> (mg L <sup>-1</sup> )
Nicotinic Acid	$y=0.1251x+0.02751$	1.0 - 40	0.9997	1.10
Nicotinamide	$y=0.1226x+0.03758$	1.0 - 40	0.9999	0.70
3-cyanopyridine	$y=0.1274x+0.02641$	1.0 - 40	0.9997	1.18

<sup>a</sup>S/N = 3

and phenol eluted much more quickly. Acetonitrile in the mobile phase, on the other hand, improved the overall peak shape, especially minimising the effect of peak broadening. To select an optimum composition of mobile phase, the content of methanol starting from scratch was increased 5 % at a time (0, 5, 10, 15, 20, 25%) at the expense of the same content of acetonitrile (40, 35, 30, 25, 20, 15 %) while holding the content of water constant at 60%. The peaks of nicotinic acid and nicotinamide were found to be too close together for quantification when the content of methanol and acetonitrile reached 25 % and 15 %, respectively. Using methanol-acetonitrile-water (20:20:60 v/v) as the mobile phase, the analytical time was shortened to about 6 min. while the peaks of nicotinic acid and nicotinamide were still evidently baseline resolved which was sufficient for a quantitative analysis of the 3 analytes. The peak of the internal standard was well separated from the 3 analytes. As a result, methanol-acetonitrile-water (20:20:60 v/v) was employed as the mobile phase in the entire work. The chromatograms of a

standard mixture of nicotinic acid, nicotinamide, 3-cyanopyridine and an internal standard, and a sample of effluent at the selected chromatographic conditions are depicted in Figure 1. The elution order of the analytes was consistent with their polarity. Nicotinic acid with the average retention time, 1.2 min was eluted first, followed by nicotinamide (1.7 min), 3-cyanopyridine (3.1 min), and then phenol (5.7 min).

## ii) Figures of Merit

### Linearity and limit of detection.

Mixtures of nicotinic acid, nicotinamide and 3-cyanopyridine with different concentrations were prepared for calibration curves. The regression equation between the peak area (mAu\*s) and the concentration of the analytes injected (mg L<sup>-1</sup>) can be expressed as  $y = mx + c$ , where  $y$  is the ratio of the peak area of the analyte to the peak area of the internal standard,  $x$  is the concentration of the analytes, and  $c$  is the intercept and  $m$  is the slope (sensitivity). It was obvious that similar, though not identical, slopes were obtained for the analytes, showing they

had matching sensitivities. The linear range and limit of detection for the three analytes were investigated, and the findings are shown in Table 1. Correlation coefficients of all regression lines were over 0.999. The limit of detection was calculated from the extrapolation of the regression line of the data, i.e. the intercept plus 3 times the standard deviations of the noise, assuming a variation of normal distribution<sup>9,10</sup>. Using the above definition, the limits of detection for the method ranged from 0.70 to 1.18 mg L<sup>-1</sup>.

**Precision and recovery.** The precision of the chromatographic determination in relation to the proposed method, expressed as a relative standard deviation (% RSD), was found by analyzing the effluent samples 5 times on 5 different days (intra-day and inter-day). As summarised in Table 2, the % RSD of the chromatographic determination varied from 0.9 to 3.9 and 1.2 to 5.6 for intra-day and inter-day, respectively. The recovery of the method, including all experimental procedures from the addition of an internal standard, sample preparation to the chromatographic analysis, was measured using the effluent samples. Known amounts of each standard were spiked into the samples which were analysed in triplicate using the developed HPLC method. The recoveries were calculated on the basis of the difference between the total amount determined in the spiked samples and the amount determined in the non-spiked samples and expressed as a mean percentage ratio between the amounts found and the amount spiked. As shown in table 3, the recoveries varied from 87% to 102%.

**Analysis of effluent samples.** The developed method in this study was applied to the effluent samples, namely LZ-A, LZ-B, LZ-C, LZ-D and LZ-E, collected on five different days from the pharmaceutical manufacturing plant. The concentrations determined ranged from 1.79 to 2.59 g L<sup>-1</sup>, 1.75 to 2.45 g L<sup>-1</sup> and 0.90 to 2.21 g L<sup>-1</sup> for nicotinic acid, nicotinamide and 3-cyanopyridine, respectively. The concentrations are summarized in Table 4 above.

## IV CONCLUSION

Table 2. Precisions for the chromatographic determination as expressed by the relative standard deviation (RSD)

Sample	Intra-day RSD (% , n=5) a			Inter-day RSD (% , n=5)		
	Nicotinic Acid	Nicotinamide	3-cyanopyridine	Nicotinic Acid	Nicotinamide	3-cyanopyridine
LZ-A	3.3	2.1	0.9	2.3	2.5	1.2
LZ-B	1.7	2.9	1.1	3.5	2.1	3.5
LZ-C	2.4	3.9	3.0	2.6	3.1	5.6
LZ-D	3.1	2.6	2.3	4.7	2.2	3.9
LZ-E	3.3	3.5	2.7	4.8	4.0	2.9

A rapid and reliable HPLC method for the simultaneous determination of nicotinic acid, nicotinamide and 3-cyanopyridine in effluent was developed. This method requires nothing but a common stationary phase and a simple tertiary mobile phase, which, more importantly, gives good resolution and peak shapes. Besides, it requires a short analytical time (6 min.) and covers a wide linear range, and is thus useful for the monitoring of these

heterocyclic compounds in related industrial effluent.

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**Table 3. Recoveries of analytes spiked in factory effluents**

Mean recovery (%; n=3) <sup>a</sup>			
Sample	Nicotinic Acid	Nicotinamide	3-cyanopyridine
LZ-A	95	90	96
LZ-B	98	92	90
LZ-C	93	87	95
LZ-D	102	91	94
LZ-E	99	93	92

<sup>a</sup>Expressed as [(amount found) / (amount spiked)] x 100.

**Table 4. Determination of the three analytes in the effluent samples, g L<sup>-1</sup>**

Mean recovery (%; n=3) <sup>a</sup>			
Sample	Nicotinic Acid	Nicotinamide	3-cyanopyridine
LZ-A	2.33	2.45	0.90
LZ-B	1.79	2.10	0.98
LZ-C	2.59	2.04	2.21
LZ-D	2.56	1.79	1.98
LZ-E	2.41	1.75	1.58

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## Uses of Liposterolic Extracts of Saw Palmetto (鋸棕櫚) for the Treatment of Chronic and Subacute Cystitis and Benign Prostatic Hyperplasia

Cheung, Hon-Yeung

**Botanical Name:** *Serenoa repens* (W. Bartram) or *Serenoa serrulata* Hook

**Plant Family:** Aracaceae

**Part Used:** Fruit

**Pharmacopoeia Name:** Sabal fructus

**Other Names:** Dark Palmetto; Fan Palm; IDS 89; Palmetto; Sabal Berries; Saw Palmetto; LSESr;

**Brand Names:** MegaBust®, ProstaMax®, Prostat®, ProstaPlus®, Prostenil®, Sabalin®, Saw, Saw Palmetto, Saw Palmetto Berries, Permixon®, Propalmex®, Stroge®; Harzol®;

### I ABSTRACT

**Saw** palmetto is an extract from the berry of the plant *Serenoa repens*. It is an important food source for the Native Indians. The fruit of this herb contains free fatty acids and phytosterols.  $\beta$ -sitosterol present in alcoholic extract of the fruit is estrogenic and can relieve bladder and urinary disturbances associated with stage I and II benign prostatic hyperplasia (BPH). Recent studies show that saw palmetto has a mild toxic effect on prostate cancer cells. It blocks testosterone from reaching prostate cells without affecting the level of testosterone in circulation. Hence, it preserves sexual function yet prevents the development and enlargement of prostate cancer and benign prostate. Saw palmetto has also been claimed effective in increasing breast sizes, sexual desire in both male and female and in acting as a mild diuretic. Due to the presence of a high molecular weight polysaccharides and flavonoids, it also possesses anti-allergic and anti-inflammatory activity.

### II DESCRIPTION AND BACKGROUND

Saw palmetto, as shown in Fig 1, is a small, shrubby and palm-like plant that grows on sandy soils in North America and the West Indies. Its botanical name is *Serenoa repens* (W. Bartram) or *Serenoa serrulata* Hook. It can be found in the coastal and southeastern regions of the United States from Carolina to Mississippi and Florida as well as California<sup>(4)</sup>. This shrubby palm usually grows from 6 to 10 feet in dense thickets beneath pine trees. It has a large underground trunk producing juicy palmate, green, white coated leaves, spanning 0.31 meter and have sword-shaped leaf blades radiating from a central point and are supported by spiny stems above ground. Flowers, blooming among the fans, are creamy white with 3-5 petals from May to July and develop yellow olive-like berries which become externally brownish-black to bluish-black when ripe and have an oily gleam due to their high content of fatty acids<sup>(4)</sup>. Ripen berries may have a few large angular depression and ridges due to the contraction of the sarcocarp, apex marked by the scar of the style, and the base either with a short stalk or stem scar. The sarcocarp and epicarp together form a thin coriaceous shell enclosing a hard but thin endocarp, which



Figure 1. Photo of fruit (left), fronds (upper right) and seeds (lower right) of Saw Palmetto. (source: <http://www.volusia.org> & from Readers' Digest)



#### Contraindications

Contraindicated for pregnant and nursing women due to antiandrogenic and estrogenic activity.

#### Undesirable Effects

Adverse effects are uncommon, although occasional dizziness, headache and gastrointestinal problems, such as stomach upset, nausea, vomiting, diarrhea and constipation have been reported.

#### Interaction with Conventional Drugs

Whenever anticoagulant or anti-platelet drugs are used, it may enhance their effects.

is externally reddish-brown and somewhat fibrous. The inner layer of endocarp, enclosing a hard, ellipsoidal or ovoid seed, is smooth. When cut transversely, it shows a thin testa, a narrow perisperm, and a large area of dense, horny, grayish white endosperm. Ripen berries of saw palmetto release aromatic odor and taste sweetish but slightly stinging.

Sabal berries have been used as food and medicines by Native Americans for hundreds of years. Indians have been using extracts of the berries to treat a variety of men's genitourinary problems since the early 1700s. It was administered to men to increase the function of the testicles. Aside from their medicinal values, both fruit and palm heart (terminal bud) have been consumed as tonic to provide nutritional needs for the reproductive systems of female and male and for reduction of inflammation in genitourinary catarrh, for problems of breast disorders in women and for nourishing, relaxation and diuretic purposes.

The berries were utilized in the similar manners by European settlers for the treatment of prostate hypertrophy and relief of bladder symptoms associated with this problem in old men. The fruit of saw palmetto was listed as official remedies in the U.S. Pharmacopoeia from 1906 to 1916 and in the National Formulary from 1926 to 1950 for urogenital ailments. But it was dropped out of the list for medicinal uses after the Second World War. Its acceptance has been sustained as it has been popular among European. More recently, the juice of the berries has been mixed with carbonated water to make a soda called "Metto" while wildlife eats the berries for food. Today, annual harvest of the fruit for different purposes has exceeded 7 million kg.

### III BIOACTIVE CONSTITUENTS

The brownish black berry of saw palmetto contains approximately 1.5% of oil. Herbal extracts are derived from the dried berry of the plant and the active ingredient in commercial preparations is the lipophilic extract of the berries (2,19,29). Solvents used for extraction of the liposterols include ethanol, hexane or supercritical carbon dioxide. Manually cold pressing of the berries may also be used in small-scale operation. The extracts contain many biologically active compounds, including both free and esterified saturated and unsaturated fatty acids such as lauric, myristic, palmitic, oleic, capric, caprylic, linoleic, linolenic, and stearic acids, flavanoids, and phytosterols such as  $\beta$ -sitosterol, campesterol, and stigmasterol (Fig 2). Besides, two biologically active monacylglycerides were also isolated. The fatty acids usually make up 80-90% of the extract, with only a small portion being other compounds (6,7).

### IV CONTEMPORARY USES

Saw palmetto tea was claimed effective in managing such genitourinary tract disturbances as benign prostate hyperplasia (BPH) (22,30), in increasing sperm production, breast size, and sexual vigor and in acting as a mild diuretic. Until a fat soluble purified extract was produced, it was believed that the plant extracts had little effect because of their very poor bioavailability. As medicine came to rely more on synthetic drugs, saw palmetto fell out of favor at one time in the United States, along with all other herbs for medicinal purposes. But French scientists in the 60' reported that its effectiveness could be maximized if the oils of this herb were concentrated. This discovery revived

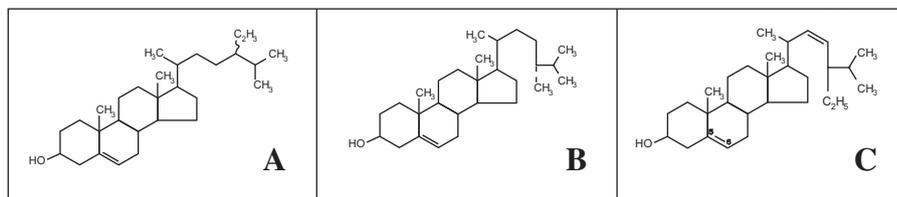


Figure 2. Chemical structure of the main liposterolic components in saw palmetto. A =  $\beta$ -sitosterol; B = campesterol; C = stigmasterol.

people's interest of its' medicinal applications. Today, saw palmetto oil is a commonly used ailment for BPH in both Japan and Europe (17,26), although other common therapies including  $\alpha$ -blockers and 5- $\alpha$ -reductase inhibitors such as finasteride or Proscar are also prescribed. Controversial views about its effectiveness, however, arise from time to time (5,16,24). Duli *et al* commended that although saw palmetto is not as effective as traditional medications in the treatment of BPH, it has fewer side effects (14). Hence, saw palmetto is one of the most frequently used complementary and alternative medicines for prostatic problems in these days (11).

Saw palmetto is used by women that wish to enhance their bust size. A feeling of fullness and firmness is achieved in most women that consume 160 mg of 85-95% extract twice daily. When mixed with other certain herbs, quicker and larger results with 10-30% bust size increases are reported. Saw palmetto when used alone usually produces results within 30-60 days. However it has been reported that results were not noticed for almost a year.

Table 1 shows all the uses of saw palmetto that have been claimed (4). Among all these claims include sexual enhancement, acne treatment and prevention of hair loss. However, scientific evidence and statistical data are still lacking.

### V MODE OF ACTION

Although the evidence for the effectiveness of saw palmetto in treating BPH is strong, the precise mechanism of its action particularly the liposterolic fraction of the berry extract remains obscure. Different explanations

about its action have been proposed (9). In general, the therapeutic benefit of saw palmetto is believed to be mainly attributable to the inhibition of types 1 and 2  $\alpha$ -reductase, competitive binding to androgen receptors in prostate cells and the inhibition of phospholipids A2 and oxidative enzymes responsible for prostaglandin synthesis (23).

#### 1. Role of liposterolic extract in the management of benign prostate hyperplasia (BPH)

BPH, a non-cancerous enlargement of the prostate, is a common problem progressive with age in men over 50 (16,18). Symptoms result when the enlargement squeezes the urethra where it runs through the prostate. BPH is thought to be caused by an accumulation of a metabolized product of testosterone in the prostate. Starting at about age 40, levels of a hormone called prolactin begin increasing in men; this stimulates an increased production of the enzyme 5- $\alpha$ -reductase, which enhances the metabolism of testosterone, resulting in an increase of the metabolic byproduct di-hydro-testosterone or DHT (Fig 3). Once within the prostate, testosterone is converted to the more potent hormone dihydrotestosterone (DHT) which, in turn, stimulates the cells to multiply excessively, eventually causing the prostate to enlarge. Although DHT has an undesirable effect of stimulating prostate cells into dividing and multiplying which causes the prostate enlargement, molecular analyses of the progression of BPH reveal that numerous candidate genes are involved (21). More than 50 percent of men age 60, and 80 percent of men age 80, are estimated to suffer from BPH (26). It is important to note that BPH does not necessarily lead to cancer; however, a man can have BPH and cancer at the same time.

Table 1. Diseases and ailments against which saw palmetto has been used (4)

Anticatarrhal/anti-inflammatory	Digestive aid	Neuralgia
Appetitic stimulant	Diuretic	Prostate gland (enlargement)
Asthma	Dysuria	Reproductive organs
Breast atrophy	Epididymitis	Respiratory congestion & infection
Breast enlargement	Expectorant	Sedative
Bronchitis	Genito-urinary stimulant	Sexual stimulant
Colds	Hormone regulation	Testicular atrophy
Diabetes	Impotence, male	Urinary tract infection & cystitis
Diarrhea and Dysentery	Kidney disease, incl. Bright's	Whooping cough

The primary therapeutic action of saw palmetto extract in the treatment of BPH is to inhibit the intraprostatic conversion of testosterone to DHT and transport. Thus, inhibition of DHT formation and expression of 5- $\alpha$ -reductase generate a positive effect in the treatment of BPH. Other possible mechanisms of action include interfering with DHT's intracellular binding, estrogen receptor-binding, or prolactin receptor-binding (10,25). Interference with the receptor-binding of these hormones would limit the action of these hormones. It is also possible that saw palmetto may have an anti-inflammatory action on prostate tissues by inhibiting enzymes that produce prostaglandins and other inflammatory chemicals.

When the effect of the lipidosterolic extract of saw palmetto was tested on molecular level associated with cell apoptosis, it was found that apoptosis in epithelial prostatic cells but not in skin fibroblasts or the breast, testes, epidermis or kidney was induced (3). The extract was also found to suppress insulin-like growth factor-I signaling and induce stress-activated protein kinase/c-Jun N-terminal kinase phosphorylation in human prostate epithelia cells (28). Besides, other molecular markers involved in the apoptotic process, i.e. the Bax-to-Bcl-2 expression ratio and activity of caspase-3 were significantly increased after patients with BPH were treated with saw palmetto (27). These results indicate that saw palmetto involves in although the progression of BPH is a complex consequence of growth factors, adrenergic stimulation, inflammatory processes and the 5- $\alpha$ -reductase activity, saw palmetto has a role to be involved. Nevertheless, at the time of this publication, the details of mechanism are still obscure.

## 2. Aphrodisiac effects

Female sexual dysfunction is a common problem particularly in surgically or naturally menopausal women. This is due to a lower than normal level of testosterone in these women. Though not generally considered an aphrodisiac, supplements containing testosterone have been found to enhance sexual drive and could be used effectively in some cases of inhibited desire when endogenous levels of testosterone are extremely low. Because of the androgenic effect and the preventive activity of conversion of testosterone to DHT by saw palmetto, it increases libido in women and could be used as an aphrodisiac to cure women's sexual frigidity (13,20).

When a plant extract of saw palmetto

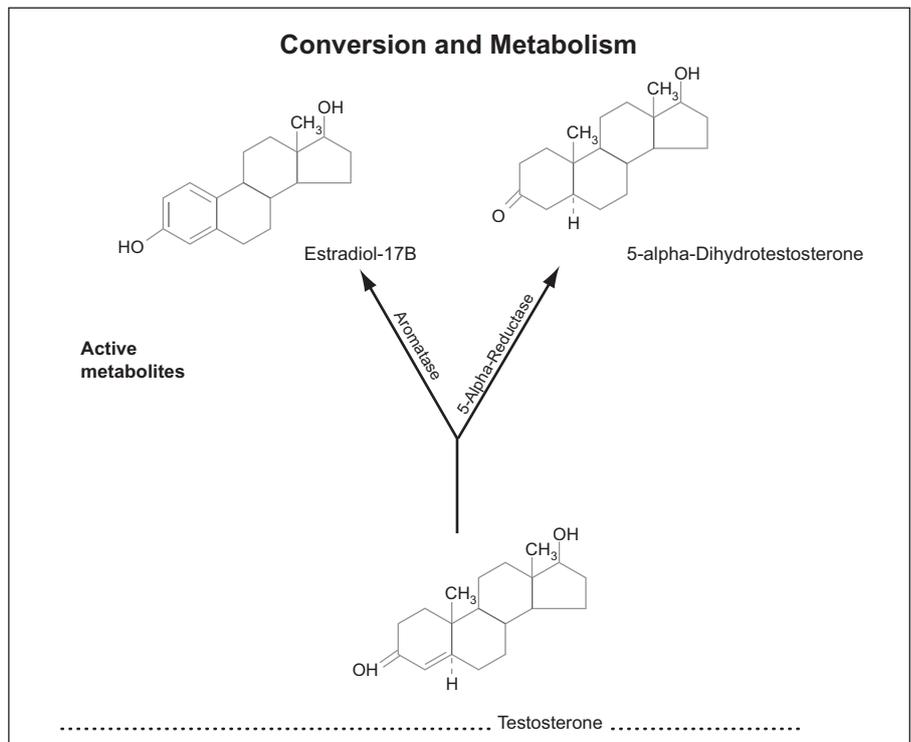


Figure 3. Enzymes involved in the conversion and metabolism of testosterone.

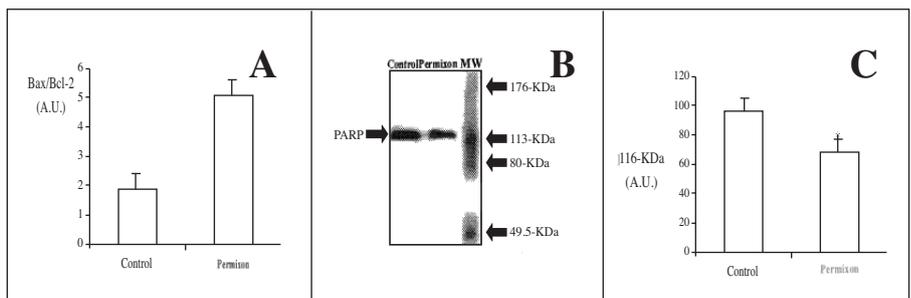


Figure 4. Changes of apoptotic index and caspase-3 activity in prostatic tissue from control and Saw palmetto treated patients with BPH. (A) Bar graph shows mean Bax-to Bcl-2 expression ratio in arbitrary units; (B) Differences of Western blot of caspase-3 activity in prostatic tissue from untreated control and Saw palmetto treated patients with BPH, and (C) Densitometric analysis of Western blots results (27).

was given to 1098 men with moderate BPH under double-blind study, it was found that the extract fared better than finasteride in a sexual function survey and gave rise to less complaints of decreased libido and impotence (12).

## 3. Breast enlargement

Saw palmetto is an estrogenic natural substance which allows estrogen to be more influential on the body. In the PDR for herbal medicine, it states "Diosgenin has been found to have an estrogenic effect on mouse mammary epithelium. Ovariectomized mice that received diosgenin (sc) at dosage levels between 20 and 40 mg/kg for 15 days had significant increases in mammary development scores. When Saw Palmetto is combined with herbs that contain diosgenin, significant increases in mammary development scores have been recorded (1). Saw

Palmetto lowers cytosol and nuclear receptor values for estrogen, which is an anti-estrogen effect. (14). But by blocking nuclear receptor sites, overall level of the bodies' own natural estrogen increases and provides the augmentation effect similar to estrogen on diosgenin (1). Thus, it is also an estrogenic substance. Breast augmentation by this way is long lasting and does not disappear upon discontinuance of the product. However, the results may vary, as level of natural estrogen and the number of empty receptor sites available for the phytoestrogens to bind varied from person to person.

Saw palmetto has also been claimed to increase sperm production and could be used as a cure for impotence in male. But these claims and uses require further systematic studies and investigations.

## VI CONTRAINDICATIONS

There are no known contraindications to saw palmetto preparations. Nevertheless, its hormonal effects suggest that it should not be used during pregnancy or lactation.

## VII UNDESIRABLE EFFECTS

Adverse effects are very rare. Occasional dizziness, headache and gastrointestinal problems such as stomach upset, nausea, vomiting, diarrhea and constipation may occur.

## VIII INTERACTIONS WITH CONVENTIONAL DRUGS

Saw palmetto has hormonal activities. It may interfere with hormonal therapies such as contraceptive pills or

patches and hormone-replacement therapy (HRT). As it has been reported to prolong bleeding time, it should be used with caution with antiplatelet drugs and anticoagulants.

## IX MODE OF ADMINISTRATION

Saw palmetto comes as standardized extract in capsule, powder, standardized solvent extract or dry berry in decoction. A tea prepared from dried berries is also a common practice.

## X DOSAGE

Although a single daily dose of 320 mg has been reported effective, the standard dosage of saw palmetto for reducing symptoms associated with stages I and II BPH is 160 mg twice a

day of an extract standardized to contain 85 to 95% fatty acids and sterols<sup>(8)</sup>. Duration of treatment has usually been 3 months, but both shorter and longer trials up to 6 months have been investigated. Taking doses more than this amount does not seem to produce a better result<sup>(23)</sup>. If saw palmetto is prepared by other ways, its administrations are different; i.e. 2-4 ml, T.I.D. of tincture; 1-2 ml, T.I.D. of fluid extract of dried berry pulp (1:1); 1,000 mg, T.I.D. of capsules; or 2 tea spoon of dried berry with 24 oz water and simmer slowly until liquid is reduced by half, take 4 oz T.I.D. as tea.

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## 同一專業同一夢，推進民康攜手創 One Profession, One Dream - Connect to Advance Health Care

### Welcome Message from the Chairlady Hong Kong Pharmacy Conference 2008

Dear Friends and Distinguished Colleagues,

It is with great excitement and honor that we warmly welcome all of you to the 21<sup>st</sup> Hong Kong Pharmacy Conference, to be held on 1<sup>st</sup> & 2<sup>nd</sup> November 2008 in the AsiaWorld-Expo, Hong Kong. The age of 21 signifies maturity, exemplified by the substantial growth of our conference since its inauguration in 1988. We treasure the connected effort of the six organizing parties -- the School of Pharmacy at the Chinese University of Hong Kong, the Department of Health, the Hospital Authority, the Pharmaceutical Society of Hong Kong, the Society of Hospital Pharmacists of Hong Kong and the Practicing Pharmacists Association of Hong Kong - to produce a high quality conference. To better suit for the growing number of conference attendees and to plan for an increase in program diversity, this year's organizing committee has chosen the AsiaWorld-Expo as our venue. The AsiaWorld-Expo is the largest, world-class exhibition venue in Hong Kong that is easily accessible by various transportation routes.

Our conference theme this year is "One Profession, One Dream - Connect to Advance Health Care", coined with inspirations from the slogan of the Beijing 2008 Olympic Games. Similar to what is portrayed in the Olympic Games, our theme expresses the common wishes of pharmacists all over the world: to collaborate and contribute to a brighter future for health care with our versatile, but unique, expertise in medication management. We believe despite our different strengths, interests and work settings, we belong to the same profession and we share the same aspiration and mission of enhancing quality-of-life for humanity. Meanwhile, we appreciate that in an advanced health care system, health care professionals from different disciplines must work as one professional team to enable optimal utilization of expertise and better delivery of patient care. With that in mind, our program subcommittee has assembled a program that will expose our attendees to the ideas of "Connect and Collaborate", "Profession and Dream" and "Advance Health care" through a variety of topics.

#### *Connect and Collaborate*

The 2008 Sichuan Earthquake is heart-wrenching and devastating. While it is difficult for many of us to take another look at this tragedy, we can visualize the importance of providing medicines and medical care in disasters as such. For decades, pharmacists in different settings have dedicated themselves to working more closely with physicians and other health care professionals to deliver better medicine and better care. With sky rocking healthcare expenses, growing prevalence of chronic disease and aging population, we see the need for more pharmacists working in collaboration with other health care professionals to demonstrate outcome improvement. It is our greatest honor to have invited Dr Bernard MH Kong, the founding president of The Hong Kong Society of Medical Professionals and deputy director of the Hong Kong East Cluster Community Service, to share with us his insights on how the medical and allied health professionals could collaborate to promote a strong and positive public image in Hong Kong and to strive for a harmonious society.

Science forms the foundation of the profession of pharmacy. More scientific data are needed to substantiate evidence-based pharmacy practice. We are extremely grateful to have Prof Barry Carter, a renowned researcher in physician-pharmacist collaboration from the University of Iowa in United States, to share with us his foresight in how to successfully demonstrate the impact of these profound collaborations. To echo on the importance of evidence-based practice, our keen colleagues, Mr Humphrey Cheng and Donald Chong, will deliver a specially designed session on evidence-based medicine to further enhance the practical aspect.

With Beijing's hosting of the Olympics Games 2008, we all noted that the integration of culture, as well as the practice of medicine, is on a rising trend. We are grateful to have invited several prestigious international and local speakers to enlighten us on the latest development in Chinese and herbal medication in a variety of illnesses. In addition, Dr Patrick Yung, Deputy Team Head of the Division of Sports Medicine at the Prince of Wales Hospital, and Ms Dora Chan, pharmacist from the Hospital Authority will educate us on a timely topic, sports medicine. These unique topics should stimulate significant interests from our community pharmacists, as well as students and practitioners in other disciplines.

#### *One Profession, One Dream*

Dreams have long been recognized to be a source of psychological inspiration with imagination and innovation instilled. Combining various theories, dreaming appears to be a result of brain activation and synthesis. It is also a necessary process for memory consolidation and mind harmonization. In order to consolidate our experience, several dedicated local pharmacists will showcase their patient-care practice models in the hospital and community settings. We invite you all to come to support and celebrate with our colleagues for their advancement.

Besides reflecting on previous experience, a forward motion such as reform in education and healthcare system are crucial in shaping the role of pharmacists. We are honored to have Prof Vincent Lee, Professor and Director of the School of Pharmacy of the

Chinese University of Hong Kong, to share with us his unsurpassed insights in the transformational changes needed to occur in the education process, healthcare system and inter-professional relationships. These changes are fundamental to the elevation of cost-effective health care in Hong Kong.

Clinical therapeutic knowledge is one clear label of the pharmacy profession and we have deliberately expanded this session in this year's program. In particular, we have invited several distinguished speakers from England and the United States to share their clinical pearls and practical experience. The topics will cover almost the entire life spectrum: from pediatrics to geriatrics care. Therefore, those of you who are entrepreneurial or actively involved in setting up new pharmaceutical services will not want to miss this session!

#### *Advance Health Care*

We know dreams sometimes may even offer previews on how future events might proceed. As highlighted by some recent high-profile medication withdrawals and regulatory decisions, it is increasingly recognized that the possibility of predicting drug response should be seriously explored. Application of Pharmacogenomics, a science that examines how the inherited variations dictate drug response, seems to be a very promising approach that may allow the dream of "personalized medicines" to come true. To prepare pharmacists for the latest and most relevant development in pharmacogenomics, we are fortunate to have invited several distinctive researchers to speak on their most cutting-edge findings. Meanwhile, advancement in pharmacy automation technologies will also be covered on day 2 to tie in with the sessions on local and worldwide initiatives for improving medication safety.

Along the line of medication safety, recent issues regarding the use of certain generic products deserve much attention. We are extremely honored to have invited Dr Lawrence Yu, Director for Science at the Office of Generic Drugs, Food and Drug Administration (FDA). Dr Yu will introduce to us the FDA's generic drug regulatory assessment and approval process, pharmaceutical quality and bioequivalence standard. He will also open up our eyes with the avant-garde role of pharmacists in ensuring the quality, safety, and effectiveness of generic drugs. On day 2, we are grateful that several well-experienced speakers will chime in with the local perspectives on selecting generic products and the patent issues.

The theme of the Beijing 2008 Olympic Games "One World One Dream" reflects the essence and the universal values of the Olympic spirit -- **Unity, Friendship, Progress, Harmony, Participation and Dream. The Hong Kong Pharmacy Conference shares the same belief.** The excitement created for our conference stands on the shoulders of the voluntary contribution of every single member in the organizing committee. The success of this conference, on the other hand, will be determined by your attendance and active participation. It is through your keen interests that the pharmacy profession is connecting, advancing and exploring new frontiers. Please come and join your pharmacist colleagues to realize the dreams we all share!

Warmest regards,



Chui-ping Lee  
Chairlady, Conference Organizing Committee  
Hong Kong Pharmacy Conference 2008

#### **Saturday, November 1, 2008**

1:00pm	Registration	
1:30pm - 2:30pm	Lunch	
2:00pm - 3:00pm	Pre-Conference Symposium: How common are liver diseases in HK?	
3:15pm - 3:30pm	Break, Poster and Exhibition	
3:30pm - 3:40pm	Opening	
3:40pm - 3:50pm	Welcome Speech by Conference Chairperson	
3:50pm - 4:10pm	Keynote Address: Dr. Bernard Kong - Good Medicine - "The Holy Grail" Finding innovative ways to team up and improve patient care	
4:10pm - 4:55pm	Theme 1: Prof. Barry Carter: Research involving physician / pharmacist collaboration: Examples and keys to success	
4:55pm - 5:15pm	Tea Break	
5:15pm - 6:00pm	Theme 2A: Prof. Vincent Lee - Education and Healthcare Reform	Theme 2B: Prof. Annie Lam - Geriatric Specialist Pharmacy Services in the US: Roles of Pharmacists across Practice Setting
6:00pm - 6:45pm	Theme 3A: Prof. Lawrence Yu - Understanding FDA's Generic Drug Approval Process and Regulatory Standard	Theme 3B: Prof. Ian Wong - The Role of Clinical Pharmacist in Paediatric and Neonatal Service
7:00 pm - 10:30 pm	Conference Dinner	

**Sunday, November 2, 2008**

8:00am - 10:00am	Breakfast		
8:30am - 9:00am	Registration		
	<b>Concurrent A</b>	<b>Concurrent B</b>	<b>Concurrent C</b>
9:00am - 10:40am	<b>Risk Management</b>	<b>Clinical: Paediatrics</b>	<b>Generics</b>
	Ms. Anna Lee HA Initiatives on Medication Safety	Dr. Penny North-Lewis Paediatric Formulation in Clinical Practice	Mr. Anthony Wong Selecting Generic Products - a Perspective from Local Public Hospitals
	Dr. Tony Mak Medication Incidents Resulted in Clinical Poisonings with Public Health Implications	Prof. Ian Wong Pharmacotherapy in Epileptic and Convulsive Disorders in Children	Dr. Lawrence Yu FDA Question-based Review for Generic Drugs: A New Pharmaceutical Quality Assessment System
	Mr. Michael Ling Connect to Advance Medication Safety - It's all about Saving Face	Dr. Sara Arenas-Lopex Drug Dosing in Children	Ms. Audrey Shum A Brief Guide to Patent Protection in Hong Kong and How it Impacts on the Operation of Pharmacies
10:40am - 11:00am	Coffee Break		
11:00 am - 12:20pm	<b>Sports Medicine</b>	<b>Clinical: Geriatrics</b>	<b>BABE &amp; EBM</b>
	Dr. Patrick Yung Sports Injuries Medicine in Primary Healthcare Setting: What pharmacist can help?	Dr. Paul Shea Medicine in Elderly - Jekyll and Hyde	Prof. Brian Tomlinson Bioavailability & Bioequivalence Tests in Hong Kong
	Ms. Dora Chan Pharmacy at the 2008 Olympic Equestrian Games Hong Kong	Prof. Annie Lam Practice Pearls and Suggestions to Enhance Hand-on Pharmaceutical Care Delivery to Older Adults	Mr. Humphrey Cheng and Mr. Donald Chong Evidence Based Medicine - the panacea to today's practice
12:20pm - 2:00pm	Lunch		
	<b>Concurrent D</b>	<b>Concurrent E</b>	<b>Concurrent F</b>
2:00pm - 4:00pm	<b>Genomics</b>	<b>Integrative Medicines</b>	<b>Practice Modles &amp; Experience Sharing</b>
	Dr. Raymond Wong Pharmacogenetics and Cancer Treatment	Prof. Kelvin Chan The worldwide development of Chinese medicine in pharmaceutical care	Prof. Barry Carter Design of a Health Services Research Study: Important design features and measurement of covariables
	Dr. Patrick Kwan Genetic Polymorphism in Drug-resistant Epilepsy	Prof. Zhijun Yang Dynamic Explanation on the Efficacy and Quality of Herb (Chinese Medicine)	Dr. Wilson Leung Disease Management in Patients with Type 2 Diabetic Nephropathy - Pharmacist in a Multi-disciplinary Team
	Prof. Joyce You Clinical Translation of Pharmacogenomics in Anticoagulation Therapy	Prof. Leung Ping Chung Diabetic Foot Problems - From Standard care to Complementary / Alternative Management	Mr. Simon So Specialised Pharmacy Services for Chronic Kidney Disease (CKD) patients: Concept, Design and
	Dr. Siu Wah Tang Personalized Medicine in Psychiatry	Prof. Joan Zuo Potential Interaction of Oseltamivir and Chinese Medicine Formulae - Preliminary Investigation in Rats	Mr. Maxwell Yung Public Relationship Survey: A Community Pharmacy Based Customer Survey
		Mr. Philip Chiu Image Building for Community Pharmacist	
Evaluation Form Collection			

**Last update: 6 June 2008**

## HONG KONG PHARMACY CONFERENCE 2008

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## New Products



**Active ingredient:**  
Sitagliptin phosphate

**Presentation:**  
Available in 25mg, 50mg, 100 mg tablets in packs of 28's

**Pharmacological Properties:**  
JANUVIA is an orally-active, potent, and highly selective inhibitor of dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones.

**Indications:**  
JANUVIA is indicated as an

adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and/or sulfonylurea, and a PPAR $\gamma$  agonist (i.e. thiazolidinediones) when treatment with a single agent alone, with diet and exercise, does not provide adequate glycemic control.

**Dosage and Administration:**  
The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, a PPAR $\gamma$  agonist (i.e.: thiazolidinediones), or metformin plus a sulfonylurea. JANUVIA can be taken with or without food.

**Contraindication:**  
JANUVIA is contraindicated in

patients who are hypersensitive to any components of this product.

**Precautions:**  
JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency.

**Drug Interaction:**  
JANUVIA is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6, and is not an inducer of CYP3A4. JANUVIA is a p-glycoprotein substrate, but does

not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

**Side Effects:**  
JANUVIA was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy. In controlled clinical studies as both monotherapy and combination therapy, with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycaemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA were similar to placebo.

**Legal Classification:**  
P1S1S3

## CERVARIX™ (GlaxoSmithKline)

### Active ingredient:

Human Papillomavirus type 16 L1 protein  
Human Papillomavirus type 18 L1 protein

### Presentation:

Suspension (0.5ml) for injection in pre-filled syringe.

### Pharmacological Properties:

CERVARIX is a non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response.

### Indications:

CERVARIX is indicated for the prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on demonstration of efficacy in women aged 15-25 years following vaccination with CERVARIX and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

### Dosage and Administration:

The recommended vaccination schedule is 0, 1, 6 months.

The need for a booster dose has not been established. It is recommended that subjects who receive a first dose of CERVARIX complete the 3-dose vaccination course with CERVARIX.

Girls aged less than 10 years is not recommended due to lack of data on safety and immunogenicity in this age-group. CERVARIX is for intramuscular injection in the deltoid region.

### Contraindication:

Hypersensitivity to the active substances or to any of the excipients. Administration of CERVARIX should be postponed in subjects suffering from an acute severe febrile illness.

### Precautions:

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

CERVARIX should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of CERVARIX.

As with other vaccines administered intramuscularly, CERVARIX should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Vaccination is not a substitute for regular cervical screening or for precautions against exposure to HPV and sexually transmitted diseases.

### Drug Interaction:

In all clinical trials individuals who had received immunoglobulin or blood products within 3 months prior to the first vaccine dose were excluded.

#### *Use with other vaccines*

Data have not been generated on the concomitant administration of CERVARIX and other vaccines.

#### *Use with hormonal contraceptive*

In clinical efficacy studies, approximately 60% of women who received CERVARIX used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of CERVARIX.

*Use with systemic immunosuppressive medicinal products*  
As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

### Side Effects:

Common adverse reactions include: headache, gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain, itching/pruritus, rash, urticaria, myalgia, arthralgia, injection site reactions including pain, redness, swelling; fatigue, and fever ( $\geq 38^{\circ}\text{C}$ ).

Uncommon adverse reactions include: dizziness, upper respiratory tract infection, induration, and local paraesthesia.

### Legal Classification:

P1S1S3

## ISENTRESS® (MSD)

### Active ingredient:

Raltegravir

### Presentation:

Available in 400mg film-coated tablets in a bottle of 60's

### Pharmacological Properties:

ISENTRESS (raltegravir, MSD) is an HIV integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1).

### Indications:

ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response

### Dosage and Administration:

For the treatment of patients with HIV-1 infection, the dosage

of ISENTRESS is 400mg administered orally, twice daily with or without food. ISENTRESS is to be given in a combination regimen with other antiretroviral agents.

### Contraindication:

ISENTRESS is contraindicated in patients who are hypersensitive to any component of this medicine.

### Precautions:

#### *Immune Reconstitution Syndrome*

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium tuberculosis*, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

### Drug Interaction:

Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, caution should be used when coadministering ISENTRESS with rifampin or other strong inducers of UGT1A1. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less strong inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used with the recommended dose of ISENTRESS.

Similar to rifampin, tipranavir/ritonavir reduces plasma concentrations of ISENTRESS.

### Side Effects:

Common adverse reactions include: diarrhea, nausea, headache, and pyrexia.

Uncommon adverse reactions include: abdominal pain, vomiting asthenia, fatigue dizziness lipodystrophy

### Legal Classification:

P1S1S3

*Unlock the possibilities in*



*Promising Efficacy in*  
1<sup>st</sup> line mRCC Clinical Trial<sup>1</sup>



*Significant Improvement in*  
refractory GIST Clinical Trial<sup>2</sup>

- Median PFS\* double with SUTENT (11 months) versus interferon alfa (5 months) in mRCC patients<sup>1</sup>
- Median TTP<sup>Δ</sup> was more than 4 times as long with SUTENT (27.3 weeks) as with placebo (6.4 weeks) in refractory GIST patients<sup>2</sup>
- Tolerability was acceptable in patients receiving SUTENT<sup>1,2</sup>

\*PFS - Progression free survival  
<sup>Δ</sup>TTP- Time to tumour progression

**References:**

1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Eng J Med* 356:2:115-124
2. Demetri GD, Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329-1338.

Detailed Prescribing Information is Available Upon Request.



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