

HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 16 NO 1 Jan - Mar 2009 ISSN 1727-2874



News & Short Communications

From Pfizer Hong Kong, Some 'Driving' Lessons

從近日藥品質量問題探究香港藥廠的經營管理

Mood Disorders: What Can A Community Pharmacist Do?

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Review on Management of Complications of Cirrhosis focusing on Ascites

The First FDA Approved Bioengineered Drug from Transgenic Goats - Antithrombin

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Use of Herba Lobellae Chinensis (半邊蓮) is Attributed to the Bronchodilation and Diuretic

Effects of Lobeline and its Derivatives

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References: 1. Data on File, MSD Hong Kong. 2. Hong Kong Product Circular (JANUVIA, MSD). 3. Goldstein BJ, Feinglos MN, Luchford JK, et al; for the Sitagliptin 036 Study Group. Effect of initial combination of sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007;30:1979-1987. 4. Hong Kong Product Circular (JANUMET, MSD).



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- Herbal Medicines & Nutraceuticals
- New Products

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Are You Putting the GOOD in Your Practices?



In the last few weeks, news about the problem of drug supply was spread around by the media in Hong Kong. These reports have attracted a lot of attention from people. All walks of life were involved in the discussion of these hot issues about the safety of drugs.

Medicine is supposed to cure diseases and save lives. But if its quality does not meet certain safety standards or efficacy requirements, it puts life in danger and may result in death instead of saving life. A recent accident causing the death of five cancer patients in hospitals because of taking Allopurinol pills contaminated with a fungus identified as the *Rhizopus microsporus* is a typical example (page 7). Although how this fungus got into the granules of these pills remains a mystery, what is obvious is the price of five lives. Following this accident, a series of other problems relating to drug supply, such as the expiry dates (page 6) and supply of unregistered drugs to Hospitals all surged to the surface. These series of problems signify inadequate manpower for monitoring the business and there are also some defects in manufacturing relevant to the implementation of Good Manufacturing Practice (GMP). Consequently, the uncovering of these problems has stirred up people's concern.

Two articles, separately contributed by Herman Leung, who is a veteran in drug manufacturing, and by DK O'Toole and HY Cheung, who are experts in

food and pharmaceutical microbiology, try to analyze these problems from the management of manufacturing (page 10) and from the microbial monitoring point of view (page 23), respectively. These authors share their views on these problems and offer some opinions how microbial contaminants could be avoided. This editorial, indeed, had pointed out some years ago in two scientific gatherings that certain microbial tests and bioassays should be included for monitoring the quality of raw materials and final products. If these hazardous were not properly addressed, they could spread and everyone of the community has to pay for the price like that experienced in shingles, which is a skin disease caused by a virus. This viral disease causes painful rashes on the body or face of a person. The details of this disease and its treatment can be found in an article written by Charmaine Chan in page 15.

Unlike other commodities, drug manufacturing always requires a very high moral standard and an assured strategy not to allow any fault to be present in the product. Hence, the operational policy of a company or regulatory body could have a significant impact on their products and services. In this issue, Mr. Stephen Leung, the CEO of Pfizer in Hong Kong, describes how he guides the company and motivates his staff as the role of a "Taxi Driver" (page 8). Whatever things are introduced or implemented in his company, nine core values are always embraced in order to keep the company growth on the right track.

Another example of good practices is the official approval of recombinant antithrombin for commercial purposes by FDA. This recombinant product had actually been successfully cloned and expressed in animal more than ten years ago by scientists in America but only until early this year, it was granted the commercial right after a decade long of further exploration. For details of this story, a brief review article written by Jabubarhameed and Leung could be found in page 20. This story exemplifies how cautious and long term commitments of the American government for the development of innovative products while our government does not. Should our government have identified a few areas, such as biotechnology, traditional Chinese medicines, creative media etc for our future, have they promoted and supported them with incentive policies for their rooting? The answer is not. Throughout the last couples of decades, our strength was weakened, our resources were burn, our creative mind were suppressed and our opportunities were lost; all because of their frequent and subtle changes in policy as well as slow responses in action. Time is running out for us and if we remain ignorant and indeterminate, our next and next generations will pay the price for what we have laid down for them. Hence, "*Let GXP be our goal and strive for it, not just a slogan*" in order to *advance Hong Kong* and excel whatever we do. (where *X* = manufacturing; laboratory; clinical; agricultural; medical; packaging; or sale etc)

Cheung Hon-Yeung

Editor-in-Chief
31st March, 2009

Removal of the Requirement of Pre-registration Analysis of Pharmaceutical Products for Registration Approval

Date: December 16, 2009

The Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certificate of Clinical Trial/Medicine Test) Committee of Department of Health decided at its meeting dated 15-Dec-2008 a new product registration guidance, in order to be in line with the registration requirement of other national health authorities.

For applications of New Pharmaceutical Product received by Department of Health from 2-Jan-2009, the requirement of pre-registration analysis of applied products by accredited laboratories or the Government Laboratory before approval of applications of registration has been removed.

This new guidance applies to applications of new chemical entities, generic products as well as other new product registrations.

Source of News:
Department of Health of HKSAR ref. #
DHPS PRIE/1-55/1

EU and China Signed Agreements to Strengthen Cooperation on Protecting Intellectual Property Rights and on Preventing Trafficking of Chemical Substances Used for Synthetic Drug Production

Date: January 30, 2009

Commissioner László Kovács, responsible for Taxation and Customs, today signed an Action Plan with the Chinese Ambassador Song to strengthen customs cooperation on protecting Intellectual Property Rights. They also signed an agreement to

enhance customs co-operation in monitoring trade and preventing trafficking and the diversion of drug precursors (chemicals that are essential to the illicit manufacture of narcotic drugs). The Commissioner commented that the agreements constitute a

step forward in customs cooperation between the EU and China.

Source of News:
http://ec.europa.eu/taxation_customs/customs/policy_issues/internnation_customs_agreemens/china

HK's First Interactive Drug Enquiry Website for Public

Date: February 19, 2009

The Chinese University of Hong Kong (CUHK) launched HK's first interactive drug enquiry website on 19-Feb-2009! AMPOULE [Ask My Pharmacist! - Online University-Led drug Enquiry] (<http://www.pharmacy.cuhk.edu.hk/ampoule/en/home/>) is an online interactive drug enquiry platform run by the School of

Pharmacy, CUHK. Bilingual AMPOULE is intended to provide personalized and professional solutions to Hong Kong citizens' drug-related queries. Visitors to the website can provide their medical and drug details for enquiries. Volunteer pharmacists will answer the queries by either e-mails or telephone within one

week. Apart from drug enquires, the website also contain sections of Health Information, Tips in Drug Use and New Medicine.

Source of News:
www.pharmacy.cuhk.edu.hk/ampoule/en/home/

UK MHRA Blocks the Use of Cold & Cough Medicines as OTC for Children Aged 6 – 12 Years Old

Date: February 28, 2009

On 28-Feb-09, the UK health authority, The Medicines and Healthcare products Regulatory Agency (MHRA), announced a controversial press release on the “safer” use of over-the-counter (OTC) cough and cold medicines for children under 12 years old.

The MHRA review found no robust evidence that these medicines work on this age-group but they can cause side effects, such as allergic reactions, effects on sleep or hallucinations.

MHRA states *“Parents and carers should no longer use OTC cough and cold medicines containing the ingredients reviewed in children under 6. For 6 to 12 year olds these medicines will continue to be available but will only be sold in pharmacies, with clearer advice on the packaging and from the pharmacist.”*

The MHRA claims she is working with industry and healthcare professionals to encourage ‘best practice’ and implement

these measures. Industry has agreed to implement changes over a period of time, including update in labeling and the legal status of these medicines when available to different groups of patients. Newly labelled products will start to appear for the 2009 cough and cold season. These changes should be completed by March 2010.

Source of News:
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902>

Electronic Cigarettes Containing Nicotine Governed by Law in Hong Kong

Date: March 4, 2009

On 4 March 2009, The Department of Health (DH) called on smokers not to use electronic cigarettes as the safety, efficacy and quality of this kind of product have to be established. A DH spokesman said initial laboratory analysis on a sample of electronic cigarettes revealed that it contained nicotine. Under the Pharmacy and Poisons Ordinance, electronic cigarettes containing nicotine and marketed as tobacco cessation products are

classified as pharmaceutical products requiring registration in Hong Kong. Investigations by DH had indicated that several brands of electronic cigarettes were found on sale on internet and in individual local shops. DH raided a shop in Sham Shui Po resulting in the seizure of nine types of electronic cigarettes. DH has also instructed the parties concerned to remove electronic cigarettes advertisements and promotional materials from their

websites. DH’s investigations are in progress. The DH spokesman said possession or sale of an unregistered pharmaceutical product, and possession of Part I poisons without authority were both liable on conviction to a \$100,000 fine and two years’ imprisonment. He urged members of the public who have been using electronic cigarette to stop using it immediately.

Source of news: <http://www.dh.gov.hk/>

License of Pharmaceutical Company Suspended

Date: March 12, 2009

On 12 March 2009, the Licensing Committee of the Pharmacy and Poisons Board suspended the manufacturer’s license of Marching Pharmaceutical Ltd for one month to facilitate investigations into the operation of the company which had failed to comply with the standard of Good Manufacturing Practice (GMP) in the production of 216 pharmaceutical products. The label expiry dates of the products concerned were found to be not substantiated by laboratory data, a spokesman for the Department of Health (DH) said. He reiterated that risk assessment made by the department so far concluded that the case only involved the stability and not the safety of the pharmaceutical products concerned.

However, DH will continue its thorough investigations into the case, with emphasis on the application by the company for de-registration of 120 of the 216 products. They will further examine if the application was related to any hidden malpractice affecting public health. On 11 March 2009, DH instructed the company to recall the 216 products orderly including setting up hotline and providing brand names of the products to the retailers and public with details e.g. collection spots.

DH reminded the company to strictly observe the recall procedures and requirements. A DH spokesman said the case had also been reported to the Police

as during the course of DH investigations, certain irregularities in the documents submitted by the company were found. Meanwhile, DH would conduct a thorough review of the existing pharmaceutical regulatory framework which included routine inspections, market surveillance and enforcement with a view to further enhancing its effectiveness to protect public health.

The brand names of the 216 pharmaceutical products are available at DH website [http://www.dh.gov.hk/english/press/2009/files/marching_list\(090311\).pdf](http://www.dh.gov.hk/english/press/2009/files/marching_list(090311).pdf).

Source of news: <http://www.dh.gov.hk/>

Drug Used by Patients in Cases of Mucormycosis Found Contaminated

Date: March 16, 2009

The Department of Health (DH) announced on 6 March 2009 that follow-up investigations into patient cases of invasive gastrointestinal mucormycosis in public hospitals in February had revealed that one of the pharmaceutical products prescribed to the patients concerned was found to be contaminated. The laboratory tests by the University of Hong Kong (HKU) on four batches of allopurinol (brand name: Purinol, registration no: HK-30662) taken from Queen Mary Hospital were found to be contaminated by a fungus called *Rhizopus microsporus*. The batch numbers are 804159, 807199, 808179 and 811015. The drug concerned was manufactured by a local pharmaceutical company called Europharm.

Rhizopus microsporus could be found in soil and decaying matter. Normal adults are not commonly infected by the fungus. Only immunocompromised patients will be infected and suffer from severe infection with high fatality. Allopurinol is commonly used to treat hyperuricemia

and chronic gout. It is also commonly used as a prophylactic treatment for patients on chemotherapeutic treatments.

DH inspected the company on 6 March 2009 and instructed the operator to immediately withhold all manufacturing operations. Pharmaceutical and environmental samples from the company have been taken for investigation. The company has also been ordered to stop the distribution of all the affected products. DH sent letters to all doctors, hospitals and pharmacists to alert them about the findings and called on members of the public to stop using Purinol, the affected pharmaceutical products produced by the company for the time being. Pharmacies and drug stores have been advised not to use Purinol and should dispense allopurinol manufactured by other manufacturers for the time being.

On 9 March 2009, DH asked Europharm to recall all Purinol tablets from the market as laboratory analysis of the four Purinol samples taken from

Queen Mary Hospital confirmed the presence of a fungus called *Rhizopus*. A DH spokesman said investigation had revealed that during the production process, there was unnecessary delay in the step of converting the mixture of Purinol ingredients into tablets.

DH is conducting a full investigation into the production of all pharmaceutical products in Europharm. More than 800 samples of raw materials and drug products were sent for laboratory tests. Between 10-16 March 2009, DH announced that laboratory analysis of 39 raw materials and 879 samples of pharmaceutical products manufactured by Europharm had indicated no growth of fungus. DH is sending out their inspectors to conduct a round of inspection at all the local pharmaceutical manufacturers. DH is also requesting the local manufacturers to add in microbial tests on the critical steps of the manufacturing processes and/or the finished products.

Source of news: <http://www.dh.gov.hk/>

『繼往開來』

自去年十一月底返回母校參加現代藥學教育在華百週年慶典後，發覺有些不同性質的慶典陸續出現，例如今年是中華人民共和國成立的六十週年，也是香港藥學會的鑽禧。十年前的金禧慶典是在較清靜的「陽明山莊」舉行，記憶猷新。目前慶祝鑽禧的活動正在積極籌備中，希望藥劑界同儕屆時均能踴躍參加此次盛會！

一個社團成立後能否繼往開來，發

揚光大，涉及的因素相當多，但最重要的因素是能否有人願意擔當「義工」。一般的專業團體均由業界會員義務性質負責不同崗位的工作，只會吃力不討好！因此要找接班人並非易事！

HKPJ創刊至今先後計算已有26年了。期刊至今仍能繼續出版，實在要多謝不少同業的無私奉獻，筆者在上一期應主編之邀以「任重道遠」作題目寫出

自己的心聲！發表後在不同場合中獲得同業的回應！令筆者覺得此期刊必定會「繼往開來」！真希望有一天像學會一樣能舉辦「創刊百週年」的慶典！雖然筆者肯定無法參加此一慶典，甚至主編先生與各位創刊的前輩也未必等到那一天。但希望你們的辛勞和貢獻可以得到後繼者的紀念！請共勉之！

柯宇春 藥劑師 2009.2.12.

From Pfizer Hong Kong, Some 'Driving' Lessons

RODRIGUEZ, Carolina; PARKER, Jackson; LEE, Pak Seng; HINAYON, Mihaela; LEUNG, Stephen
Pfizer Corporation Hong Kong (Ltd), 16/F., Stanhope House, 738 King's Rd., North Point, Hong Kong

ABSTRACT

Pfizer Hong Kong is positioning itself as an international Center of Talent, where adaptive and emotionally intelligent leaders are molded and cultivated. Pfizer's Country Manager, Stephen Leung, believes in taking the "Taxi Driver" approach: guiding both the company and its people to reach their goals and career destinations.

Key Words: *Pharmacy practice; Core values; Equality; Management; Center of talent; Collegiality*

INTRODUCTION

Country Manager Stephen Leung just got himself a new title: *Taxi Driver*. His rationale is that his job in Pfizer Hong Kong is mainly to transport people and take them exactly in the direction they want to go. Quite an interesting choice for a title, but not one to talk about himself, Stephen shifts the focus to his passengers and their common journey. During one of his sharing sessions with us Management Trainees, he points out road signs that guide him as he takes Pfizer Hong Kong to their destination of choice.

ONE WAY

To get to a certain place, both the driver and the passenger must agree on a specific route—a clear path of action. In the case of everyone at Pfizer Hong Kong, they are united by their core values and a culture that fuels them to move forward.

In a society where values have become secondary to the pursuit of profits, Pfizer Hong Kong has placed great importance on their nine core values: *Customer Focus, Respect for People, Integrity, Teamwork, Innovation, Community, Leadership, Quality, and Performance*. These values are not imposed on their employees, but serve as guidelines that are understood and accepted more and more through normal daily interactions. Each working team embraces core values and seeks to promote them even more throughout the company.

The nine core values are the foundation on which Pfizer Hong Kong has created a culture of openness and camaraderie. Pfizer Hong Kong's people-centered approach acknowledges that when people feel comfortable and cared for, it translates into how well they perform.

Employees are the main assets of any organization, and through Pfizer Hong Kong's culture they are encouraged to grow, innovate, and practice leadership skills. Pfizer Hong Kong implements an "Open Door Policy," where colleagues are able to readily ask for help or find a partner when needed, and are also encouraged to share their ideas, no matter how far up the corporate ladder their target audience is.

Another mainstay of this culture is the theme of "*Continuous and Never-ending Improvement (CAN I)*," or innovation and learning. Everyone is required to constantly think of ways to better Pfizer Hong Kong and better themselves and share those ideas, significant or not.

NO "U" TURN

Imagine someone getting into a taxi in his local city and telling the driver exactly where to go and which route to take. Unless he is very knowledgeable about all of the possible routes, traffic patterns, and construction areas, he has a much better chance of getting to his destination faster if he works together with the driver and use some of the driver's vast experience. It is then the responsibility of both to listen to each other and come up with a preferred route.

In Pfizer Hong Kong, there is no such thing as an individual "I" or "U"; there is always the culture of "We". Individual efforts are recognized within the organization but teamwork among colleagues is highly encouraged. Pfizer Hong Kong understands that together, colleagues will be able to undertake projects that would be impossible alone. Promoting teamwork not only endorses the skills and capabilities of individuals, but also goes along with Pfizer Hong Kong's *CAN I* culture; enriching one's personal character by absorbing numerous lessons, habits, values, and skills from their colleagues.

Collaboration drives performance, but in every group there must be a leader to motivate, bring focus, and showcase the team's various skill sets. This is why Pfizer Hong Kong promotes adaptability as one of the most critical abilities a leader must have for long-term success. This applies not only to market situations and business decisions, but in dealing with people inside or outside of the organization. Every individual needs a different style of leadership at different

times. Sometimes people need a push to be motivated (coercive style) while at other times they need a leader to help them come to a conclusion by themselves (coaching style). When a leader is able to understand how people are feeling and use that to motivate them, he is able to have followers that want to follow him and share his vision.

The ability to adapt is one thing; the ability to know *when* to adapt is another. This is where emotional intelligence (EQ) can be one's greatest tool. People are the most important part of any organization, and the ability to put yourself in their shoes will make managing easier and make colleagues feel better about coming to you with problems. Having a high EQ is very important to determining which leadership styles to use and how to use "win-win" situations to best draw out a colleague's strengths.

(WO)MEN WORKING

A typical day for a taxi driver involves roaming the streets nonstop until someone calls his attention, gets in the backseat, and directs his course. Both driver and passenger reach an understanding on how to arrive at their destination and the ride begins, often with either party initiating a conversation. The conversation may take different turns but more often than not, it is usually bound to touch on the subject of work.

The taxi driver, therefore, with all the passengers he has met, must have a good feel for how important it is to enjoy one's job and to have a passion for it. Being at work himself, he can relate to each passenger and get a grasp of how it must be for them.

At Pfizer Hong Kong, for example, the work environment is enhanced through a *CARE* culture. A *CARE* culture is one where people are put first, through *Communication, Aspiration, Recognition & Reward, and Empowerment & Encouragement*. Every leader then makes it a habit to have good communication skills, an understanding of people's aspirations and the willingness to assist colleagues in achieving their goals. He must also recognize good ideas and reward them when necessary, and finally he must empower people to take responsibility for their actions and encourage them when they need guidance.

Equality is expected in the workplace regardless of gender, race, or background. The idea is to provide colleagues with a nurturing environment that they look forward to and want to be a part of.

Each person may have a different passion or skill but Pfizer Hong Kong

ensures that these talents are allocated in such a way that they will be developed and maximized to their full potential, therefore adding value to the company.

THE DESTINATION

Individuals have their own set of dreams,

each one going to a different direction. But what Pfizer Hong Kong has done is to meet at a common point, where driver and passenger agree on a destination. Success, after all, is a set of journeys that recycles experiences, promotes strengths, and inspires people to achieve greater things.

Now there's a visionary behind the wheel and the passengers are all set. Where to?

Pfizer Hong Kong is on its way to making Hong Kong a "Center of Talent", recruiting and developing adaptive and emotionally intelligent leaders who will have a lasting impact on the corporation. As Asia takes its place as the world economic center, Hong Kong should also take its place as a talent center, exporting its culture and knowledge throughout the world.

Authors' background

RODRIGUEZ, Carolina (Colombia), **PARKER, Jackson** (USA), **LEE, Pak Seng** (Malaysia) and **HINAYON, Mihaela** (Philippines) are part of Pfizer Hong Kong's first-ever Management Trainee Program. This one-year internship allows the trainees to rotate through different departments and projects to gain valuable experience, adding value to themselves and Pfizer. **LEUNG, Stephen** email: Stephen_leung@pfizer.com



The project began in September 2008 under the initiative of Human Capital Lead Polly Cho and aims to promote diversity and learning throughout the organization. Pfizer Hong Kong views the project as a step towards realizing Country Manager Stephen Leung's dream of making Hong Kong a "Center of Talent". "Over the years, Stephen has been actively serving the community and cultivating leaders both locally and overseas. His excellent contributions to the community have not gone unnoticed. Stephen was bestowed with the prestige HR Leadership award at the World HRD Congress held in Mumbai on February 6, 2009."



陳棠律師：

香港高等法院律師 Solicitor of the High Court of Hong Kong
英國高等法院律師 Solicitor of the Supreme Court of England
香港律師公會會員 Member of the Law Society of Hong Kong
英國律師公會會員 Member of the Law Society of England
英國倫敦大學榮譽藥劑學學士 Bachelor of Pharmacy (Honours), London Uni.
英國皇家藥學會會員 Member of the Royal Pharmaceutical Society of G.B.
香港藥學會會員 Member of the Pharmaceutical Society of H.K.
香港及英國註冊藥劑師 Registered Pharmacist in H.K. and G.B.
中國國家衛生部註冊資深藥劑師 Registered Senior Pharmacist, PRC
工商管理學碩士 Master of Business Administration

陳棠律師事務所 Tong Chan & Co., Solicitors

各類私人及企業法律事務 – 樓宇轉讓及按揭、有限公司、合股生意、商標、產品設計、專利及出版權、平安書、遺產承辦、家庭問題、調解糾紛、仲裁、民事及刑事訴訟和其他服務

陳棠律師事務所

香港九龍尖沙咀廣東道30號新港中心1座509室

Tong Chan & Co., Solicitors

Room 509, Tower 1, Silvercord, 30 Canton Road, Tsimshatsui, Kowloon, Hong Kong.

電話 Tel.: 2375 7872 傳真 Fax.: 2375 2702

電郵 Email: chantong@netvigator.com

亞洲企業發展服務有限公司 Asiabest Limited

成立各類公司或法人團體、
長年公司秘書服務、融資貸款

亞洲企業發展服務有限公司

香港九龍尖沙咀廣東道30號新港中心1座508室

Asiabest Limited

Room 508, Tower 1, Silvercord, 30 Canton Road, Tsimshatsui, Kowloon, Hong Kong.

電話 Tel.: 2375 3776 傳真 Fax.: 2730 2015

電郵 Email: asiabestltd@yahoo.com.hk

從近日藥品質量問題探究香港藥廠的經營管理

梁靄明

香港註冊藥劑師/現為藥劑顧問

ABSTRACT

With the recent drug quality incidents, it reflects that certain aspects of pharmaceutical manufacturing process and GMP concepts, such as storage condition and holding period of granule, microbial test, compliance of pharmacopoeia standards, stability tests and expiry date are not properly applied. Hence, the quality of drugs and management of a few pharmaceutical entrepreneurs in Hong Kong inevitably do not meet the cGMP requirements.

Key Words: Drug Manufacturing; Quality; Packaging; cGMP; Microbial contaminants; Pharmaceutical industrial operation

有鑑於近日香港的藥品連續出現問題，作為一位藥劑師及曾經是藥廠的生產技術管理者，本人希望發表一些意見，並且同時更正一些非專業人士對藥品生產管理及質量的誤解。本人目前已經脫離製藥行業，但以往一直在外資藥廠中工作，對藥廠的管理有一定程度的了解。而且本人作為香港90年代GMP的推動者，對目前的情況深表痛心。

藥品顆粒儲存的規定

藥片顆粒儲存時間及儲存環境問題：其實，藥品的種類繁多，每一種藥品的原料及生產過程的「中間體」，例如顆粒，均有不同的化學及物理特性，有些需要低溫儲存，有些需要真空密封儲存，有些不能在光線下儲存，甚至有些是不准許儲存的，因此，國際是公認不可能為藥品的原料及生產過程的「中間體」定立劃一的儲存標準。

實際上，藥品的原料及生產過程的「中間體」的儲存標準是由製藥工程師在產品開發時根據各種藥品及「中間體」的特性個別定立的。在產品開發時，工程師們需要為藥品定立配方、標準生產流程及各式各樣的質量標準，其中便包括中間體的質量標準及儲存標準。

根據cGMP標準，所有藥品的配方，生產流程、質量標準及生產設施均需要通過驗證，以保證藥品連續生產中的質量。而歐美及中國更加規定藥品的註冊報批過程中，必須同時出具三批以上的「生產驗證」資料才可以取得「生產准許」及「藥品的註冊」。而香港GMP則規定藥廠必須為藥品進行「生產驗證」，但香港沿用WHO GMP標準，未有規定藥品在申請註冊時便需要出示「生產驗證」資料，而只是要求在每年的GMP檢查時能夠出具驗證報告。

通常，如果生產過程的「中間體」例如顆粒，不是敏感性的，工程師會定下儲

存在例如溫度20°C，相對濕度50%，密封儲存不超過3天的儲存標準。而在生產驗證過程中，生產工程師則需要試產三批（正常生產，下限生產及上限生產），其中包括將「中間體」按標準儲存3天後檢驗合格看有沒有問題，才可通過驗證批准這個生產流程。以後如果生產中出現「差異」，例如因儲存期間空調關掉令至溫度出現差異，或因生產排期問題而令至儲存超過3天，則質量總監便會按規定將這批顆粒定為「不合格」而需要按GMP規定進行「差異處理」及填寫報告，而最大的可能便是整批予以報廢。

根據以往國外的GMP檢查不合格的經驗，違反得最多的便是「中間體」例如顆粒的儲存沒有按照規定，例如為儲存超過三天，或為了省成本而晚間關掉空調，至令儲存期間的溫度及濕度偏高等。但以往的歐美及國內的藥廠在這方面的違規，通常只是多儲存1-2天，不會對產品質量產生太大的影響，通常都是作出警告。但好像香港歐化藥廠這樣未有作出適當的生產驗證，藥廠本身亦不知道顆粒應當的儲存期有多長，及顆粒儲存達到14天之久，則非常罕見及不尋常，有關當局需要重視。而本人曾經負責的集團公司亞太地區的多個廠房中，其中有數個廠房製粒車間與壓片車間是分開幾十公里的；按照規定，整個顆粒的運輸以至貨倉儲存均要先取得驗證方可正式生產。

按照現時藥廠的設計，藥廠的生產環境是經常保持在20°C左右，而濕度是在50%，而且是一個相對無塵無菌的潔淨環境；再者生產過程均有一定的滅菌作用，顆粒在長期的儲存中大量生長霉菌仍然是一個非常不尋常的問題，如按國外的經驗，這一情況只會是廠房在儲存產品及「中間體」期間違規停下空調及潔淨系統，令廠房內濕度及溫度反彈，增加中間體的「倒汗水」積聚，藥品及中間體如果經過多次的「冰火」處理下，生長細菌及霉菌是很必然的事，而且，一定影響藥品的穩定性及雜質含量。

目前香港藥廠出現顆粒儲存的問題，便正是香港的藥廠違反了(1)在藥品開發過程中未有為「生產流程」及「中間體」儲存定立標準及(2)未有按GMP要求進行全面的「生產驗證」，(3)為了節省成本或因為生產定單太多未能協調每一工序，所以在未經驗證後更改了「生產流程」或儲存條件。

而根據歐美及中國GMP，以上三種情況均是屬於嚴重違反GMP的行為，藥品的註冊或會即時被取消，並且處以罰款及停牌的處分。

衛生檢查

目前，香港沿用的英國藥典，美國藥典及

中國藥典均要求藥品除了含量，釋放度，雜質等檢查外，更必須進行衛生檢查。衛生檢查的項目中便包括了細菌及霉菌的數量，如果不合格便不能放行。香港在開始推行GMP時，一些藥廠以香港未有足夠的人才進行衛生檢查為理由，聯合向衛生署施壓要求寬免，最後衛生署同意延期執行這一項要求。

但是，香港醫管局及衛生署的藥品採購中是另有規定的，在藥品採購中除規定藥品需在香港已取得註冊外，更需要證明藥品的有效性(例如另外通過生物等效或臨床實驗)及完全符合藥典的要求(即衛生、雜質含量等)。

根據歐美及中國等國家的規定，藥品未有完全按照藥典的規定檢查合格，是不准在標籤上使用「符合XX國藥典(即BP, USP或CP)」的字眼。所以如果香港某些藥廠未有按藥典規定進行衛生檢查，原則上不能說產品是符合BP, USP或CP。

藥品的有效期及穩定性實驗

藥典中並沒有列明每一藥品的有效時間的。藥品的配方，生產工藝，包裝方法，儲存環境及各國的天氣差異等均會影響藥品的有效期，而正好以上的每一項均是各家藥廠的獨特的地方。所以各國藥典及政府均不會對各種藥品提出統一的有效期的規定。

事實上，藥品的有效期亦是由藥品工程師在產品開發時提出，並通過實驗數據(穩定性實驗及穩定性報告)來加以證明，藥品的審批部門則按各藥廠在藥品申請註冊時的穩定性報告來作出批准。按照規定，如藥廠提出藥品的有效期是3年的話，藥廠就必須將藥品在原包裝下按「衛生署指定的儲存環境下」或按「藥廠起草的特別儲存環境下」儲存3年，期間定時進行檢查，如儲存3年後的檢驗報告證明藥品仍然達符標準，方可以在標籤上印上3年的有效期。有一些新藥品，未有足夠3年或以上的長期穩定性報告，則可以利用一個比較高溫及高濕度的儲存環境下進行一個6個月的「加速穩定性實驗」，如藥品能夠通過6個月的「加速穩定性實驗」，則衛生署可以批准藥品印上一個臨時的2年有效期。但仍然需要通過藥品的留樣來進行「長期的穩定性報告」來證明藥品的有效期。

在香港萬輝藥廠出現的問題，主要應是藥廠未能按照規定為藥品進行「長期的穩定性報告」，或甚至是使用虛假的數據來申請註冊，這是非常嚴重違反GMP及藥品註冊法例的行為。英美各國亦曾經在90年代發生多次，美國FDA對這種行為的處罰是非常嚴厲的，因為這是極有可能危害病人的生命，所以當時美國的處罰是對藥廠作出極嚴厲的罰款及取消牌照，而當事人更負上數年以上的監禁。

藥品的註冊及包裝

琪寶供應給醫管局的「甲福明」，其中500片裝的未有註冊，但1000裝的已經取得註冊，而醫管局未能查明，錯誤採購。

藥品在不同的包裝下，會有不同的穩定性特徵，所以國內外均會規定就算是同一藥品，不同的包裝均要單獨提交穩定性數據，及新包裝的規格及標籤等資料，經藥品審批部門同意下方可取得註冊。

目前，香港已註冊的藥品是可以通過衛生署的網站來查詢的，或可以直接至電香港衛生署。現時的網上藥品註冊查詢系統使用非常方便，但是，只能列出藥品的名稱，主要成份，註冊編號及藥廠的名稱；網上不能查詢藥品的各種包裝規格，有效成份的含量及有效期，藥品的分類等重要資料。這對使用者例如醫生，藥店的藥劑師及醫管局的採購人員是很不方便，而且亦沒有其他渠道取得這些資料。現時，藥店的藥劑師是沒有渠道來核實藥品的成份，藥品的標籤及藥品的有效期是否符合藥品的註冊來印刷。這便出現一些藥廠亂印有效期，甚至不按規定包裝產品，私自更改包裝，私自更改配方，出現一個註冊有多個包裝的情況。

廠房及設備清潔程序

在電視上看到歐化藥廠停產，員工正完成當天清潔由車間出來的片段時，員工們手持掃帚，地拖，垃圾鏟，水桶等。按照目前歐美及中國 cGMP 規定，藥廠的生產車間是不可使用掃帚及地拖的，因為掃帚及地拖已證實是細菌污染及交叉污染的源頭，而且亦根本沒有可能為地拖及掃帚做「清潔驗證」以證明他們不帶有污染。目前，美國的藥廠通常只用淨室專用吸塵機、冷或熱的純水(Purified Water BP, USP or CP)，甚至是注射用水(Water for Injection BP, USP or CP)、食品或藥品級清潔劑及一次性潔布去作清潔。廠房清潔完後亦要做清潔驗證及衛生檢查。

有沒有『包裝GMP』？

報章報導香港有藥廠其實只從事藥品包裝。藥品本身是在中國的廠房加工製造，香港的藥廠只從事「GMP包裝」。電台訪問世衛官員時，官員說未有聽過「包裝GMP」！那究竟有沒有「包裝GMP」呢？

本人曾工作的公司的德國及法國工廠，其顆粒工廠，壓片工廠及包裝工廠都是分開的，三個工廠距離由有數公里至十多公里。顆粒工廠只負責生產顆粒，而壓片工廠會根據不同國家註冊了的藥片形狀來生產不同的藥片(同一藥品，例如專供亞洲地區，專供美洲地區，專供歐洲地區等)，生產好的各個地區的藥片又再運到包裝工廠，再按各地的定單包裝成不同的規格，例如中文盒，馬來西亞文盒等。那麼，是否只是「顆粒藥廠」及「壓片藥廠」需要領有生產牌照及GMP認證，而那包裝藥廠則不需牌照呢？亦不用按GMP來管理？那藥品的質量如何保證？好像「源輝」私自包裝藥品，甚至更改有效期，或甚至同一批產品，用來印刷標籤有效期的幾部電腦不同而出現不同的有效期等問題，是不是不用監管？衛生署又不必追究呢？

凡是接觸藥品，或為藥品包裝，包括

更換包裝，貼上標籤等，均存在風險，所以必須按照藥廠管理法規來接受政府監管（即必須領有藥廠牌照）。藥品生產的廠房，當然是需要領有藥品生產牌照，而藥品包裝的廠房，亦必須領有藥品包裝牌照。在外國，沒有生產牌照及包裝牌照之分，所有藥廠，不論是生產，或只是包裝，均需要領有生產牌照，但牌照上會註明廠房只可以作那些用途，例如「只可生產非青霉素類片劑、硬膠囊劑」，或「只可包裝非青霉素類片劑、硬膠囊劑」等。

負責包裝藥品的廠房，不論是直接接觸藥品，或只是間接接觸藥品，均需要按照全套GMP來管理，即包括需要做標籤管理，清潔/清場工作及有關驗證，包裝設備，包裝貼標籤機、打印批號的設備等等亦需要做「功能驗證」。包裝亦要有全套的包裝指令及記錄，原則上，更需要由藥劑師管理。

包裝藥品的廠房當然需要通過GMP檢查並通過GMP認證！而GMP證書上列明「只可包裝非青霉素類片劑、硬膠囊劑」等字眼。所以，世衛官員沒有說錯，確實是沒有「包裝GMP」。但是，不代表藥品的包裝及有關的廠房不用管理，亦不用通過GMP；事實上，他們仍要通過全面的GMP認證並接受藥品法規的監管。(編者註：雖然沒有『包裝GMP』這用語，但確實有『GMP包裝』或『GMP的包裝』[GMP(Packaging)]批核許可証)。

中國及外國GMP

其實中國藥品GMP是非常嚴格的，而且已經在執行cGMP。中國亦只有一個GMP標準，沒有所謂省級及國家級標準的。目前，中國的GMP水平只是比美國及英國GMP低一點點，與澳大利亞GMP (TGA GMP) 水平看齊，更加是遠高於WHO及其他地區的GMP。

與歐美各國一樣，中國的藥廠GMP檢查通常是規定每年檢查一次，期間亦會不定期進行不通知的「突擊檢查」，近三年來，這些「突擊檢查」通常是最小一年2次，如果記錄不好，甚至是一年4次。

中國的GMP檢查組通常是3名組員的，組員必須是來自不同省份，每次檢查前隨機抽選配對。檢查人員在每次檢查任務安排前數天才會被通知按時到達北京，在出發前一天才會發放密封的任務及配對成多個檢查組，然後立即出發，當到達目的省市才可以打開任務包的。

香港的GMP檢查基本上與英國及美國GMP的檢查差不多，沒有好像中國般的保密規定。但是，美國和英國的GMP檢查是非常重視驗證及差異的處理，而香港目前仍然是保留在藥廠的質量記錄及生產標準操作程序(SOP)方面，這可能是因為歐美各國製藥人才及水平較高，產品的質量及工作流程均已取得保證。中國方面，GMP的檢查主要是針對原料的來源及檢查，及輔助設施(純水，潔淨系統)的保養及使用情況，及生產標準操作程序(SOP)方面。

雖然中國近來發生不少藥品及食品的問題，但我們不能在未了解便說中國的藥品GMP比香港差。實際上，香港的GMP水平與中國還有一段比較大的距離。

其實，GMP只是一個法定的藥品質量生產規範，GMP不能完全杜絕問題藥品的出現，但最小可以減小問題的發生。而更重要的一點，GMP不能防止企業及藥廠刻意做假，故意隱瞞數據記錄，這些問題均需要GMP檢查員好像偵探查案一樣在檢查中抽絲剝繭才可以找到的真相。

藥品的質量不是從監督中得出來的，是由整個生產工序中建立出來的。要有良好優質的藥品，應從人、事、物的企業管理由始至終做起。目前，很多香港的藥廠的真正高級管理人員(老闆)均沒有專業資格，水平很低，眼光短小。藥廠只聘用少量的藥劑師放在質量部門來應付衛生署的檢查，平時的產品開發，生產管理，質量監控等等均由非專業人員來負責。而且，最重要的一點，香港仍未規定藥廠必須有藥劑師在公司的董事局內，及藥劑師對技術、質量和生產等一票的否決權，這亦是香港藥廠水平低下的主要原因。

結語

自70年代全球各國推行GMP開始，香港的藥廠已經錯失了一次機會。當時香港的藥廠出口業務蓬勃，產品出口到東南亞各國及歐美市場，但當時香港的藥廠拒絕投資GMP，至令香港的製藥企業由東南亞的龍頭大哥地位跌成每年只有一二千萬元生意額的三流企業。要不是香港衛生署在2000年時不理藥廠的反對下強力推行GMP，令香港的藥廠在別無他法下進行改造，從而慢慢取得香港衛生署及醫管局的接受而成為合格的供應商，香港可以說是再沒有製藥行業了。

現在香港的藥廠又一次因管理者的短小眼光而面對另一次危機，如果藥廠們不在這次危機中吸取教訓，如香港的衛生部門仍然姑息藥廠而不定下更嚴格的規定及監管制度，相信香港的藥廠已經到了盡頭。

(本文獲信報允准修改並轉載，謹此鳴謝。原文標題是《藥品質量由企管做起》，並在2009年3月25日《信報財經新聞》刊登。未經版權持有人書面授權，不得複印、轉載或分發。20090330159)

Author's background

LEUNG, Herman did his pharmacy degree at School of Pharmacy, University of Bath, UK, specialised in Pharmaceutical Technology. He established Apotec Pharmaceutical Co., Limited (now APT Pharmaceutical Co., Ltd) in 1991, and in 1999. The company was merged with Merck and was renamed as Merck Apotec Pharmaceutical Co., Ltd. Herman Leung was the Deputy CEO and General Manager of the company responsible for all technical operations of the company. He was also appointed as a member of Merck Senior Working Group responsible for all Merck's plants in the Asia Pacific Region, overseeing all the technical and quality management in the region. Due to a change of global manufacturing strategy, Merck sold off the HK and China Manufacturing Operations and the plants with the generic business was sold to Jacobson in 2005. Herman Leung became a part-time consultant in 2006 and has been assisting foreign pharmaceutical companies to develop global product development strategy and GMP strategy aiming at US, European and China markets. Mr. Leung's email: hermanleung909@msn.com

Mood Disorders: What Can A Community Pharmacist Do?

CHENG, Wai-Ring Caroline

Watson's the Chemist, Hong Kong SAR, China

ABSTRACT

Shortage of healthcare professionals serving the psychiatric specialty has become a hot topic recently as the demand for services has increased dramatically. A few more mood disorders have been identified in addition to anxiety, bipolar disorder and depression, namely affective disorders, conduct disorders, antisocial and borderline personality disorders. In view of the under-estimated prevalence and wide influence related to the symptoms, community pharmacists may encounter such cases and inquiries in the daily practice. Knowledge of supplements and healthy solutions would be useful for public health education so as to improve the patients' quality of life.

Key Words: *Mood disorders; Psychiatric problems; Anxiety; Assessment tools; Treatments*

PREVALENCE, COSTS AND CONSEQUENCES

Looking into the newspapers recently, there has been an increased incidence of events related to mood changes. The association between environment and human emotions was well identified years ago.⁽¹⁾ Research and surveys done so far suggest that stimuli originating from drug use, environment, family, hormones, illnesses, stress, threat, weather, etc. influence physical and psychological performance in our daily living.⁽²⁻⁸⁾ Mild disturbances of mood exist in which the symptoms are not severe enough to meet the criteria for classification as a major depressive or hypomanic disorder, but may, nevertheless, cause considerable suffering to the patients because they are often accompanied by characteristic somatic symptoms like anorexia, weight loss, headache, pain, insomnia and others resulting in a lower quality of life.^(9,10) Symptoms typically fitting into the observed criteria should be attended by clinicians by whom specific treatment could be initiated and monitored for an individual patient.

Prevalence studies in different countries reflect its importance. In the US, the National

Comorbidity Survey Replication survey found a lifetime prevalence rate of 28.8% for anxiety disorders.⁽¹¹⁾ A study published in 2008 found that borderline personality disorder was much more prevalent in the general population than previously recognized, with a lifetime prevalence of 5.9%, with occurrence rates similar amongst men and women.⁽¹²⁾ Antipsychotics users rose from 0.72% in 1996-1997 to 1.17% in 2004-2005, while the average age significantly declined from 49 to 43 years.⁽¹³⁾ In Germany, the 12-month prevalence for any mental disorder (including psychotic disorders, substance abuse, depression, bipolar mood disorders, anxiety disorders, somatic and eating disorders) was 31%, with comorbidity rates ranging from 44% (alcohol abuse) to 94% (generalized anxiety disorder).⁽¹⁴⁾ In an Australian study, 24.8% were found to have psychological problems (14.2% for depression and 10.7% for anxiety), which was almost twice the NHS estimate for psychological problems.⁽¹⁵⁾ In Morocco, 25.5% of subjects met the criteria of at least one current anxiety disorder in a cross-sectional study.⁽¹⁶⁾

Particular populations may be more likely to suffer, as observed in adolescents, elderly people and pregnant women.⁽¹⁷⁻²¹⁾ Deterioration of health and performance results in lower quality of living and economic loss in terms of both healthcare costs and lower productivity.⁽²²⁾ Amongst the anxiety disorders, generalized anxiety disorders are a potential cost driver in Canada as they are highly prevalent in the general medical sector and have been shown to be very disabling since patients also frequently present with irritable bowel syndrome and other discomfort.⁽²³⁾ Moreover, as many as 75% of the patients hurt themselves, and 6-10% commit suicide.⁽²⁴⁾ [Among patients with major depressive disorders, suicide attempts have a strong association with dependent personality disorders in men and antisocial personality disorders in women (adjusted odds ratio 3.81 and 2.71 respectively).⁽²⁵⁾ The total costs of brain disorders in Finland constituted 45% of all healthcare costs, where the three most common disorders are migraine, anxiety disorder and affective disorder.⁽²⁶⁾ The estimated number of cases of brain disorders in Italy was highest for migraine,

anxiety disorder and affective disorder as well. Brain disorders represented 14% of the total direct healthcare costs and 7% of the total drug sales in Italy.⁽²²⁾

In Hong Kong, the incidence rate and self-reporting rate has risen dramatically in recent months.⁽²⁷⁾ Increased numbers of patients lead to an unavoidable reduction in consultation time from eight to five minutes at the front line. In return, more resources have been input for expanding the outreach service. There were 600,000 patients attending clinics primarily for mood problems in 2005-2006, with an estimated 10% annual growth in the number of cases and another 20% patients among other specialties believed to suffer from mood problems as well.⁽²⁸⁾ Available data indicate an adverse impact on families looking after patients with anxiety disorders, and the burden on caregivers in obsessive-compulsive disorders is equivalent to that of severe mental disorders, suggesting the need for further research and support in the area.⁽²⁹⁾

CLASSIFICATION AND BIOCHEMISTRY OF MOOD DISORDERS

Classification and diagnosis of mood disorders are reviewed from time to time. The 4th edition of Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association in 2000 (DSM-IV-TR) is widely used across different disciplines in the clarification of psychiatric nosology for early onset disorders.⁽³⁰⁾ Commonly discussed are generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder and depression. However, the document includes only some of the conditions reported in the vast developmental, learning, psychiatric and health literature that are known to confront limitations for practicing psychologists. In addition, further studies on epidemiology, causes and treatments of the complex disorders are not fully reviewed.⁽³¹⁾ The number of categories and specifiers for mood disorders

has increased with each successive edition.⁽³²⁾ Anxiety was often associated with depressive disorders at all levels of severity. Episodes may coexist or alternate in mixed affective states.

Lifetime anxiety disorder is associated with an increased lifetime chance of an antisocial diagnosis. The association remains significant even after controlling for various confounding factors and is consistent across surveys conducted in different countries. People with comorbid anxiety and antisocial diagnoses have higher levels of disability, distress, dysfunction and impairment than those with either disorder alone, resulting in poor quality of life and even stronger suicidal ideation. From a public health perspective, healthcare providers and health policy makers should be aware of the co-occurrence of anxiety disorders, antisocial behaviors, conduct disorders, attention deficit hyperactivity disorders, substance abuse and suicidal ideation, so that it may be worth prioritizing aggressive treatment to reduce the onset of symptoms, especially among adolescents. The burden of such disabilities and distress may ultimately result in institutionalization.⁽³³⁾

The aetiology of interactions between psychological and biochemical mechanisms is believed to be mediated through alterations in the levels of central neurotransmitters, namely serotonin, dopamine, histamine, acetylcholine and gamma-aminobutyric acid (GABA). Drugs that modify human behavior include hallucinogenic agents which produce hallucinations and other manifestations of psychoses; tranquilizers that relieve anxiety and various psychiatric symptoms; antidepressants which elevate negative moods and increase interest and drive.⁽³⁴⁾ Anxiolytic treatment should be limited to the lowest possible dose for shortest possible duration. However, antidepressants must be administered for four to six weeks to obtain their effects due to some secondary effect of reuptake inhibition rather than the direct inhibition itself for improving mood. Some antidepressants are licensed for use in anxiety and related disorders, chronic anxiety, generalized anxiety disorder, seasonal affective disorder and panic disorder.

Choice of drug therapy is mainly based on safety as there is little difference in terms of clinical efficacy among different drug classes. Advantages from fewer unpleasant side effects could be beneficial to the patient and in turn enhance patient compliance to optimize the treatment.⁽³⁵⁾ The NICE guidelines recommend that atypical agents should be considered

when an individual suffers unacceptable side effects from conventional agents, and switching from conventional to an atypical agent in patients whose symptoms are well controlled is not necessary.⁽³⁶⁾ Both dependence and dropout are particularly likely in the patients with a history of substance abuse, therefore healthcare professionals should watch for prescription and over-the-counter medication abuse while monitoring compliance throughout the treatment for optimum efficacy.^(35,37)

ASSESSMENT TOOLS

The use of appropriate and standardized assessment tools enables healthcare professionals to identify longitudinal patterns with greater precision and higher sensitivity. In recent years, observer-rated and self-completed instruments were introduced for the assessment of depressive, manic and psychotic symptoms. Traditionally, the assessment of depressive symptoms was based on the Hamilton Depression Rating Scale (HDRS), which was mainly designed to rate the severity of symptomatology but was criticized for psychometric flaws and conceptual limitations, such as excessive weight to somatic and anxiety features. Although several expanded versions have been proposed, the original 17-item version was still the most widely used. The Montgomery-Asberg Depression Rating Scale (MADRS) was aimed at the sensitivity to changes during treatment and emphasized psychic aspects rather than those medication side effects related to somatic symptoms. The Bech-Rafaelsen Melancholia Scale (MES) has satisfactory psychometric properties with the addition of a unidimensional characteristic and validity for non-English versions. Nonetheless, motor retardation was not covered by the MADRS while mood and atypical symptoms were not rated by the HDRS, MADRS or MES. In view of that, the Bipolar Depression Rating Scale (BDRS) was specially designed to address the symptoms experienced by depressed patients with bipolar disorders. The Bipolar Inventory of Symptom Scale (BISS) includes both a depression and a mania sub-scale. The Beck Depression Inventory (BDI) is the most frequently used self-rated depression scale, with such valuable features as the coverage of appetite, sleep, agitation and irritability; and limitations as the prominent weight on cognitive symptoms and the neglect of motor retardation.

Manic symptoms can be assessed by using the Manic State Rating Scale (MSRS) which relies on patient's observation rather than verbal report. Over the last three

decades, the Bech-Rafaelsen Manic Scale (MAS) has been used in clinical trials to measure the severity of manic states. Nowadays, the most frequently used is the Young Mania Rating Scale (YMRS) which doubles the weight on irritability, speech rate and amount, thought content and disruptive behavior to elevated mood, increased motor activity, sexual interest, sleep, thought disorder, appearance and insight. Less commonly used is the Mania Rating Scale (MRS) derived from the Schedule for Affective Disorders and Schizophrenia (SADS) which includes a manic symptom sub-scale and a behavior and ideation sub-scale, with an additional item on impaired insight. Another instrument also used in a number of studies is the Scale for Manic States (SMS) with items relevant to mania and mixed states.

Self-rated scales are increasingly used for daily monitoring, and allow the patients to become informed collaborators in their treatment. The widely used self-report Zung Depression Scale (ZDS) covers agitation and irritability but not atypical depression symptoms and motor retardations. The Inventory of Depressive Symptomatology (IDS) has been used for patient self-assessment in several studies, and its clinician-rated version covers irritability and symptoms of melancholic and atypical depression as well. Routinely used assessment tools are also included the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), the Life Chart Methodology (LCM), and the Patient Mood Chart (PMC). Recently, the specificity, sensitivity and consistency of Mood Disorder Questionnaire (MDQ) for screening was validated in different settings including Hong Kong.^(38,39)

WHAT CAN A COMMUNITY PHARMACIST DO?

As a community pharmacist, we are one of the most easily accessible healthcare professionals. Hence, we should keep ourselves up to date with relevant information for public health education and awareness of cases for which referrals are appropriate. Support and healthy lifestyle should be encouraged and promoted to the public. Complementary and alternative medicines are used by 35% of patients with functional bowel disorders, which is significantly associated with female gender, higher education, depression and anxiety.⁽⁴⁰⁾ Therefore, a community pharmacist should have knowledge on common mood enhancing herbs and supplements as well. Increased plasma levels of serotonin, norepinephrine, β -endorphin may result in the alleviation

of sleep disturbances and depressive symptoms, showing positive effects on the treatment of patients with sleep disturbances, depressive symptoms, anxiety disorders, headache, pain and fibromyalgia.⁽⁴¹⁾

Combination of nutrients including B vitamins are important for healthy functioning of the adrenal glands, where stress hormones are produced. Together with niacinamide and vitamin H, it can help to overcome anxiety and insomnia. The therapeutic uses of St. John's Wort was documented over 2000 years ago in European countries. The major active ingredient Hypericin is thought to work by suppressing serotonin reuptake in the brain, thus helping to enhance sleep and reducing feelings of anxiety. People taking St. John's Wort should be aware that it can affect the efficacy of contraceptive pills and induce photosensitivity, and should not be consumed if antidepressants are already prescribed. Minerals (e.g. Pearl powder), oyster shell (e.g. Muli) and fossil of the skeletons of ancient large mammals (e.g. Dragon Bones from deer and rhinoceros) can calm the liver and mood, thus relieve

symptoms of sadness, insomnia, dizziness and other associated problems.⁽⁴²⁾

Kavalactones found in Kava pepper root extracts demonstrated their uses in anxiety, convulsion, insomnia, nervousness and pain. Driving or operating heavy machinery should be avoided as it may cause drowsiness. It may interact with some drugs, including drugs used for Parkinson's disease. More importantly, consumption of Kava tops has been reported to cause liver damage.⁽⁴³⁾ Anxiety scores are significantly lowered after consumption of *Passiflora incarnata* without differences in psychological variables in the post-anesthesia care unit and recovery of psychomotor function.⁽⁴⁴⁾ Valerian root extract is used in sleeping disorders, restlessness and anxiety, as it has been demonstrated to interact with the GABA receptors. The mechanism of action and long term safety are yet to be determined.^(45,46)

Since tryptophan is the substrate for producing serotonin in the human body, increased intake of this essential amino acid in the diet was believed to raise

brain serotonin content as the processing enzymes are normally unsaturated. Food rich in tryptophan include milk, yogurt, cheese, eggs, beans, meat and nuts. Some research has suggested that depressed patients have lower blood levels of eicosapentaenoic acid (EPA), which has an important role in brain function and development. Nonetheless, further research may clarify whether extra intake of EPA is recommended for relieving the symptoms or not.

Caffeine and nicotine, on the other hand, are stimulants which accelerate the fight or flight response and thus interfere with sleep and mood. Though alcohol seems to decrease anxiety level initially, it can aggravate anxiety after a few hours and increase the risk of a panic attack.⁽⁴⁷⁾ Therefore, patients concerned with mood disorders should limit their consumption of these stimulants and alcohol.

Author's background

CHENG, Caroline obtained her pharmacy degree in National Defense Medical Center in Taiwan and pursued an MPhil degree in the Chinese University of Hong Kong. She is currently practicing in Watson's The Chemist.

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SHINGLES

CHAN, Charmaine

Chuen Cheong Dispensary, Shop 4, G/F, 368 Queen's Rd. Central, Sheung Wan, Hong Kong

ABSTRACT

Shingles (Herpes zoster) is an acute infection of the CNS involving primarily the dorsal root ganglia, and characterized by a vesicular eruption and neuralgic pain in the cutaneous areas supplied by peripheral sensory nerves arising in the affected root ganglia. Painkiller drugs are normally used to relieve the pain but anti-viral drug is also required.

Key Words: *Shingles; Slithering snake; Herpes zoster; Dorsal root ganglia; Vesicular eruption; neuralgic pain*

WHAT IS SHINGLES?

Shingles is a common disease caused by the Herpes zoster virus that triggers a painful rash. The Herpes zoster virus is a late manifestation of the chickenpox virus, varicella zoster. The chickenpox virus stays dormant in the dorsal root and/or cranial nerve ganglia and shingles develops if it becomes active again and attacks the nerves.⁽¹⁾ For this reason, a person who has already had chickenpox can only get shingles if infected again. When the virus activates, it travels unilaterally along sensory nerve fibres with small blisters breaking out on one side of the body or face.⁽²⁾ This gives the appearance of a 'slithering snake' wrapped across the affected area and thus its Chinese medical name "生蛇".



Figure 1. *Shingles spread across the back of a body.*

Shingles can affect the eyes and the ears. This is because the nerves connected to these organs may have been infected with the virus. Early diagnosis and treatment is important to minimise the symptoms and reduce the risk of

complications that may compromise vision and hearing. Although extremely rare, the infections can spread to internal organs, such as the lungs and the central nervous system in patients with immuno-deficiency. Shingles can recur, particularly, in a person who is under any physical or emotional stress.

WHO IS AT RISK FROM SHINGLES?

Very often, there is no obvious reason why the chickenpox virus becomes active again and causes shingles. It is found that it can affect people of any age but older people are much more susceptible. Most cases of shingles occur in people over 60.⁽³⁾ Someone with weakened immune system is equally prone to get it. Certain diseases may render a person to become more susceptible, such as some forms of cancer and HIV and AIDS. Some treatments and drugs can make a person more vulnerable, such as radiation, chemotherapy and high doses of steroids. Infections, injuries and surgery may also weaken the immune system of a person. A person under physical and emotional stress can also be at risk, while those vaccinated with varicella vaccine are not considered to be at risk.

WHAT IS SHINGLES LIKE?

Shingles causes a painful rash usually in a band across one side of the face or body (Figure 1). The early symptoms of shingles, however, are often vague and can easily be mistaken for other illnesses. The first sign of attack is often a tingling or prickling sensation followed by pain or numbness on one side of the body. At this stage, the patient may feel that they are catching flu and have a high temperature. During these early stages, rash may not develop. It will, nonetheless, appear some time within the first few days of the illness. The rash consists of fluid-containing blisters in groups or bands on one side of the body or face. Once the new rash stops appearing, the blisters will usually form scabs and then heal over the next two to three weeks. The skin will then appear a bit discoloured or scarred.

Pain will, however, continue to be felt by some for up to a month or even longer after the blisters have healed. The degree of pain caused by shingles varies from person to person. It may be an 'ache', or it could be a 'shooting' or 'stabbing' pain.⁽⁴⁾ Some may feel the sting of the rash and the itch as it heals, very like chickenpox. Others may suffer from painful post-herpetic neuralgia (PHN) that continues or returns weeks or months after the blisters have healed.

HOW IS SHINGLES SPREAD?

It is believed that shingles is not an air-borne disease and it is also not spread by close contact with the patient, not even touching the rash itself will cause the disease. However, it is possible for someone who has never had chickenpox before to catch shingles from a person with the herpes zoster virus, although one can never catch it from someone with chickenpox. Once infected, one should avoid contact with a group of vulnerable people such as babies, young children and pregnant women who have not had chickenpox before and people with compromised immune system, such as cancer or HIV and AIDS patients.

HOW IS SHINGLES TREATED?

Early reporting of signs and symptoms to the doctor is important in the treatment of shingles. How the disease is treated depends on where the rash is and on how badly it affects the sufferer. Antiviral drugs, such as acyclovir, famciclovir or valaciclovir, should be started within two to three days of the rash appearing for them to work and to ensure no permanent scars are left.⁽⁵⁾ These drugs will shorten the attack of shingles and will usually alleviate the pain. Antibiotics may be used if a secondary infection occurs. Painkillers are used to relieve the pain while on the one-week or ten-day course of antiviral drugs. Their use is to be continued after the antiviral drug treatment course is finished if persistent pain remains.⁽⁷⁾

The most common complication of shingles is the pain that continues or

returns three months after the shingles rash started. This medical condition is post-herpetic neuralgia or PHN.⁽⁶⁾ When the chickenpox virus becomes active again and causes shingles, the nerves it attacks either recover completely or become permanently damaged, and PHN occurs when the nerves are damaged.⁽⁷⁾ The damaged nerves send confused messages to the brain that register as pain.

Although older people are more likely to suffer from PHN, many people are also affected by it. Different descriptions are used to express the pain intensity. Some describe it as a tender, burning pain but others describe it as intense 'aching', 'throbbing' or 'stabbing' pain. Clothes rubbing against the body or the effect of wind on the face can make the pain unbearable. PHN makes the life of the sufferer miserable and quite often causes depression, weight loss and difficulty in sleeping.⁽⁸⁾ Unfortunately, ordinary painkillers have little effect on PHN, therefore early diagnosis and treatment of PHN is essential in reducing considerable pain. Nortriptyline and amitriptyline, although originally developed for the treatment of depression, are used to treat PHN due to their effect on nerve pain.⁽⁹⁾ A nightly low dose of nortriptyline or amitriptyline is used as soon as shingles is diagnosed. Early treatment with these antidepressants helps to prevent long term pain. Higher doses may be required when the pain does not stop after being treated for six weeks. Continued use of these antidepressants is necessary three months after the pain disappears and only then is the dose gradually reduced. Medication may need to be re-started again if the pain begins to come back.⁽¹⁰⁾

Newer drugs such as gabapentin⁽¹¹⁾ and pregabalin,^{(12) (13)} are used in the treatment of PHN for their similar effectiveness but fewer side effects than the antidepressants which may cause dry mouth and drowsiness.

Some creams and lotions, although not a cure, provide immediate local relief when put directly on the rash. The cream made with capsaicin can be helpful but might sting or burn when first applied.⁽¹⁴⁾

Keeping clothes away from the rash, when the tender painful 'burning' sensation is caused by the rubbing of clothes against the body, can help reduce the discomfort. Cotton clothing inflicts less pain. If the rash is around the waist, trousers and skirts without a waistband can be worn and not tucked in. If the rash is around the hips or thighs, boxer shorts, baggy trousers and skirts are recommended. Loose or low cut underwear is also helpful. If the rash is on

the back, it is best not to wear a bra. If wearing one is the only option, an old one that has lost its elasticity is a better choice.

Other treatments, including physiotherapy, transcutaneous electrical nerve stimulation (TENS),⁽¹⁵⁾ laser and ultrasonic therapy, are found to be useful in PHN. Acupuncture, aromatherapy, hypnotherapy and homeopathy are the alternative treatments that offer PHN relief. Relaxation is a very important part of managing pain. Listening to favourite music, lying in a warm bath, or just watching television are all useful ways to relax oneself.

While suffering from the disease, it is important to eat a healthy diet in order to have an early recovery and to reduce the risk of suffering from long term pain.

CAN SHINGLES BE PREVENTED?

Shingles, although not considered to be life threatening, will affect the quality of life of some patients who suffer long term pain. To avoid the spread of shingles, chickenpox can be prevented. Varicella vaccine is now being recommended for the prevention of chickenpox, especially for the most at risk group of pregnant women, children, the elderly and those with lowered immune systems. In 1995 a live attenuated viral vaccine against chickenpox was licensed in the U.S. and was found to have 95% efficacy in preventing chickenpox.⁽¹⁶⁾ The vaccine, however, cannot prevent the manifestation of the shingles virus that already exists and lays dormant in the body. It is also not known if the vaccine can prevent shingles from developing in those who have had chickenpox, although it is thought that it is possible that the vaccine may intensify the immune system in preventing the development of shingles in those who have had chickenpox as children or adults with previous episodes of shingles.

For those who have never had chickenpox before, it is recommended that they should avoid contacting anyone with chickenpox or shingles, especially the contagious excreting fluid from shingles lesions.

For people other than those at risk, the best prevention is to avoid stress, to maintain a healthy life style by eating a balanced diet, exercising regularly, going to bed early, drinking plenty of fluid and not smoking. A healthy body and mind prevent not just chickenpox and shingles but also other disease including most of the infectious ones. Acupuncture, aromatherapy, hypnotherapy and ultrasonic therapy, are found to be useful in PHN.

Author's background

CHAN, Charmaine is a holder of a BSc degree in Pharmacy and a MSc degree in Pharmacology. She currently is working at: Chuen Cheong Dispensary, Shop 4, G/F, 368 Queen's Rd. Central, Sheung Wan, Hong Kong. Her email address is: bdmchaney@yahoo.com.

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Management of Complications of Cirrhosis Focusing on Ascites

CHUNG, Kenneth

Queen Elizabeth Hospital, Hong Kong SAR, China

ABSTRACT

Ascites is the most common complication of cirrhosis. It is associated with an increased risk for the development of infections, dilutional hyponatremia, renal failure and mortality. Prognosis is particularly poor in patients who develop refractory ascites or hepatorenal syndrome. The pathogenesis of renal sodium retention and ascites formation in cirrhosis is a subject of much controversy. The most acceptable theory for ascites formation is peripheral arterial vasodilation leading to underfilling of circulatory volume. However, the mechanism is complex involving rennin-angiotensin-aldosterone system, sympathetic nervous system and non-osmotic release of vasopressin. Management of ascites includes negative sodium balance, and is composed of salt restriction, bed rest and diuretics. Paracentesis and albumin infusion are applied to tense ascites. Transjugular intrahepatic portosystemic shunt is considered for refractory ascites. Treating ascites is important, not only because it improves the quality of life of cirrhotic patients, but also because spontaneous bacterial peritonitis, one of the lethal complications of cirrhosis, does not usually occur in the absence of ascites. The development of ascites in cirrhotic patients is an indication for referral for evaluation of liver transplantation, which constitutes the ultimate treatment for ascites and its complications. This article focuses on the diagnosis, pathophysiology and current management of ascites in cirrhosis.

Key Words: *Cirrhosis; Ascites; Hepatic injury; Bacterial peritonitis; Etiology; Medications*

INTRODUCTION

Chronic liver disease and cirrhosis was the tenth leading cause of death in Hong Kong in year 2007⁽¹⁾ while in the United States, it ranked twelfth and claimed 26,000 deaths in year 2004.⁽²⁾ Ascites is the most common of the 3 major complications of cirrhosis; the other complications are hepatic encephalopathy and variceal hemorrhage.^(2,3)

Approximately half of patients with compensated cirrhosis develop ascites during 10 years of observation.⁽³⁾ Cirrhotic patients who develop uncontrolled ascites have poor prognosis with probabilities of survival being 85% at 1 year and 56% at 5 years without liver transplantation.⁽²⁾

CIRRHOSIS

Cirrhosis can be defined as a chronic disease of the liver with hepatic parenchymal cell injury and hepatocyte destruction. The non-specific pathologic process may ultimately cause anatomic and functional abnormalities of blood vessels and bile ducts, which serve as the basis for jaundice and the development of portal hypertension and the associated complications. The 3 major and potentially fatal complications of cirrhosis of the liver result from portal hypertension and include variceal bleeding, ascites, and encephalopathy.⁽³⁾

Pharmacological treatment depends on the type and stage of cirrhosis. It aims at stopping the progress of cirrhosis if at all possible, reversing the damage that has already occurred and treating complications that are disabling or life threatening.

In brief, offending medications and alcohol should be stopped. Bleeding varices are treated by upper endoscopy with banding or sclerosis, drug therapy with terlipressin or octreotide,⁽⁴⁾ and prophylactic treatment of varices by beta-blockers. Ascites (excess abdominal fluid) is treated with diuretics, fluid and salt restriction, and removal of fluid (paracentesis). Coagulopathy may be treated with blood products or vitamin K. Encephalopathy is treated with the medication lactulose, which acts by reducing the production and absorption of ammonia. The initial dose of lactulose is 30 to 45ml given three times daily and titrated to either resolution of symptoms or the production of three soft stools per day.⁽⁵⁾ Sometimes antibiotics like neomycin (dose: 1 to 2 g orally four times a day) are used and patients should avoid a diet high in protein.

Spontaneous peritoneal infection is treated with antibiotics. If cirrhosis progresses and becomes life threatening, a liver transplant should be considered.

ASCITES

Ascites is not solely caused by cirrhosis or liver diseases. Ascites is caused by cirrhosis in around 75% of total cases, malignancy in 10%, and cardiac failure in 5%; other causes account for the remaining 10%.⁽⁶⁾ Hepatic causes also include acute alcoholic hepatitis, and portal vein or splenic vein thrombosis, etc. Non-hepatic causes include congestive heart failure, constrictive pericarditis, nephrotic syndrome, and peritoneal carcinoma etc.

Generally speaking, ascites is the accumulation of fluid in the peritoneal cavity with full and bulging of abdomen.⁽⁷⁾ As it is the building-up of fluid (percussion of flank), the distended abdomen can be differentiated from other causes like obesity, pregnancy, gaseous distention, and bladder distention, etc by flank dullness or fluid wave. A fluid wave can be observed by having patients lying on his or her back. While supporting one side of the abdomen with one hand, use the second hand to tap the opposite side of the abdomen. A wave of fluid moving across the abdomen should be visible.⁽⁵⁾ However, an abdominal ultrasound may be required to determine with higher certainty that ascites is present in obese patients.⁽³⁾

PATHOPHYSIOLOGY

The formation of ascites in cirrhosis is due to a combination of abnormalities in both renal function and portal and splanchnic circulation. Originally, four theories can be used to explain the pathophysiology of accumulation of ascitic fluid in patients with end-stage liver diseases.⁽⁵⁾

- Underfill theory: the increase hydrostatic pressure decreases perfusion of vital organs and the decrease of oncotic pressure increases lymph production.

Decreased effective blood volume trigger vasoconstriction leads to sodium and water retention mediated by the renin-angiotensin-aldosterone system.

- Overfill theory: sodium retention and plasma volume expansion create excess fluid overflows in to the peritoneal cavity.
- Lymph imbalance theory: visceral edema from an imbalance in lymphatic flow stimulates retention of salt and water by the kidney. Increases in visceral lymph production results in ascites.
- Peripheral arterial vasodilatation hypothesis: peripheral arterial vasodilation is the initiating event that causes a decrease in effective blood volume and a compensatory increase in sodium and water retention by the kidney.

Nowadays, the peripheral arterial vasodilation hypothesis is generally accepted by practitioners.^(2,6) However, recent data do not seem to conform to the theory. In a cirrhotic patient, the architectural distortion of the liver secondary to fibrous tissue and regenerative nodules leads to obstruction of blood flow with increase in intrahepatic vascular tone.^(2,8,9) Portal hypertension due to increase in sinusoidal pressure activates the vasodilatory mechanisms. Mediated by nitric oxide overproduction, splanchnic and peripheral arteriolar vasodilation follows. The next step is a baroreceptor-mediated activation of the renin-angiotensin-aldosterone system, sympathetic nervous system and anti-diuretic hormone secondary to underfilling of the arterial vascular compartment.^(2,8-10) The final consequence is renal sodium and water retention leading to the formation of ascites.

NON-PHARMACOLOGICAL TREATMENT

Alcohol-induced liver injury is perhaps the most reversible cause of liver disease. For alcoholic cirrhosis, one of the most important steps in treating ascites is to convince the patient to stop drinking alcohol³. In a period of months, abstinence can result in dramatic improvement in the reversible component of alcoholic liver disease.

There is an assumption that an upright posture in patients with cirrhosis and ascites is associated with marked activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, reduction of glomerular filtration rate and sodium excretion, and a decreased response to loop diuretics.^(3,9) Moreover, moderate physical exercise has been demonstrated to induce greater stimulation of the renin-aldosterone and sympathetic nervous systems in cirrhotic patients with ascites than in healthy persons. So, bed rest may be a useful treatment of ascites in cirrhosis, particularly in patients who respond poorly to diuretics or patients with a large amount of ascites. However, it is not routinely recommended as it is not supported by clinical trial⁽³⁾ and it is often impractical and could cause decubitus ulcers and muscle atrophy.⁽⁹⁾

Moreover, dietary sodium restriction is a mainstay in the treatment of cirrhotic ascites. Reduction of sodium intake is particularly beneficial to those with severe sodium retention that does not respond or responds only minimally to diuretics.⁽²⁾ Non compliance will worsen total body volume overload and hinder the effectiveness of diuretic therapy. A low-sodium diet (60 to 90 mEq per day, equivalent to approximately 1.5 to 2 g of salt per day) may facilitate the elimination of ascites and delay the re-accumulation of fluid. More stringent restriction is not recommended because it is poorly tolerated.⁽²⁾

Fluid intake has to be monitored in cirrhotic patients. Fluid restriction is not necessary in treating most patients with cirrhosis and ascites.⁽³⁾ Fluid intake should be restricted (to approximately 1000ml per day) in patients with dilutional hyponatremia, a condition characterized by a serum sodium concentration of less than 120-125 mmol per liter⁽³⁾ in the presence of ascites, edema, or both.

Several herbal and naturalistic therapies have been reported as having benefit in patients with cirrhosis. None have clearly been proven to be effective, although some continue to be studied. Importantly, patients should be cautious about taking herbal medications since some herbal therapies may be severely toxic to liver.

2-GRAM DIET

A 2-gram sodium diet can limit high

sodium foods in patients' diet. No table salt is allowed at meals or during cooking. The amount of milk should also be limited because of the amount of sodium it contains. The goal of a 2-gram sodium diet keeps patients' body from holding extra fluid. However, too low amount of sodium (hyponatremia) in the blood may cause nausea and confusion.

Asking patients to read food labels is a good way to teach them to learn how much sodium is in foods. Food labels list the amount of sodium in the food in milligrams. Patients should avoid foods that contain more than 500 mg of sodium in one serving. They should also avoid using salt and ingredients such as baking soda and soy sauce that are high in sodium. Patients should also avoid these during food preparation, and at the table. Meals eaten at restaurants, especially fast food restaurants, are often high in sodium.

PHARMACOLOGICAL TREATMENT

Despite the institution of non-pharmacological management, addition of diuretics is required in most patients to achieve net sodium loss. The initial diuretic of choice is spironolactone, an aldosterone antagonist. The usual starting dose is 50 to 200 mg⁽²⁾ a day given as a single dose. The dose can be increased as necessary to a maximum of 400 mg a day. Patients must be cautioned to avoid potassium-rich foods, including salt substitutes containing potassium chloride. Spironolactone can cause painful gynecomastia, in which case amiloride (5 to 10 mg per day², maximum 40 mg³) can be substituted.

In patients with inadequate initial response to spironolactone or in those with fluid overload presenting as peripheral edema, a loop diuretic such as furosemide (20 to 40 mg per day, maximum 160 mg per day) is often added to increase natriuresis. Conveniently, potassium loss induced by furosemide is usually counteracted by the potassium-sparing effect of spironolactone. Furosemide should be used with caution because of the risk of excessive diuresis.⁽²⁾ The dose of both oral diuretics (spironolactone/furosemide) can be increased simultaneously every 3 to 5 days (maintaining the 100mg:40mg ratio) if weight loss and natriuresis are inadequate as this ratio maintains normokalemia.⁽³⁾

The recommended weight loss to prevent renal failure of pre-renal origin is 300 to 500 g per day in patients without peripheral edema, and 800 to 1000 g per day in those with this condition.⁽²⁾ The response to diuretics can be evaluated on the basis of changes in body weight and by physical examination. Treatment should be very cautious since there are potential complications including encephalopathy, hypochloreaemic alkalosis, and azotaemia.

LARGE VOLUME PARACENTESIS

It is a method used on patients with large-volume ascites or tense ascites. Therapeutic paracentesis with albumin infusion has been shown to have significantly lower complications compared with diuretic therapy. Albumin is usually given in doses of 8 g/litre of ascites removed^(2, 9) while the American Association of Study of Liver Disease (AASLD) recommends 5 to 10g/litre. However, removal of large amounts of ascitic fluid by paracentesis without the use of plasma expanders is associated with a derangement in circulatory function.^(2,5) It will be associated with a high rate of recurrence of ascites, development of hepatorenal syndrome or dilutional hyponatremia.

Since the use of albumin in this setting remains controversial because of its high cost and the lack of a documented survival benefit, the use of synthetic plasma expanders in combination with paracentesis has been explored. Dextran 70, hydroxyethyl starch, and even saline have been advocated.⁽³⁾ In conclusion from several studies, albumin has a greater protective effect on the circulatory system than other expanders from different review journals,⁽²⁾ while hydroxyethyl starch should not be used since it can even cause portal hypertension in patients without underlying liver disease.⁽³⁾

Although severe local complications related to paracentesis such as infection or intestinal perforation may occur, they are exceedingly rare if the procedure is performed with an appropriate technique and with an appropriate needle.⁽²⁾ The incidence of clinically significant bleeding at the puncture site or hemoperitoneum is also extremely low. The risk of bleeding complications in patients with more severe coagulopathy is unknown and warrants investigation.

SPONTANEOUS BACTERIAL PERITONITIS^(2,3)

Spontaneous bacterial peritonitis is characterized by the spontaneous infection of ascitic fluid in the absence of an intra-abdominal source of infection.⁽²⁾ An abdominal paracentesis must be performed and ascitic fluid must be analyzed before a confident diagnosis of ascitic fluid infection can be made. A neutrophil count greater than 250/mm³ (0.25 × 10⁹/L) in the absence of an intra-abdominal source of infection in ascitic fluid is suggestive of spontaneous bacterial peritonitis and should prompt administration of antibiotics Cefotaxime at a dose of 2 g every 8 hours or a similar third-generation cephalosporin, administered intravenously for 5 to 7 days, is the treatment of choice. Aerobic gram-negative bacteria, primarily *Escherichia coli*, are the most common isolates. Oral ofloxacin (400 mg every 12 hours) has been shown to be as effective as cefotaxime in the treatment of uncomplicated spontaneous bacterial peritonitis of patients with better conditions. Prophylactic treatment of spontaneous bacterial peritonitis has been suggested in patients with variceal hemorrhage. Norfloxacin 400 mg twice per day orally for 7 days helps prevent infection in such patients.

HEPATORENAL SYNDROME

Hepatorenal syndrome is characterized by renal failure due to severe vasoconstriction of the renal circulation.⁽²⁾ Hepatorenal syndrome develops most commonly in the setting of decompensated liver disease with refractory ascites.⁽⁶⁾ Pathogenetically, hepatorenal syndrome consists of renal failure of hemodynamic origin resulting from extreme underfilling of the arterial circulation, triggering the mechanism of unopposed vasoconstriction, including increased plasma endothelin levels, coupled with an exquisite sensitivity of the renal circulation to vasoconstrictors.⁽⁶⁾ Clinically, it is characterized either by a progressive oliguria associated with a rapid rise of the serum creatinine concentration, known as type 1; or a moderate increase in the serum creatinine concentration with no tendency to progress over time, known as type 2.⁽²⁾

Hemodialysis is frequently used to control azotemia and maintain electrolyte balance.⁽³⁾ Drug treatments involving the traditional drug dopamine and the use of vasoconstrictor drugs (vasopressin analogues or (alpha)-adrenergic agents), in combination with albumin (10 to 20 g per day), are effective in approximately two thirds of patients. Octreotide (200 microgram subcutaneously three times per day) is reported to be beneficial when given in combination with midodrine (titrated up to 12.5mg three times per day). These agents may increase the likelihood of patients surviving long enough to undergo liver transplantation². In the absence of liver transplantation, established hepatorenal syndrome has a 100% mortality rate.^(3,6)

Author's background

CHUNG, Kenneth graduated from the School of Pharmacy in the Chinese University of Hong Kong. He is currently the resident pharmacist of Queen Elizabeth Hospital, Hong Kong SAR, China.

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The First FDA Approved Bioengineered Drug from Transgenic Goats - Antithrombin

JABUBARHAMEED; LEUNG, Fo-Man

Research Group for Bioactive Products, Department of Biology & Chemistry, City University of Hong Kong, Hong Kong SAR, China

ABSTRACT

ATryn®, the brand name of recombinant antithrombin, is the first ever therapeutic protein produced by bio-engineered goats which has been approved by the FDA recently. Along with the approval of ATryn, the FDA's Center for Veterinary Medicine also approved GTC's New Animal Drug Application, the first of its kind to regulate genetically engineered animals. GTC has granted OVATION the right to market ATryn in the U.S. and pursue further clinical development. ATryn is expected to reach the services to the public in the second quarter of 2009. In this review article, the need for this bioengineered drug, its production and ethical aspects are briefly discussed.

Key Words: ATryn®; Recombinant antithrombin; Transgenic goats; Blood clots; Factor Xa; Goat milk

INTRODUCTION

ATryn® is the first recombinant antithrombin product approved through the centralized procedure in the European Union. It is now also the first recombinant antithrombin product approved by the FDA. People with hereditary antithrombin deficiency are at increased risk for venous thromboembolic events, including pulmonary embolism and deep vein thrombosis, which can be life-threatening, particularly in high risk situations. Antithrombin is a natural anticoagulant that plays an important role in controlling the formation of blood clots. Purified recombinant antithrombin has the same amino acid sequence as antithrombin derived from human plasma. ATryn was developed to provide a safe and consistent supply of recombinant antithrombin.

ANTITHROMBIN

Antithrombin is a serine protease inhibitor that inhibits thrombin and factor Xa. (1-4) Human Antithrombin, which is synthesized in the liver, is normally present in plasma at levels of 14 to 20 mg/dL. (5, 6) It has a

molecular weight of approximately 58,000 Da and contains 432 amino acids, three disulfide bridges, and four carbohydrate side chains, which account for 15% of the total mass. (7, 8) Decreased levels of AT may be found in the serum of individuals who have either a hereditary deficiency of AT or an acquired deficiency, which can result from a number of pathological conditions. (3) Antithrombin products that were available before are derived from human plasma. The complex structure of antithrombin precludes its efficient production in traditional bioreactors.

Antithrombin acts as a relatively inefficient inhibitor on its own. However, when it is able to bind with heparin, the speed with which the reaction that causes inhibition occurs is greatly accelerated; this makes the antithrombin-heparin complex a vital component of coagulation. This interaction is also the basis for the use of heparin and low-molecular weight heparins as medications to produce anticoagulation.

Antithrombin-deficiency

Antithrombin deficiency is a rare hereditary disorder that generally is

identified when a patient suffers recurrent venous thrombosis and pulmonary embolism. This was first described by Egeberg in 1965. This is of two types.

Type I antithrombin deficiency: heterozygous mutations lead to a complete loss of the mutant antithrombin protein result in immunologic and functional levels that are 50% or less than normal. The genetic basis of type I mutations includes major gene deletions or point mutations, with point mutations accounting for most of these cases. The mutations appear to cause a quantitative reduction in antithrombin synthesis by various processes, including premature termination of translation, aberrant RNA processing, and production of unstable antithrombin molecules that have short plasma half lives. (9)

Type II antithrombin deficiency: single amino acid changes that result in functional deficits in a molecule that is otherwise synthesized and secreted into the plasma in a normal fashion. The variant antithrombin molecules may have abnormalities at the reactive site or the heparin binding site. Most cases of type II antithrombin deficiency are also heterozygous, although rare cases

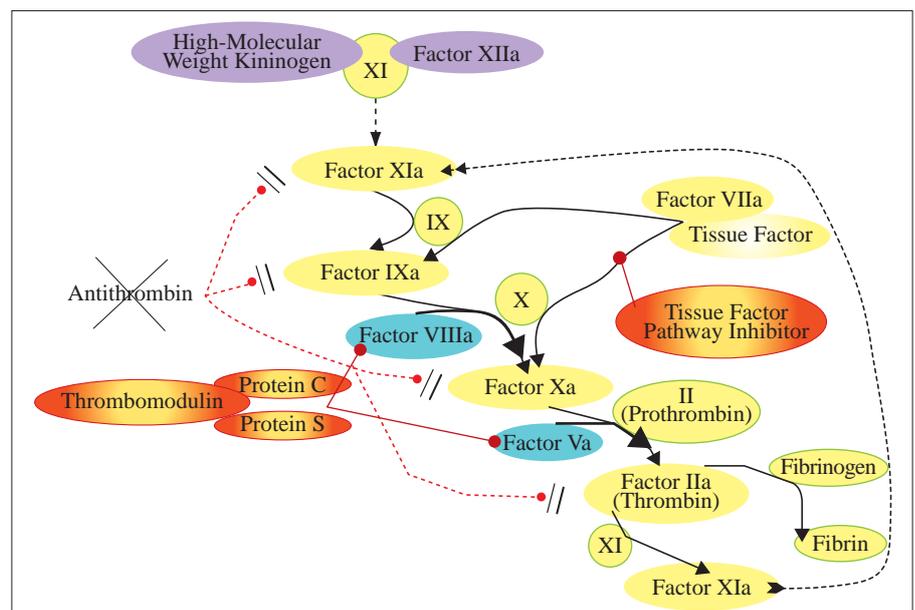


Figure 1. Action of antithrombin on blood coagulation.

of homozygous type II deficiency have been described.⁽¹⁰⁾

In patients who develop venous thrombosis, the prevalence of hereditary antithrombin deficiency (AT deficiency) is between 1:20 and 1:200.⁽³³⁾ Among the subtypes of antithrombin deficiency, type II antithrombin deficiency is at least twice as common as type I antithrombin deficiency in the general population.⁽¹¹⁾ However, in symptomatic patients, cases of type I antithrombin deficiency represent about 80% of the total cases.⁽¹²⁾ The frequency of acquired antithrombin deficiency (AT deficiency) depends on the frequency of the associated disease process.

Mechanism of action of antithrombin deficiency

Antithrombin is a potent inhibitor of the reactions of the coagulation cascade. Although the name, antithrombin, implies that it works only on thrombin, it actually serves to inhibit virtually all of the coagulation enzymes to at least some extent. The primary enzymes it inhibits are factor Xa, factor IXa and thrombin (factor IIa). It also has inhibitory actions on factor XIIa, factor XIa, complex of factor VIIa and tissue factor.⁽¹³⁻¹⁶⁾ Its ability to limit coagulation through multiple interactions makes it one of the primary natural anticoagulant proteins. Its numerous interactions are depicted in Figure 1.

PRODUCTION OF RECOMBINANT PROTEINS BY TRANSGENIC ANIMALS

Many human therapeutic proteins are currently produced with the aid of recombinant DNA technology in microbial bioreactors. Although extremely cost-efficient, the prokaryotic microbial production system has many inherent limitations. Bacterial bioreactors can produce human proteins with correct amino acid sequence, but can not carry out post-translational modifications, such as glycosylation, or fold the newly synthesized protein properly to ultimately generate a biologically active entity. Moreover, even though the production of the proteins as such is inexpensive, the downstream processing of the final product may be extremely difficult

and costly. This could be overcome by employing eukaryotic yeast and large-scale animal cell cultures for the production of proteins of pharmaceutical interest (Table 1). However, the use of animal cell bioreactors is unacceptably expensive due to generation time and the requirement for rich culture media. With the advent of transgenic technology, the production of human pharmaceuticals in large transgenic animals has become more and more attractive. As shown in Figure 2, the use of targeted gene transfer, the expression of the transgene of interest can be directed to occur in the mammary gland of large farm animals, such as pigs, sheep, goats or dairy cattle, and hence the transgene product is ultimately being secreted into the milk. However, this new application of biotechnology also raises a number of questions regarding risks and ethical implications.

Troubleshoots

- In most cases, it has been difficult to achieve protein yields superior to 1 mg/ml with cDNA derived constructs⁽¹⁷⁻²⁴⁾ and sometimes the transgenes are transcriptionally silent. However, the use of a genomic construct does not always ensure high expression levels.⁽²⁵⁾ The weak performance of cDNA-containing transgenes could be caused by sensitivity to the silencing influences of chromosomal sequences surrounding the integration sites.
- Proper post-translational modification of milk-produced recombinant proteins is also an issue of concern. A recent study⁽²⁶⁾ compared the two N-glycosylation sites of human interferon-7 (IFN- γ , Asn25 and Asn97) in recombinant protein samples obtained with three expression systems: Chinese hamster ovary (CHO) cells, baculovirus-infected SF9 cells, and the mammary gland of transgenic mice. The transgenic mouse-derived IFN- γ had predominantly complex sialylated biantennary N-glycans at Asn25, similar to the CHO cell-derived IFN-7. An increased proportion of oligomannose at Asn97 was found in transgenic mouse-derived material as compared to the CHO cell IFN-7. An increased incidence

of oligomannose glycans could affect clearance by the mannose receptor of the recombinant protein.

- The effect of the expression of the transgene on the production animal is another concern. In problem cases, the expression of the heterologous protein can either influence the physiology of the mammary gland and disrupt lactation,^(27, 29-33) or have a systemic effect on the transgenic animal, affecting its viability and reproductive performance.^(28, 33-35)

Transgenic animals have the ability to process highly modified proteins, although not always with total efficiency. There are species-specific and tissue-specific characteristics. However, it seems that transgenic systems are flexible and that, when needed, processing enzymes can be coexpressed with foreign products to obtain more humanized recombinant proteins. The further characterization of each bioreactor's capability, and an improved ability to introduce specific genetic modifications, should lead to more sophisticated transgenic production herds.

METHODOLOGY

The transgenic goat was obtained by microinjection of the transgene into the pro-nucleus of a goat embryo. It is a simple mechanical process in which a needle roughly 0.5 to 5 micrometers in diameter penetrates the cell membrane and/or the nuclear envelope. The desired contents are then injected into the desired sub-cellular compartment and the needle removed. Microinjection is normally performed under a specialized optical microscope setup called a micromanipulator. This transgene is composed of the gene of interest (human AT cDNA) and the regulatory regions of goat beta casein gene (CSN2) to direct tissue specific expression in goat mammary gland.

Goat breeding is then accomplished through a combination of natural breeding and artificial insemination. The herds were predominantly constituted of "Swiss breed" dairy goats (namely Saanen, Alpine, Toggenburg breeds and mixtures thereof). Transgenic goat may

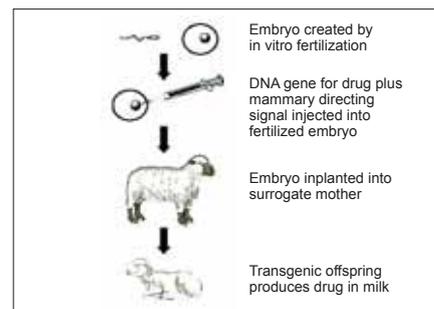


Figure 2. Step by step process in transgenic animal production

Table 1. Generalized feature of proteins of different biological origin

Protein feature	Prokaryotic bacteria	Eukaryotic yeast	Eukaryotic mammalian cells
Concentration	High	High	Low
Molecular weight	Low	High	High
s-s bridges	Limitation	No limitation	No limitation
Secretion	No	Yes/ no	Yes
Aggregation state	Inclusion body	Singular, native	Singular, native
Folding	Misfolding	Correct folding	Correct folding
Glycosylation	No	Possible	Possible
Retrovirus	No	No	Possible

(Source: Pharmaceutical Biotechnology by Daan J. A. Crommelin, Robert D. Sindelar, Bernd Meibohm page 50)

be obtained from any combination of these breeds. Considerable efforts were made to identify the genotype of the goats, and the "genetic consistency" of the herd has been greatly improved.

The purification process begins with the thawing, pooling and clarification of the goat milk. Purification is accomplished by a series of column chromatography steps and filtration through a virus filter. The validation of removal of goat milk impurities by the purification process has been adequately addressed by conducting further analysis on the raw materials and products from the first validation study, and by performing a second validation study. Suitable validated analytical methods were used to assess removal of these impurities. (Source: <http://www.emea.europa.eu/humandocs/PDF's/EPAR/atryn/058706en6.pdf>)

ETHICAL ASPECTS

The main problem lies in the novelty of these methods and the corresponding uncertainty about the dimensions and the exact nature of the risks associated with

them. The pharmaceuticals produced might be contaminated by animal pathogens dangerous for humans (or which become so by interaction with endogenous substances), not only for the users of the pharmaceuticals but also for persons coming into contact with them in the context of production. Risks resulting in the course of the production, distribution and consumption of transgenic products constitute the primary ethical concern with Pharming. The welfare of animals might be compromised by Pharming either directly, by the substances they are expected to produce in their organisms, or indirectly by changes resulting from the presence of these substances in their organisms or from their altered genome. In each individual case of a transgenic animal it has to be examined whether the risks for the welfare of the animal by introducing changes in its genome and by breeding and keeping it for human purposes are proportional to the expected benefits. Though animal Bio-engineering seems to be a promising technique for the production of specific pharmaceuticals, one has to emphasize that it is still in its beginnings. There are only few examples of a successful creation of transgenic

animals used for the production of pharmaceutical ingredients.

CONCLUSION

The approval of ATryn marks a significant milestone in the development of this innovative recombinant technology and delivers a new therapeutic option to benefit hereditary antithrombin deficient patients who are undergoing surgery or childbirth procedures. Similar drugs could be available in the next few years for a range of human ailments. However, this technology should be used properly considering the proportion of ethical and environmental effects. This would ensure safety and well being of all living forms in nature.

Author's background

JABUBARHAMEED obtained his BSc degree with first class honour from SRM University in India and currently works as a voluntary researcher in Dr CHEUNG Hon-Yeung's laboratory in CityU. **LEUNG Fo-Man** is a part-time MPhil student working on a recombinant project. For further information about this article contact Dr Cheung via his email: bhhonyun@cityu.edu.hk

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Microbial Contamination and Monitoring of Non-Sterile Pharmaceutical Products Should Not Be Over Looked

O'TOOLE, Desmond K; CHEUNG, Hon-Yeung*

GMP Information Centre, Department of Biology and Chemistry, City University of Hong Kong, Hong Kong SAR, China

ABSTRACT

A brief overview of the problems associated with microbial contamination is presented along with some solutions and monitoring actions that may be taken to reduce risk.

Key Words: Microbial contamination; Non-sterile pharmaceuticals; Opportunistic pathogens; Microbial monitoring; Microbial control; Water activity

INTRODUCTION

The recent death of five patients in Hong Kong after taking some fungal tainted pills of Allopurinol, usually used for the treatment of gout, illustrates that microbial contamination of non-sterile pharmaceuticals should not be over looked, primarily because some microorganisms can be opportunistic pathogens.⁽¹⁾ When they get into patients with poor immune function, death can follow.

Microbial contamination of sterile products, e.g. eye drops, has been recognized as a problem with consequences for many years. For example Aslund et al (1978) analyzed 436 samples from drip and pipette delivery systems for eye drops at an Outpatients Eye Clinic in Sweden.⁽²⁾ They found 10 of the samples, that happened to be from pipette bottles, were contaminated with bacteria, namely *Staphylococcus epidermidis*, *Propionibacterium* sp. and microaerophilic Gram positive cocci. They also found that although the ophthalmic preparations were sterile to begin with, handling of the multi use containers can result in contamination and that proper training in aseptic technique significantly reduces contamination.

A further study of sterile solutions prepared for irrigation purposes that are used to bathe open wounds or body cavities as well as for other purposes, were also found to be contaminated within 24 hr of being opened.⁽³⁾ Organisms found included *St. epidermidis*, *Propionibacterium* sp., *Corynebacterium* sp., *Micrococcus* sp., alpha haemolytic streptococci, *Peptococcus* sp., and *Moraxella* sp., amongst other genera of bacteria, all of which are part of the microflora found on skin and the upper respiratory tract.

Given the dangers associated with

the contaminants stringent guidelines and high standards have been introduced and implemented for sterile or liquid products.⁽⁴⁻⁷⁾

MICROBIAL CONTAMINANTS IN NON-STERILE PRODUCTS

A range of both pharmaceutical products and cosmetic preparations are produced for which sterility is not obligatory but for which high contamination always occurs^(8,9) and can be a problem when they are used under certain circumstances such as when applied to damaged epithelium. Contamination may also include opportunistic pathogenic species whose opportunism may rely on the application site and the health of the recipient. Examples of cosmetic type products so affected by contaminants include eye ointments, eye drops, tablets, capsules, powders, jellies, inhalants, topical anaesthetics, hand creams, detergents, talcum powder, cellulose wadding and antiseptics. Specific examples of infections arising from such contaminated products include tetanus in a neonate due to talc contaminated with *Clostridium tetani* (neonate intestines are very susceptible to this organism due to a lack of bacterial competitors in the intestines), neonatal infection with *Ps. aeruginosa* from cleansing solutions and hand creams, and a fatality in a granulocytopenic patient who suffered a scalp infection from contaminated diluted shampoo. Consequences from infection of the eyes resulting from the use of contaminated products include loss of eye sight after using a *Ps. aeruginosa* contaminated saline solution during an intraocular operation, and severe eye disorders due to *Ps. aeruginosa* contaminated cortisone ointment. Other organisms that may occur in these products and cause problems include *St. aureus*, *Streptococcus pyogenes*, *Ps. aeruginosa* and *Klebsiella pneumoniae*. There was a series of reports indicating that some microbial contaminants could survive and wait for opportunities even in the presence of disinfectants.⁽¹⁰⁻¹⁴⁾

Why one set of conditions might be hazardous and they may not be in another depends on a number of parameters. For example, the intended use of a drug is important: is it a topical application or is it ingested; the pathogenicity and/or the virulence of any organism involved, is it an opportunistic organism or a known pathogen; the immunological state of the

patient is a growing significant problem; the number of organisms in the product as well as the kind of substrate in the product, e.g. very few salmonellae in a fat based substrate will result in infection but in a water based product a much larger number is needed to initiate an infection.

Although creams and water based products that incorporate non-sterile components can be expected to contain some microbes, tablets may also be contaminated.⁽¹⁵⁾ In one study, from 18% of the tablets studied, live cultures of *Saccharomyces* sp., *Rhodotorula rubra*, coagulase-negative staphylococci and *Penicillium* sp. could be isolated but under the microscope up to 61% of tablets showed surface contamination.⁽¹⁶⁾ In another study of cough syrups 5% contained *Candida albicans* and up to 30% of the syrups contained insufficient preservative to control fungi/yeasts.⁽¹⁷⁾

CONSEQUENCES OF MICROBIAL CONTAMINATION OF PHARMACEUTICALS⁽¹⁸⁾

Any impact on the health of the patients is of paramount importance but the presence of microbial contamination can have other effects.

Spoilage

A spoiled product is one that is obviously unfit for its intended use. The spoilage may manifest itself in a range of ways that include visible effects on the product or packaging, such as bulging packets, or leaking or exploding containers, olfactory and taste effects, effects on texture and the active ingredient.

Visible effects

Liquid products, including shampoos, may contain sediment, be turbid or be capped by a pellicle. On solid preparations, such as creams, bright yellow micrococcus colonies may occur or mould colonies may be present. The very metabolically versatile *Pseudomonas* sp. may cause colour changes due to soluble pigment production or changes in ingredients in the product. Change might also be due to change in the pH or the reduction-oxidation potential. The addition of organic material greatly increases the chances of growth due to algae, mould, bacteria or yeast in a range of poorly preserved pharmacopoeia solutions. On the other hand, emulsions may become

thin, and separate owing to hydrolysis of the oil phase or change in pH of the aqueous phase so the two phases become visible.

Olfactory and taste effects

These two are related. Some bacteria are aroma-producing and yeast growth can result in an alcoholic odour. Microorganisms produce over 100 different compounds that affect flavor and aroma. These compounds include alcohols, aldehydes and ketones.

Textural effects

Creams may be lumpy and the viscosity of liquids may change; changes that may be detected on skin application. Dense growth of fungi in cosmetic powders may cause serious change in its mechanical properties.

Degradation of active constituents

A wide variety of microorganisms have been found able to inactivate potent drugs and antimicrobial agents. For example, alkaloids, analgesics, thalidomide, barbiturate and steroids have been shown to be susceptible to microbial inactivation. *Corynebacterium* and *Pseudomonas* spp. are able to destroy atropine in eye drops and the fungus *Cladosporium herbarum* is able to transform hydrocortisone in dermatological creams.

SOURCES AND ROUTES OF MICROBIAL CONTAMINATION ⁽¹⁵⁾

There is also a wide range of products coming from the pharmaceutical industry that, by their nature, are not specifically sterile. The microbial contamination of non-sterile and topical, cosmetic or oral products, however, has not been taken seriously even though microbes can be found everywhere. There are many natural products used in pharmaceutical products that by their nature carry microbial loads. Some studies have revealed loads that vary enormously. Total bacterial counts on ground *folia sennae* have been recorded at 1.5×10^6 per g while on unground samples counts have been at about 2.2×10^5 per g, while counts on ground *digitalis* has been measured at 2.8×10^5 per g. Animal products are also an important source including pancreatin, thyroid extract and lactose (ca 3000 per g). Animal products can be the source of serious pathogens such as the salmonellae.

In water based products it is common to rely on preservatives but when testing for preservative action the test organisms can be reduced in number and almost knocked out but on further incubation the residual live organisms can adapt to the preservative and grow to large numbers.

So within a manufacturing plant it is inevitable that microbial contamination is present. Special care is necessary to

achieve sterility in those products where sterility is mandatory. Further, cross contamination between ingredients can also be a problem, especially where an ingredient may be in a powder form. Two problems may arise from this, contamination with the actual component that would be a significant hazard, e.g. penicillin, or contamination with microorganisms that are native to an ingredient.

One important component is the water supply to the manufacturing plant and the distribution system in the plant. Biofilms build up in water systems and microorganisms from the biofilms slough off into the water. If the water is used in preparation of the formulation those organisms end up in the wet mixture formed. In addition, the equipment used for formulating and dispensing the product can also be contaminated and careful cleaning of the equipment is needed. In high volume food production "clean-in-place" systems are used because they are the most efficient at controlling contamination in the machinery.

Nevertheless, microbes are still present. In the formulation of such products as tablets the actual processing can help reduce levels of microbes. For example, in the case of tablets viable organisms can be reduced by up to 100% due primarily to the high pressure used and heat formation. Drying methods such

as fluid-bed granulation also reduces microbial load but does not necessarily completely kill all microbes.

CONDITIONS PREVENTING THE SPREAD OF MICROBES

Having reduced microbes to a low level it is then important to minimize or eliminate the chance of microbial growth in the product. One way of doing this is to control water activity. Water activity is a much better way of assessing the hazards from water content of a product because both microbial, enzymatic and chemical activity are affected by it. Water activity is related to the amount of bound water in a product. The water molecules become closely associated with other hydrophilic molecules and become "bound". The binding can be strong or weak and the water molecules are no longer able to move as freely as in pure water. In an enclosed container at equilibrium it means that fewer water molecules are able to escape from the surface of the water so the partial pressure of the water is lower, or put another way the relative humidity is lower (See Figure 1). As the measured water activity drops fewer and fewer microbial species can grow until at a water activity of 0.60 no microorganisms have been found that can grow at that water activity level (See Table 1). So, one control mechanism is to ensure that relevant products are at a low enough level to control microbial growth.

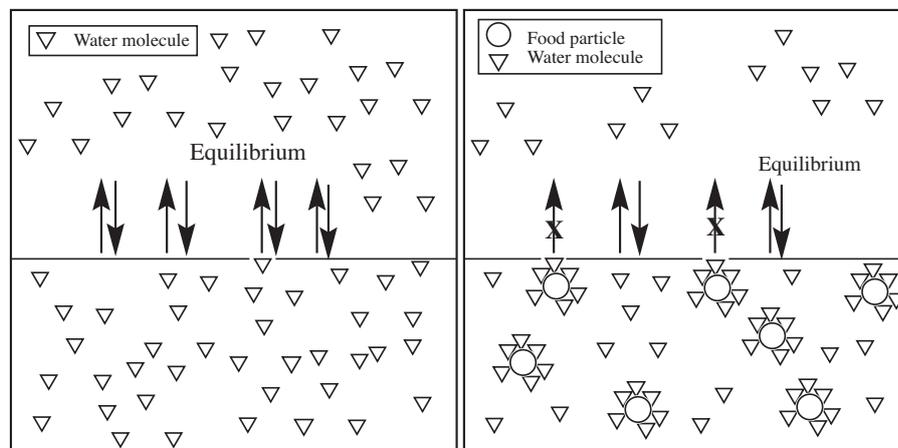


Figure 1. Hydration shells around salts and other hydrophilic compounds loosely bind H₂O molecules. Consequently some H₂O molecules in or on the hydrophilic compounds are unable to evaporate from a surface compared with pure water. Thus water activity (a_w) = P/P_0 , where P = partial vapour pressure of hydrophilic compound @ temperature T ; P_0 = partial vapour pressure of pure water @ T .

Table 1. Minimum A_w for growth of some representative microorganisms.	
Organism (Bacterium, Fungus, or Yeast)	A_w
<i>Pseudomonas</i> spp.	0.95
<i>Escherichia coli</i>	0.95
<i>Salmonella</i> spp.	0.92
<i>Bacillus</i> spp.	0.90–0.95
<i>Micrococcus</i> spp.	0.86–0.93
<i>Staphylococcus aureus</i>	0.86
<i>Aspergillus fumigatus</i>	0.82
<i>Saccharomyces cerevisiae</i>	0.80
<i>Penicillium chrysogenum</i>	0.79
<i>Aspergillus niger</i>	0.77
<i>Zygosaccharomyces rouxii</i> (osmophilic)	0.62
<i>Xeromyces bisporus</i> (xerophilic)	0.61

Therapeutic Goods Association, Australian regulatory guidelines for OTC medicines (ARGOM) 1 July 2003

MICROBIAL MONITORING AND TESTS

Prior to several outbreaks of diseases and death of patients due to medications of some pathogen contaminated drugs in the late 1960's, most non-sterile pharmaceuticals were not required to analyze for microbiological contents. It was in 1973, the incorporation of the "Microbial Limits Tests" in the USP signified the beginning of wider scale of microbial tests.⁽¹⁹⁾

Microbiological monitoring may include enumeration and identification of colonies found during the Total Aerobic Plate Count test. The reports about the contamination of *Ps. cepacia* (currently named as *Burkholderia cepacia*) and its survival in disinfectants led to the addition of requirements in the 21 CFR to ensure that there are no "objectionable organisms" in products released to market instead of merely "absence of *Ps. Aeruginosa* assay".

The importance of identifying all isolates from either or both Total Plates Count testing and enrichment testing depends upon the product and its intended use. Obviously, if an oral solid dosage form such as a tablet is tested, it may be acceptable to identify isolates when testing shows high levels. However, for other products such inhalant aerosol, topical cream and ointment or nasal solutions where there is a major concern for microbiological contamination, isolates from plate counts, as well as enrichment testing, should be identified. Hence, identification of "objectionable organisms" is the responsibility of manufacturers and somehow has become a mandatory exercise even though it is a non-sterile product.

Based on the minimal requirement of water activity for the growth of each organism, one recommended way of dealing with tablets (or other Oral Solid Dosage Forms) that have $A_w < 0.85$, testing for United States Pharmacopeia indicator organisms, e.g. *E. coli*, could be exempted. For example, if a product is at a $A_w < 0.75$, then no microbiological testing of that product have to be done. This must be confirmed for a product based on development and validation activities. Acceptable Total Aerobic Counts for these products should be established in terms of alert and action levels, which could be 1000 cfu/g/mL and 10,000 cfu/g/mL, respectively. A Total Aerobic Count that is $>20,000$ cfu/g/mL would be unacceptable. For tablet type products intended for use by known immune-compromised patients, as a safety factor the alert and action levels should be reduced by one or two log.

Another approach is that of the Australian Therapeutic Association that has introduced microbial limit tests in non-sterile pharmaceuticals and even raw materials to safe guard product quality. The tests designed should be able to distinguish absence of objectionable microbes and absence of specified microbes. These standards are set out in Table 2.

CONCLUSION

It is important to remember that it is important to maintain good manufacturing practice to ensure microbes are kept under control as we have seen recently in Hong Kong.

Author's background

O'TOOLE, DK is an Australian. He holds a BSc and MSc degrees some forty years ago in food microbiology. He was awarded a PhD degree from Queensland in the 1990's. Coming up through the microbiology laboratory, Dr O'Toole has served many times in court as expert witness in food microbiology and currently is the Honourary Staff of CityU. Dr CHEUNG Hon-Yeung is a pharmacist and had several years of experiences in the manufacturing of sterile products before pursuing his PhD degree in Pharmaceutical Microbiology and subsequently post-doctoral training in Molecular Biology and Biotechnology in NIH. He is currently the Associate Professor of Pharmaceutical Microbiology and Biotechnology. He is also the Director of GMP Information Centre in City University of Hong Kong. For further information about this article contact Dr Cheung via his email: bhonyun@cityu.edu.hk

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Table 2. Guidelines for assessing the results of microbiological tests on non-sterile OTC medicines.

Category	Type of preparation	Suggested limit
Products for topical application (including those for use in body cavities)		
1a	For use on broken* and unbroken skin (other than antiseptics and corticosteroids)	TAMC** not more than 10 ² per mL or per g, amongst which there should be: <ul style="list-style-type: none"> • no pseudomonads • no Staph aureus
1b	Antiseptics, corticosteroids	TAMC** not more than 10 per mL or per g, amongst which there should be: <ul style="list-style-type: none"> • no pseudomonads • no Staph aureus
Products for oral use		
2a	Products other than those containing raw materials of vegetable or animal origin	TAMC** not more than 10 ³ per mL or per g, amongst which there should be: <ul style="list-style-type: none"> • not more than 10² yeast and mould in 1 mL or 1 g • not more than 10² enterobacteria in 1 mL or 1 g, with • no <i>E. coli</i> in 1 mL or 1 g • no salmonellae in 10 mL or 10 g
2b	Products containing raw materials of vegetable or animal origin	TAMC** not more than 10 ⁴ per mL or per g, amongst which there should be: <ul style="list-style-type: none"> • not more than 10² yeast and mould in 1 mL or 1 g • not more than 10² enterobacteria in 1 mL or 1 g, with • no <i>E. coli</i> in 1 mL or 1 g • no salmonellae in 10 mL or 10 g
* broken skin - refers to minor cuts and abrasions; products intended for use on large open wounds or severely damaged skin should be sterile.		
** Total aerobic microbial count		
From Therapeutic Goods Association, Australian regulatory guidelines for OTC medicines (ARGOM) 1 July 2003		

Use of *Herba Lobellae Chinensis* (半邊蓮) is Attributed to the Bronchodilation and Diuretic Effects of Lobeline and its Derivatives

ZHANG, Zhongrong; CHEUNG, Hon-Yeung*

Research Group for Bioactive Products, Department of Biology & Chemistry, City University of Hong Kong SAR, China

Botanical Name: *Lobelia chinensis* Loureiro

Plant Family: Campanulaceae

Pharmacopoeia Name: *Herba Lobellae Chinensis*

Part Used: Dried leaves and stems or whole plant

Other Names: Banbianlian, 半邊蓮; Chinese Lobelia; Lobelia; Hanpenren

ABSTRACT

Lobelia is a fall wildflower commonly growing in China. It reduces swelling and has good anti-inflammatory effects. The herb is used by the Chinese for cooling the blood in what they called fire toxin, such as tonsillitis and for asthma treatment and reducing the toxicity of insect stings and snakebites. It has significant and prolonged diuretic effect. Modern TCM practitioners use lobelia for the treatment of ascites in the later stages of schistosomiasis, a parasitic disease. Lobeline is one of the main alkaloids present in the herb. It has both temperature-dependent and-independent neuroprotective effects against methamphetamine toxicity.

Key Words: *Herba Lobellae*; Lobeline; Anti-inflammatory; Neuroprotective; Detoxification; Diuretics

DESCRIPTION AND IDENTIFICATION

There are about 380 species recognized in the genus *Lobelia* L., of which more than 20 species are spread throughout China.⁽³⁾ Some of the species share similar components and pharmacological effects, while others do not. Thus HLC plants are not easy to distinguish from some other *Lobelia*. Additionally, a few misusages of the medicine are caused by the similarity of the drug names. As an example, HLC (Banbianlian in Chinese) is sometimes confused with *Herba Scutellariae Barbatae* (Banzhilian in Chinese) in therapeutic treatment, regardless of their distinct effective components and medicinal properties.⁽⁴⁾ Currently, the identification of HLC is primarily based on observation of the macroscopic appearance, microscopic features and chemical tests.

Macroscopic appearance of dried herb

The crude drug of HLC is always coiled into a ball due to desiccation (Figure 2). The roots are tiny with a diameter from 1 to 2 mm; the root surface is light brown, smooth or vertical-grained. The slender branching stems are hairless, about 20 cm in length and grayish green in color. Plenty of nodes are apparent on the stem, from which leaves or branches grow in alternative arrangement. The leaves are wrinkled and are olive-brown in color. After wetting with water and expansion, it can be observed that the leaves are mainly narrow-lanceolate and a few are narrow-ovate in shape, 1 to 2 cm long and 0.2 to 0.5 cm wide, and there are shallow and sparsely distributed teeth around the leaf edge. Small solitary axillary flowers can usually be found, with the characteristics of slender pedunculate, grayish green sepal, and pale-purple corolla which is 5 to 7 mm long. The flowers are tubular

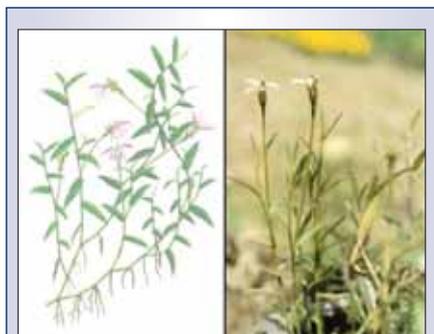


Figure 1: Illustration of whole plant of *Herba Lobellae Chinensis* (left), and photo of the over ground part.



Contraindications

Use with caution in pregnancy, nursing or in administration to children. Qi deficient should also avoid treatment with this herb.

Undesirable Effects

Adverse effects rarely occur; occasionally produces nausea, vomiting, sweating, headache, abdominal pain, diarrhea and elevation of blood pressure. Overdose of lobelia may generate rapid but feeble pulse, coma and even death.

Interaction with Conventional Drugs

No obvious adverse event in combination with other herbs. Combine use of lobelia and ethanol, however, increases genotoxicity in cells exposed to mutagenic agents. Lobeline is a partial nicotinic agonist.

INTRODUCTION

Herba Lobellae Chinensis (HLC) is a plant used in traditional Chinese medicine (TCM), which is called Banbianlian in Chinese. The medicine is prepared from the whole plant with roots of *Lobelia chinensis* Lour., family Campanulaceae, as shown in Figure 1. The plant is distributed throughout China but more commonly in the reaches of the Yangtze River and the south provinces of China, mainly in Jiangsu, Zhejiang and Anhui; it can also be found in Korea and Japan.⁽¹⁾ The medicinal material is collected in summer, washed to eliminate the mud and sand, dried in the sun or in shade.⁽²⁾ HLC is commonly used as a clinical Chinese medicine either in the form of a crude drug or as processed products. Obvious medicinal properties of this herb has been documented.



Figure 2: Photo of *Herba Lobellae Chinensis* crude drug (Scale bar = 1cm).

shaped at the corolla base and separate to five lanceolate lobes (leaning to one side) at the upper part. White-colored hairs appear inside the flowers.^(2,5)

Microscopic identification of dried herb

1) Transverse section of stem

In the cross section of the stem, one layer of epidermis cells are packed compactly outermost, the cortex inside is composed of 9 to 11 layers of parenchyma cells, containing a small quantity of calcium oxalate crystal clusters; tubular conductive vessels of xylem show a radial arrangement; marrow is present in the center.⁽⁵⁾

2) Leaf Surface and transverse section

Both upper and lower epidermises of the leaf consist of one layer of subrectangular cells which are covered with cuticle. Beneath the upper epidermis, one layer of rectangular cells (palisade tissue) and 3 to 5 layers of subround parenchyma cells (sponge tissue) can be observed. The main vein in collateral arrangement passes through the palisade tissue. Collenchyma is present in both lower epidermis and vascular bundles.⁽²⁾

Upper epidermal cells are irregular and the anticlinal walls of each cell are wavy. The stomata are irregularly distributed, surrounded by 3 to 7 subsidiary cells. Lower epidermal cells are polygonal and have thickened cell walls. The lower epidermal stomata are also distributed irregularly.^(2, 5)

3) Powder

HLC powder of stem and leaf is grayish green yellow or light brownish yellow in appearance. Both reticulate vessel and spiral vessel can be found

inside the powder.⁽²⁾ Adhering on the slender vessels of the corolla usually are butterfly shaped crystals.

Chemical tests

To carry out the identification test, an extract of a certain quantity of the crude drug (usually 1 g) should be prepared according to the standard procedures in the Pharmacopoeia of the People's Republic of China.⁽²⁾ One of the most popular and rapid methods is based on the thin layer chromatography technique, through comparison of the sample spectrum obtained to that of the standard medicinal extract. The tested crude drug can be distinguished as HLC according to the position and color of the spots shown in the spectrum.⁽²⁾

Based on effective components contained in HLC, some chemical identification tests can be applied by examination of certain commercial compounds. For instance, the bismuth potassium iodide test: a orange yellow precipitate should appear in the HLC extract droplet after addition of bismuth potassium iodide solution; the mercuric potassium iodide test: a white precipitate should appear in the extract droplet after addition of mercuric potassium iodide solution; the silicotungstic acid test: a yellowish white precipitate should appear in the extract droplet after addition of 10% silicotungstic acid solution.⁽⁵⁾

Currently, more advanced methods are being investigated for identification of HLC. Zhou *et al.* have established the chromatographic fingerprints of HLC by RP-HPLC aiming to enhance the identification of HLC and quality control during HLC production; and they have suggested that the fingerprint established by RP-HPLC was stable and replicable based on their results and promoted its suitability for HLC production control.⁽⁶⁾

BIOACTIVE COMPOUNDS

Analyses of chemical compounds in HLC have been carried out continually during the passed half century with the development of chemical separation techniques. It has been proved that the primary constituents are alkaloids, polyacetylenes, flavonoid glycosides, saponins, amino acids and polysaccharides; new components keep being isolated and identified from HLC and its material plant *Lobelia chinensis* Lour. (LC).⁽⁷⁻⁹⁾

Alkaloids

The alkaloids present in HLC/LC are mainly piperidine derivatives. Until the 1970s, various kinds of alkaloids, including lobeline, lobelanine, lobelanidine and isolobelanine representatively, had been isolated and identified.^(7,10) The structures of these four alkaloids are similar as shown in Figure 3. At present, investigations of alkaloids in *Herba Lobellae* are still in progress. Radicamines A and B are two newly isolated pyrrolidine alkaloids present in this herb.⁽¹⁾

Polyacetylenes

Isolation of polyacetylene compounds was the most impressive result in studies of the genus *Lobelia* in the 1990's, as polyacetylene compounds suggested an ability to kill some cancer cells. In 1991, Ishimaru *et al.* found two new polyacetylenes: lobetyolin and lobetyol, that were not the expected alkaloid lobeline, from the hairy root culture of *Lobelia inflata* L; both of the two compounds had a conjugated diyne structure (Figure 4).⁽¹¹⁾ Subsequently, one more polyacetylene compound, lobetyolinin, was isolated from *Lobelia inflata* hairy root culture by this research group in 1992.⁽¹²⁾ Lobetyolinin had a β -(1 \rightarrow 6) diglucose in its molecular

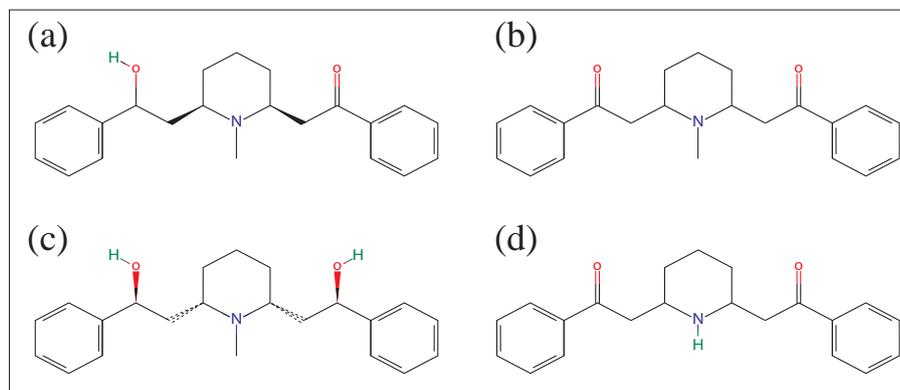


Figure 3. Chemical structures of the main alkaloids found in *Herba Lobellae Chinensis*. (a) Lobeline; (b) Lobelanine; (c) Lobelanidine; (d) Isolobelanine.

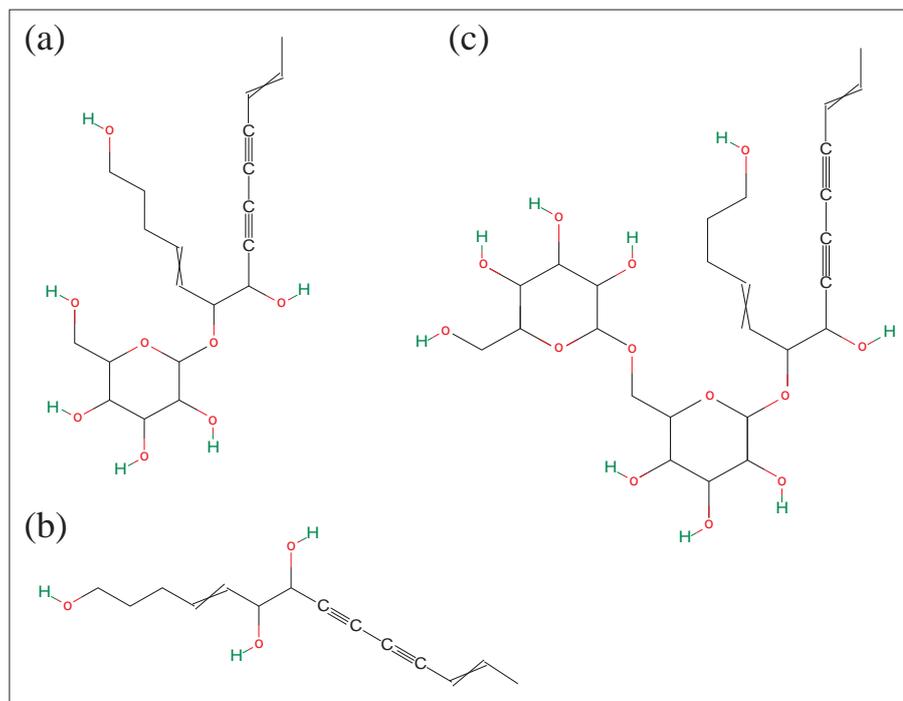


Figure 4. Chemical structures of the polyacetylene compounds isolated from *Herba Lobellae Chinensis*: (a) Lobetyolin; (b) Lobetyol; (c) Lobetyolinin.

structure (Figure 4). After that, these polyacetylene compounds were also successfully isolated from hairy root culture of LC by Tada *et al.* in 1995.⁽¹³⁾ Recently, Qiao *et al.* determined lobetyolin and lobetyolinin in the crude drug HLC by means of HPLC; and suggested an applicable method based on the HPLC technique for determination of polyacetylenes in HLC.⁽¹⁴⁾

Others constituents

Flavonoid glycosides are the main components in LC.⁽⁷⁾ According to the accessible literature, apigenin 7-O-rutinoside, luteolin diosmin, and linarin have been isolated and identified from other Campanulaceae plants through standard techniques.^(15,16) HLC is generally believed to share similar groups of main components with others in the closely related group, but there are far more unclear flavonoid compounds that are not well understood; there is still need of more systematic analyses concerning flavonoids components in HLC/LC.

Thanks to benefits from advances in mixture separation methods and spectrum technology, lots of saponins in species from the genus *Lobelia* have been isolated and identified, such as caffeoylferulyl β -coumaryl delphinidin-3-rutinoside-5, 3', 5'-triglucoside, an anthocyanin that is unstable in the neutral aqueous environment;⁽¹⁷⁾ Lobelinin A and

Lobelinin B, two novel anthocyanins stable in aqueous solution;⁽¹⁸⁾ and two new glucosides, (-)- epiafzelechin-7-O- β -D-glucopyranoside and protocathechuic acid 3-O- β -D-glucopyranoside.⁽¹⁹⁾

Beside the amino acids and polysaccharides commonly present in plants, *p*-hydroxybenzoic acid, fumaric acid and succinic acid have also been isolated from HLC.⁽⁷⁾ Inulins are common polysaccharides found in HLC;^(7,20,21) the rhizome of LC contains plenty of lobenin.^(7,22)

PHARMACOLOGICAL EFFECTS

The medicinal properties of LC were first recorded in *Dian nan ben cao* (滇南本草),⁽⁷⁾ records of this Chinese herb also occurred in other ancient books of TCM, including *The Compendium of Material Medica* (本草綱目). From the ancient times it has been well used alone or in combination with other medical herbs by Chinese people for clearing heat, detoxification, diuresis and the relief of swelling.⁽⁷⁾

Diuretic effect

The alkaloid contained in HLC has been proved to have a diuretic effect in the animal experiments and during clinical observations. Anesthetized dogs, after injection of 0.1 g/kg HLC infusion or 6.6 mg/kg HLC alkaloid extract, and

the normal rat, after taking 1 g/kg HLC infusion, both showed a remarkable and enduring diuretic effect, and the chloride contained in the urine increased considerably.⁽⁷⁾

Detoxification effect

The detoxification effect of HLC has been well known as recorded in ancient books, and has been strongly corroborated by large numbers of clinic examples.^(23,24) Because of both detoxification and diuretic effects of HLC, it provides a great help to eliminate toxins from the human body, so it is commonly used in the clinical treatment of advanced schistosomiasis patients with ascites, ascites due to cirrhosis, snake-bite poisoning, poisoned sores and so on.^(3,7) HLC is most famous in treating snake-bite poisoning, in animal experiments, the HLC apotem and sodium salts of succinic acid fumaric acid, hydroxybenzoic acid extracted from it, showed relatively high protection (59.1 to 93.1%) to mice after injection with a minimum lethal dose of cobra-venom.^(7,25)

Effect as central stimulant

Some of the alkaloids in HLC, such as lobeline, are generally believed to be able to act as central stimulants.^(3,7) The mechanism was suggested to be similar to that of nicotine, for they could excite the chemical sensors of the carotid arteries, the vomiting center, the vagal center of the medulla oblongata, the respiration center, etc.⁽³⁾ As a stimulant for the respiration system, HLC are generally used in therapy for respiratory failure, asphyxia neonatorum and other respiratory diseases. Clinical research has showed it is especially helpful in dealing with respiratory diseases of infant patients.^(26,27,28)

Influences on cardiovascular system

Atherosclerosis is a chronic inflammatory response in the walls of arteries characterized by the formation of multiple plaques within the arteries. The developmental process of atheromatous plaques (atherogenesis) is a process of remodeling of the arteries involving the concomitant accumulation of fatty substances. Ross *et al.* first introduced the response-to-injury hypothesis to explain the causes of atherosclerosis. They suggested that atherogenesis arose as a result of some form of "injury" to the arterial endothelium, followed by the smooth muscle cells (SMC) of the tunica media migrating and proliferating

to intima responding to signal from damaged endothelial cells.⁽²⁹⁾

Endothelin is a 21-amino acid polypeptide first extracted from the aortic endothelial cells of porcine by Yanagisawa *et al.* in 1988.⁽³⁰⁾ It has been reported to be one of the strongest vasoconstricting peptides known, and to exhibit mitogenic activity for a number of cell types, including vascular smooth muscle cells (VSMC).⁽³¹⁾ There are three isoforms (endothelin-1, -2, -3) with varying regions of expression, among the three, endothelin-1 has been investigated the most with regard to its functional mechanism. In the earlier 1990s, Zamora *et al.* concluded endothelin participates in the whole process of atherogenesis,⁽³²⁾ and later on it was proved to be associated with a lot of other cardiovascular disorders, such as essential hypertension, heart failure, pulmonary hypertension, and coronary artery disease.⁽³³⁾ Based on the latest reviews on endothelin, endothelin (ET) has been reported to be implicated in various vascular diseases of several organ systems, including the heart, general circulation and brain.^(34, 35)

As long as some cardiovascular diseases are actually inflammations in the cardiovascular system, it is not unreasonable to suppose that a TCM with the function of subduing inflammation may be able to relieve these diseases, e.g. atherosclerosis, so HLC has become a promising reach direction for those working on TCM.

In 1993, Zhang *et al.* found for the first time that the HLC content in an anti-snake venom herb medicine could transiently relax an isolated ET-contracted rat aortic ring. HLC together with *Paris polyphylla Smith* (PPS) inhibited vascular contraction and blood pressure elevation induced by ET-1 and extended the survival time on tested mice while partly antagonizing the lethal effect of ET-1.⁽³⁶⁾ This research group carried out further studies in 1995 to evaluate the anti-ET effect of HLC and PPS and compared them to ET antiserum, phosphoramidon, and ETA antagonists (BQ123 & JKC301) and found that the aqueous extracts of HLC and PPS could work against the vasoconstricting and blood pressure increasing effects of ET. Further, the tested mice injected with ET were found to survive longer and with a much lower death rate after HLC or PPS treatment.⁽³⁷⁾

Wang *et al.* used LC and other anti-snake venom Chinese herbs to test the antagonizing effect on ET-1 and sarafotoxin 6b (S6b) to mice in 1997. Oral administration showed that both the water and alcohol extracts from LC were helpful in reducing the acute death of mice caused by ET-1 and S6b ($p < 0.05$); and the potencies of alcohol extracts from all these Chinese herbs were greater than water extracts from them.⁽³⁸⁾ An oral compound of the Chinese medicine, *Bi Tong Tang*, for primary hypertension patients invented by therapists Hu *et al.* was found to have a marked effect on plasma ET reduction.⁽³⁹⁾

In 1999, Du *et al.* applied the immunohistochemical technique in *en face* preparation of arterial endothelium, in order to quantitatively analyze the relationship between synthesis and release of ET and endothelium injury caused by hyperlipidemia; and to investigate whether the anti-snake venom compound TCM, containing HLC, PPS and several other TCMS, could offer protection to vessel endothelium in hyperlipidemia mice. It was found that plasma ET increased significantly the positive rate of IgG- and ET-positive cells, indicative of epithelial injury, and were both much higher in hyperlipidemia mice group compared to the normal group, which indicated hyperlipidemia could cause damage of endothelium and leap of synthesized and released ET. On the other hand, the plasma ET and the positive rate of IgG- and ET-positive cells in the tested group all decreased significantly after being treated with the compound Chinese medicine, indicating that HLC and other anti-snake venom TCMS could protect endothelium by directly abating the synthesis and release of ET without serum lipid reduction.⁽⁴⁰⁾

With the aim of assessing the arterial endothelium protection of different effective elements from HLC, Li *et al.* determined the blood total cholesterol (TC), triglycerides (TG), ET-1, endothelial nitric oxide synthase (eNOS) and the positive rate of ET in *en face* preparations of arterial endothelium of the Wistar rats, fed with high cholesterol diet, after 60 days' treatment of the A001 element and the B001 element from HLC respectively. It was found that concentration of TC and TG did not show marked change in the tested hyperlipidemic rats compared to those of the control rats. Morphological injury of the arterial endothelium eased, the blood ET-1 and positive rate of ET in arterial

endothelium decreased significantly ($P < 0.05$) and the blood eNOS increased ($P < 0.05$) for rats treated with B001, while the rats treated with A001 did not show any comparable change. Hence, Li *et al.* suggested that B001 was the effective element of HLC which was able to protect the arterial endothelium and arrest the development of atherosclerosis.⁽⁴¹⁾ In 2003, the same research group carried out a further investigation of the active pharmaceutical ingredient of HLC in atherosclerosis therapy. The two integrates, A001 and B001, were applied to hyperlipidemic rats by lavage for a 60-day period to observe their effects on the ET-1 of arterial endothelial cells, the metabolism of eNOS, the positive rate of ET-1, aortic media SMC proliferation and the thickness of aortic media. After 60 days treatment with B001, the plasma ET-1 concentration, the positive rate of ET-1 in arterial endothelium and media SMC, and the thickness of aorta media was reduced significantly ($P < 0.05$), the blood eNOS showed a significant rise ($P < 0.05$) in the tested hyperlipidemia rats group compared with the control group; and morphological injury of the arterial endothelium was also alleviated, apparently based on microscopic observations. On the other hand, no considerable changes could be found in hyperlipidemia rats of the A001 group. The results indicated the B001 component was the active principle in HLC because it was helpful in protecting the arterial endothelium and arresting the proliferation of VSMC, which corresponded with their previous study.⁽⁴²⁾

In 2005, Chen *et al.* carried out a contrast study of total saponin in *Paris chinensis Franch* (PCF) and alkaloids extracted from LC looking at their effect on synthesis of ET and eNOS. The positive rate of ET on *en face* preparation of arterial endothelium, concentration of ET in plasma and concentration of eNOS in plasma were measured in hyperlipidemic rats fed on PCF total saponin and alkaloid from LC for 60 days. The results indicated that both PCF total saponin and LC alkaloids could suppress the synthesis and release of ET; LC alkaloids could also promote the synthesis and release of eNOS while PCR total saponin could not. Therefore it was suggested by Chen *et al.* that LC alkaloid had a better curative effect on atherosclerosis than PCF saponin.⁽⁴³⁾

In the same year, Fan *et al.* observed the injury effect of ET on human vascular endothelial cells and studied the inhibitory role of LC alkaloids on this

effect. The concentrations of tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1), indicators of fibrinolysis, in supernatants of human vascular endothelial cell (HVEC) culture were assayed using the enzyme linked immunosorbent assay technique. It came out that the concentrations of PAI-1 were higher in the ET groups than in the control group ($P < 0.01$). The PAI-1 concentration in the tested group treated with alkaloids extracted from HLC were significantly lower than the HVEC culture of the ET group ($P < 0.01$). The concentration of tPA in the LC alkaloids group were reported slightly higher than that of ET group, but it was not high enough to make a statistical difference. So Fan *et al.* concluded that the effects of LC alkaloids were similar to those of the ET B receptor antagonist, BQ788; they can offer protection to HVECs against the influence of ET. ⁽⁴⁴⁾

Effects of LC alkaloids on the proliferation of cultured vascular SMC induced by ET-1 were investigated by Wang *et al.* in 2006 by a comparison study. Human umbilical artery vascular SMC were cultured and divided into five groups: ET group, ET + alkaloid group, ET + BQ123 group, ET + BQ123 group, ET + staurosporine (ST) group and a control group. The cell proliferation activity was subsequently quantified using the cell counting kit-8 (CCK-8) and $[^3\text{H}]\text{-TdR}$ incorporation, and the toxicity of LC alkaloids to vascular SMC was assessed by means of trypan blue exclusion method and lactate dehydrogenase (LDH) method. The results were that LC alkaloid (100, 200 and 400 mg/L), BQ123 (10-6mol/L), ST (10-7mol/L) could all suppress the ET-1 induced vascular SMC proliferation significantly ($P < 0.05$); the $[\text{Ca}^{2+}]$ fluorescent intensity in cells decreased; the suppression effect of LC alkaloids was directly related to the dose of alkaloids applied; and LC alkaloids did not show any influence on the probability of vascular SMC survival. This revealed that LC alkaloids could suppress the ET-1 induced vascular SMC proliferation dose-dependently, the effect was not due to nonspecific cytotoxicity, and the mechanism might be related to reducing Ca^{2+} concentration in the cell. ^(45,46) In 2007, they focused on one main active ingredient in LC, alkaloid lobeline, and investigated the effect on ET-1 and the proliferation of vascular SMC in hyperlipidemic rats. The results showed that the increased cell numbers and enhanced $[^3\text{H}]$ thymidine incorporation induced by ET-1 were inhibited and the

transition of cells from static phase (G0/G1) to DNA synthesis (S) and mitotic phase (G2/M) was held back by lobeline in a concentration-dependent manner. Confocal microscopy demonstrated that lobeline markedly decreased the fluorescent intensity of intracellular $[\text{Ca}^{2+}]$ with a significant difference from ET group. Therefore, they concluded that lobeline could inhibit the proliferation of human umbilical vascular SMC induced by ET-1 in a dose-dependent manner, which is a novel biological effect of this alkaloid, and the anti-proliferative effect was involved in the reduction of increased $[\text{Ca}^{2+}]$, rather than nonspecific cytotoxicity. ⁽⁴⁷⁾

Recently, Zhang *et al.* studied the effect of LC alkaloids on ET-1 expression based on examining both ET-1 protein product and its mRNA. Compared with the sham operation group, the positive rate of ET-1 mRNA in peripheral blood leucocytes ($34.64\% \pm 8.39\%$ vs. $9.34\% \pm 4.47\%$, $P < 0.05$), the positive rate of ET in arterial endothelium ($7.42\% \pm 0.24\%$ vs. $1.58\% \pm 0.24\%$, $P < 0.05$) and the plasma concentration of ET (221 ± 24 ng/L vs. 138 ± 19 ng/L, $P < 0.05$) were increased significantly in hypertensive rats. After being treated with LC alkaloids for 8 weeks, compared with the hypertensive group, ET-1 mRNA expression ($20.38\% \pm 11.31\%$ vs. $34.64\% \pm 8.39\%$, $P < 0.05$), ET synthesis ($3.53\% \pm 0.21\%$ vs. $7.42\% \pm 0.24\%$, $P < 0.05$) and ET release (191 ± 21 ng/L vs. 221 ± 24 ng/L, $P < 0.05$) were significantly inhibited in the tested group. Consequently, they suggested that LC alkaloids could inhibit the expression of ET at the transcriptional and translational level which may be effective in the prevention and treatment of the renal hypertension. ⁽⁴⁸⁾ Afterwards, Zhang *et al.* further investigated the effect of LC alkaloids on vascular remodeling in renal hypertension. The rennin activity in plasma (PRA) was determined by radioimmunoassay after the 8 weeks treatment of hypertensive rats with LC alkaloids or captopril. The parameters of vascular remodeling, including media thickness (MT), luminal internal diameter (LD), ratio of MT/LD and ratio of media cross-sectional area to lumen area (MSCA/LA) were measured through the Weigert staining photos of the abdominal aorta of the treated and control groups of hypertensive rats; and expressions of collagen and collagen I were measured by the methods of Masson staining and immunohistochemistry respectively. They reported that the PRA was much higher in hypertensive rats compared to the sham

rats ($P < 0.05$), the PRA was significantly reduced in LC alkaloids group, while no inhibitory effect on PRA was observed in captopril group compared to control group. The MT, the ratio of MT/LD, MSCA and the collagen expression of abdominal aorta in hypertensive rats were all markedly higher than those in sham rats ($P < 0.05$). LC alkaloids and captopril could significantly reduce these raised parameters in hypertensive rats ($P < 0.05$). Based on the results, they suggested that the vascular remodeling would occur in renal hypertensive rats; LC alkaloids could inhibit the synthesis of the collagen and could reduce PRA, which alleviated the vascular remodeling in renal hypertensive rats like captopril but with different mechanism. ⁽⁴⁹⁾

Anticancer property

HLC are generally thought to be an anticancer TMC and commonly used in the clinical therapy of malignant tumors such as liver cancer, stomach cancer, intestinal cancer, and mammary cancer. ⁽⁷⁾ However, research on the mechanism of the anticancer properties of HLC are deficient, hence the actual effective components and detailed mechanism still remain unclear.

In 2002, Gao *et al.* studied the influence of HLC on the cytoplasmic free Ca^{2+} density of Hela cells and discussed its mechanism in relation to the anticancer properties. The changes of free Ca^{2+} concentration were tested based on the fluorescent intensity which was characterized by fluorochrome Fura 2 combined with free Ca^{2+} under the stimulation of a certain wavelength of light. The results showed that HLC had no obviously inhibitive effects on Hela cell proliferation, however it was able to stimulate outflow of the stored cytoplasmic calcium and extracellular Ca^{2+} inflow, and to raise the density of cytoplasmic free Ca^{2+} . ⁽⁵⁰⁾

Gao *et al.* supposed that HLC extract could induce apoptosis in hepatoma cells related to the calcium pathway. Thus they measured the level of cytoplasmic free Ca^{2+} by fluorescent colorimetry and detected cell apoptosis by AO-EB double fluorescent staining, flow cytometry and DNA electrophoresis. The results showed that HLC could significantly increase the level of cytoplasmic free Ca^{2+} in HepG2 cells ($P < 0.01$), and HepG2 cells showed typically apoptotic characteristics, which indicated that HLC could cause HepG2 apoptosis and that an increasing level

of cytoplasmatic free Ca^{2+} should be the main mechanism. ⁽⁵¹⁾

Recently, Su *et al.* tested the inhibitory effect of rough alkaloids which were extracted from LC with standard methods on the growth of stomach cancer cells, and found that the extracted alkaloids could inhibit the proliferation of stomach cancer cell BG-380. The inhibition was aggravated with a rise in the alkaloid concentration applied. When 300 mg/L of alkaloids was applied to the BG-38 cell culture for 48 hours, the inhibitory rate climbed to the highest, 85.6%. Also, the inhibitory rate was found to increase with the period of alkaloid treatment at first, and then reached the peak at 16 hours (90.3%), and decreased markedly after further treatment. ⁽⁵²⁾

Other effects

Oral ingestion of HLC apozem may gently stimulate evacuation of the bowels. ⁽⁷⁾ A small quantity of lobeline extracted from HLC or plant LC was proved to be able to stimulate and subsequently inhibit the muscle's tension and peristalsis of isolated rabbit intestine while a large quantity would lead to intestinal paralysis. ⁽²²⁾

In *in vitro* experiments with HLC apozem inhibitory effects on common pathogenic fungi and bacteria such as *Staphylococcus aureus* and *Escherichia coli* experiments were revealed. ^(7,21) Recently, Kuo *et al.* reported the inhibitory effects of LC on herpes simplex virus type 1 (HSV-1) based on a plaque reduction assay. BALB/c mice were injected subcutaneously with HSV-1 (2.5×10^6 PFU/50 μ l), treated orally thrice a day with acyclovir (60 mg/kg/dose) or methanolic extracts from LC (20 and 50 mg/kg/dose) for 7 days, and inspected daily for signs of disease. The animals infected with HSV-1 developed progressive zoster lesions starting at 2 days post infection and the infection appeared most serious at 4–5 days post infection. In contrast to the control mice, treatment with acyclovir or 50 mg/kg/dose LC resulted in a sustained protective effect, as the HSV-1 titers and DNA levels in ground skin samples were markedly reduced by LC, and the 50% inhibitory concentration (IC_{50}) of LC on HSV-1 replication is 139.2 μ g/ml. In addition, no apparent toxic effect on liver and kidney functions could be found after LC treatment. Therefore, they concluded that LC could significantly block HSV-1 replication in HeLa cells without apparent cytotoxicity and was a potent inhibitor of the *in vitro* and *in vivo* replication of HSV-1. ⁽⁵³⁾

CONTRAINDICATION AND UNDESIRABLE EFFECTS

According to TCM theory, the patient who has low energy (Qi deficient) should avoid treatment with HLC. Adverse effects rarely occur when the dosages are under control. Occasionally toxic conditions such as nausea, vomiting, sweating, headache, abdominal pain, diarrhea, and blood pressure elevation may occur. Among the clinical applications, HLC have caused some anaphylaxis of the patients under treatment, ⁽⁵⁴⁻⁵⁶⁾ severe anaphylactic reaction like anaphylactic shock also once happened after HLC injections. ^(57,58)

QUALITY CONTROL OF THE RAW HERB

The quality standard system of raw herb of HLC is based on the Pharmacopoeia of China published in 2005. Water content and water-soluble extracts of this herb should be determined through the first edematous amanorrhoea determination method in Appendix IX H and water-soluble contract determination method in Appendix X A, respectively. The edematous amaenorrhoea in rough drug should not exceed 13.0% and the water-soluble extracts in hot water should not be lower than 35.0%. ⁽²⁾

MODE OF ADMINISTRATION & DOSAGE

The rough drug of HLC is usually administered orally with apozem, and sometimes also with pounded juice. The apozem of pounded juice of fresh drug herb can be applied directly with a higher dose. A compound HLC injection solution is also produced by Chinese medical manufacturers, with other TCM intergrated including *Herba Scutellariae Barbatae* and *Hedyotis Diffusa Willd.* The pound paste and juice of HLC can be directly applied to the skin for external use.

A single daily dose of 9 to 15 g of HLC rough drug as apozem or pounded juice for adults has been suggested by the Pharmacopoeia of China; and 30 to 60 g fresh herb ingestion has been reported to be suitable. ⁽²⁾ The compound HLC injection solution is used one to twice per day, 1 to 2 ml per application. Since the side effect of HLC is rarely reported, duration of use of the herb is not a concern.

Author's background

ZHANG, Zhongrong obtained her BSc degree with first class honour from City University of Hong Kong and currently pursues an MPhil degree in the same institute under the supervision by Dr CHEUNG, Hon-Yeung, who is the Associate Professor of Pharmaceutical Microbiology & Biotechnology. Dr Cheung's email address: bhonyun@cityu.edu.hk

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Lectures on Pharmacy Legislation 2009

The Department of Health and the Pharmaceutical Society of Hong Kong (PSHK) will co-organise a series of five lectures on Pharmacy Legislation of Hong Kong. This will be a good learning opportunity for anyone who is interested in gaining knowledge and latest updates in this aspect and for the candidates who will be sitting the Hong Kong Pharmacist Registration Examination on Pharmacy Legislation.

Venue: PSHK Headquarters
1303 Rightful Centre,
12 Tak Hing Street,
Jordan, Kowloon.

Time: 6:30 pm – 8:30 pm

Date	Topic	Lecturer
24.4.2009 (Friday)	Classification of Poisons Labelling of Poisons and Pharmaceutical Products	Lot CHAN LAM Chi-hang
8.5.2009 (Friday)	Control of Antibiotics Wholesale & Retail Sale of Poisons Undesirable Medical Advertisements	Aster CHAN Kevin LO
15.5.2009 (Friday)	Registration of Pharmaceutical Products Manufacture of Pharmaceutical Products	Henry LAU Vincent CHIANG
22.5.2009 (Friday)	Licensing of Authorised Sellers of Poisons and Listed Sellers of Poisons Import/Export Control of Pharmaceutical Products and Dangerous Drugs	CHEUNG Yee-kay Brenda LAM
29.5.2009 (Friday)	Classification and Sale of Dangerous Drugs Questions and Answers	Clive CHAN

All PSHK members and non-members are welcome to attend the lectures. Each individual lecture is offered at HK\$150 for non-members. PSHK members will enjoy a special privileged deal of HK\$150 for all the 5 lectures. Membership joining and payment for lectures can be made on-site or in advance by mail by completing both the Membership Application Form and the Pharmacy Legislation Lectures 2009 Registration Form.

PSHK Membership Application Form can be downloaded from the "downloads" section of the web site: <http://www.pshk.hk/>

Membership Fee:

Entrance Fee: HK\$200 (for all membership except CUHK student chapter membership)

To celebrate the 60th Anniversary of PSHK,

the entrance fee is waived if application is received before 30 June 2009.

Annual Fee:

HK\$200 (for pre-registration membership)
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Lecture Fee:

Member: HK\$150 for 5 lectures
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For payment by cheque, please make cheque payable to "The Pharmaceutical Society of Hong Kong".

Please refer to the following table for fees calculation.

Fees Calculation

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Old Member	All	Paid Up	Paid Up	\$150	\$150
New Member	Voting	Waived	\$400	\$150	\$550
New Member	Pre-Reg	Waived	\$200	\$150	\$350
New Member	Associate	Waived	\$600	\$150	\$750
New Member	CUHK	Waived	\$20	\$150	\$170
Non Member	N/A	N/A	N/A	\$150	\$750

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The Pharmaceutical Society of Hong Kong
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Yau Ma Tei, Kowloon

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Surname _____ First Name _____

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Membership Type (Please circle) Voting Pre-reg Associate CUHK

Lectures Attending (Please circle) L1 L2 L3 L4 L5 All

Payment (Cheque only if by mail. Cheque or Cash if on site)

Cheque : Amount _____ No. _____ Cash : Amount _____



Active Ingredient:
Pegfilgrastim

Presentation:
6mg of Pegfilgrastim in 0.6ml solution for injection.

Pharmacological Properties:
Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance.

Pegfilgrastim increases white blood cell count, this increase is transient and is consistent with the pharmacodynamic effects of pegfilgrastim. Pegfilgrastim and Filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.

Indications:
Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes)

Dosage and Administration:
One 6mg single pre-filled syringe of Neulastim is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic

chemotherapy. Neulastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Neulastim therapy should be initiated and supervised by physicians experienced in oncology and/ or hematology.

Contraindications:
Hypersensitivity to pegfilgrastim, filgrastim, E.coli derived proteins, or to any excipients.

Precautions:
Limited clinical data suggest that the effect on time to recovery of severe neutropenia between pegfilgrastim and filgrastim is comparable in patients with de novo acute myeloid leukemia. The long term effects of Neulastim have not been established with this condition therefore should be used with caution.

The safety and efficacy of Neulastim have not been investigated in patients with myelospastic syndrome, chronic myelogenous leukemia, and in patients with secondary AML, therefore it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukemia from acute myeloid leukemia.

Rare pulmonary adverse effects in particular interstitial pneumonia have been reported after G-CSF administration, patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome.

In such circumstances, Neulastim should be discontinued at the discretion of the physician and the appropriate treatment given.

Very rare cases of splenic rupture in some cases fatal have been reported. Spleen size should be monitored, patients complaining of left upper abdominal and/ or shoulder tip pain should be evaluated for an enlarged spleen or rupture.

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Physicians should exercise caution when considering the use of pegfilgrastim.

Drug Interactions:
Concomitant use of Neulastim with any chemotherapy agent has not been evaluated in patients. In animal models, co-administration with 5-Fluorouracil or other antimetabolites has been shown to potentiate myelosuppression. Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes.

Side Effects:
Bone pain, injection site pain, chest pain (non-cardiac), pain, headache, arthralgia, myalgia, and back, limb musculo-skeletal, and neck pain.

Forensic Classification:
P1S1S3



Active Ingredient:
Rotigotine

Presentation:
Neupro 2mg/24h transdermal patch (10cm² patch contains 4.5mg rotigotine)
Neupro 4mg/24h transdermal patch (20cm² patch contains

9.0mg rotigotine)
Neupro 6mg/24h transdermal patch (30cm² patch contains 13.5mg rotigotine)
Neupro 8mg/24h transdermal patch (40cm² patch contains 18.0mg rotigotine)

Pharmacological Properties:
Rotigotine is a non-ergolinic D3/D2/D1 Dopamine agonist for the treatment of Parkinson's disease. It is believed to elicit its beneficial effect by activation of the D3, D2 and D1 receptors of the caudate-putamen in the brain. Rotigotine alleviates signs and symptoms of idiopathic Parkinson's disease.

Indications:
Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (i.e. without Levodopa) or in combination with Levodopa, i.e. over the course of the disease, through to late stages when the effect of Levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on-off" fluctuations).

Dosage and Administration:
Neupro is applied once daily. The patch should be applied to clean, dry, intact healthy skin on the abdomen, thigh, hip, flank, shoulder or upper arm at approximately the same time every day. The patch remains on the skin for 24 hours and be replaced by a new one at a different site. Reapplication to the same site within 14 days should be avoided. If the patient forgets to apply the patch at the usual time of the day or if the patch becomes detached, another patch should be applied for the remainder of the day. The patch should not be cut into pieces.

Dosing in patients with early stage Parkinson's disease:
A single daily dose should be

initiated at 2mg/24h and then increased in weekly increments of 2mg/24h to an effective dose up to a maximum dose of 8mg/24h. 4mg/24h may be an effective dose in some patients. For most patients an effective dose is reached within 3 to 4 weeks at doses of 6mg/24h or 8mg/24h respectively. The maximum dose is 8mg/24h.

Dosing in patients with advanced stage of Parkinson's disease with fluctuations:

A single daily dose should be initiated at 4mg/24h and then increased in weekly increments of 2mg/24h to an effective dose up to a maximal dose of 16mg/24h. 4mg/24h or 6mg/24h may be effective doses in some patients. For most patients an effective dose is reached within 3 to 7 weeks at doses of 8mg/24h up to a maximum dose of 16mg/24h.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns.

Precautions:

External heat (excessive sunlight, heating pads and other sources of heat such as sauna, hot bath) should not be applied to the area of the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the site of application, consider dose reduction or termination of therapy. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome. Compulsive behaviors and hallucinations have been reported in patients treated with Neupro. Caution should be advised when treating patients with severe hepatic impairment.

Unexpected accumulation of rotigotine levels may also occur at acute worsening of renal function.

Special Precautions for Storage:

The product should be stored between 2 to 8 degrees Celsius to reduce the occurrence of crystallization of the active substance.

Drug Interactions:

Because rotigotine is a dopamine agonist, it is assumed that dopamine antagonist, such as neuroleptics (e.g. phenothiazines, butyrophenones, thioxanthenes) or metoclopramide may diminish the effectiveness of rotigotine and co-administration should be avoided. Because of possible additive effects, caution should be advised when patients are taking sedating medicinal products or other CNS depressants (e.g. benzodiazepines, antipsychotics, antidepressants) or alcohol in combination with rotigotine.

Side Effects:

Nausea, vomiting, somnolence, dizziness, anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhea, dry mouth, dyspepsia, hyperhidrosis, erythema, pruritis, asthenic conditions, peripheral oedema, loss of consciousness or visual disturbance.

Forensic Classification:

P1S1S3



Active Ingredients:

Dasatinib

Presentation:

20mg, 50mg and 70mg white to off-white, bioconvex, film-coated tablets.

Pharmacological Properties:

Dasatinib, at nanomolar

concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2 and PDGFRbeta. Dasatinib is predicted to bind to multiple conformations of ABL kinase. In vitro, it is active in leukemic cell lines representing variants of imatinib sensitive and resistance diseases. It also inhibited growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines over expressing BCR-ABL.

Indications:

Sprycel is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib. The effectiveness of Sprycel is based on hematologic and cytogenetic response rates. It is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with resistance or intolerance to prior therapy.

Dosage and Administration:

The recommended starting dosage of Sprycel for chronic phase CML is 100mg administered orally once daily, either in the morning or in the evening. For accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140mg/day administered orally 70mg twice daily. The tablet should not be crushed or cut, it should be swallowed whole.

Contraindications :

None

Precautions:

Myelosuppression

Treatment with Sprycel is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML. Complete blood counts

should be made weekly for the first 2 weeks, then monthly or as clinically indicated. Myelosuppression is generally reversible and managed by withholding the drug temporarily or by dose reduction.

Bleeding Related Events:

Thrombocytopenia, platelet dysfunction (in vitro), severe CNS hemorrhages, including fatalities, in less than 1%, severe gastrointestinal hemorrhage occurred in 4%, other cases of severe hemorrhage occurred in 2% of patients. Caution should be exercised if patient are required to take medications that inhibit platelet function or anticoagulant.

Fluid Retention:

Severe fluid retention was reported in 8% of patient, including pleural and pericardial effusion in 5% and 1% of patients respectively. Severe ascites and generalized edema were reported in less than 1% of patient. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be investigated.

QT Prolongation:

Sprycel should be administered with caution in patients who have or may develop prolongation of QTc, or patients with hypokalemia or hypomagnesemia, with congenital long QT syndrome, taking anti-arrhythmic medicines or drugs that can prolong QT interval.

Pregnancy:

May cause fetal harm when administered to pregnant women.

Side Effects:

Bleeding, low blood cell counts, swelling, weight gain, shortness of breath, nausea, vomiting, diarrhea, headache, musculoskeletal pain, fatigue and skin rash.

Forensic Classification:

P1S1S3

Hong Kong Pharmaceutical Journal: Detail Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of Hong Kong Pharmaceutical Society. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: **Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drug & Therapeutics; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology and New Products.** It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

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INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

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- (1) Cabello-Hurtado F, Durst F, Jorin JV, Werck-Reichhart D. et al. (1998). Coumarins in *Helianthus tuberosus*: characterization, induced accumulation and biosynthesis. *Biochemistry*, 49(1):1029-1036.

- (2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids*. 2nd Ed, pp. 79-105. Springer Verlag, New York.
- (3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn O, (Eds.), *Comprehensive Natural Products Chemistry*, Vol. 8. pp. 137-196. Pergamon, Oxford.

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Abbreviations

About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μM , mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS
Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^1H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μm , mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[\text{M}]^+$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M,
Nuclear magnetic resonance: ^1H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation sec^{-1})
Repetitive manipulations: once, twice, x3, x4, etc.
 RR_i (relative retention time), R_1 (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H₂O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: l, (litre), μl , ml
Weight: wt, pg, ng, μg , mg, g, kg

Inorganics, e.g. AlCl_3 (aluminum chloride), BF_3 (boron trifluoride), Cl., CO_3 , H_2 , HCl , HClO_4 (perchloric acid), HNO_3 , H_2O , H_2O_2 , H_2SO_4 , H_3BO_3 (boric acid), He, KHCO_3 (potassium bicarbonate), KMnO_4 (potassium permanganate;), KOH, K-Pi buffer (potassium phosphate buffer), LiAlH_4 (lithium aluminium hydride), Mg^{2+} , MgCl_2 , N_2 , NH_3 , $(\text{NH}_4)_2\text{SO}_4$, Na^+ , NaBH_4 (sodium borohydride), NaCl, NaI_0_4 (sodium

periodate), NaOH, Na_2SO_3 (sodium sulphite), Na_2SO_4 (sodium sulphate), $\text{Na}_2\text{S}_2\text{O}_3$ (sodium thiosulphate), O_3 , PPI (inorganic phosphate), SO_4^{2-} , Tris (buffer).

Organics, e.g. Ac_2O (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), CHCl_3 (chloroform), CH_2N_2 (diazomethane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetraacetic acid), Et₂O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), HCO_2H (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran). ^1H NMR solvents and standards: CDCl_3 (deutero-chloroform), D_2O , $\text{DMSO}-d_6$ [deuterodimethylsulphoxide not $(\text{CD}_3)_2\text{SO}$], pyridine- d_5 (deuteropyridine), TMS (tetramethylsilane).

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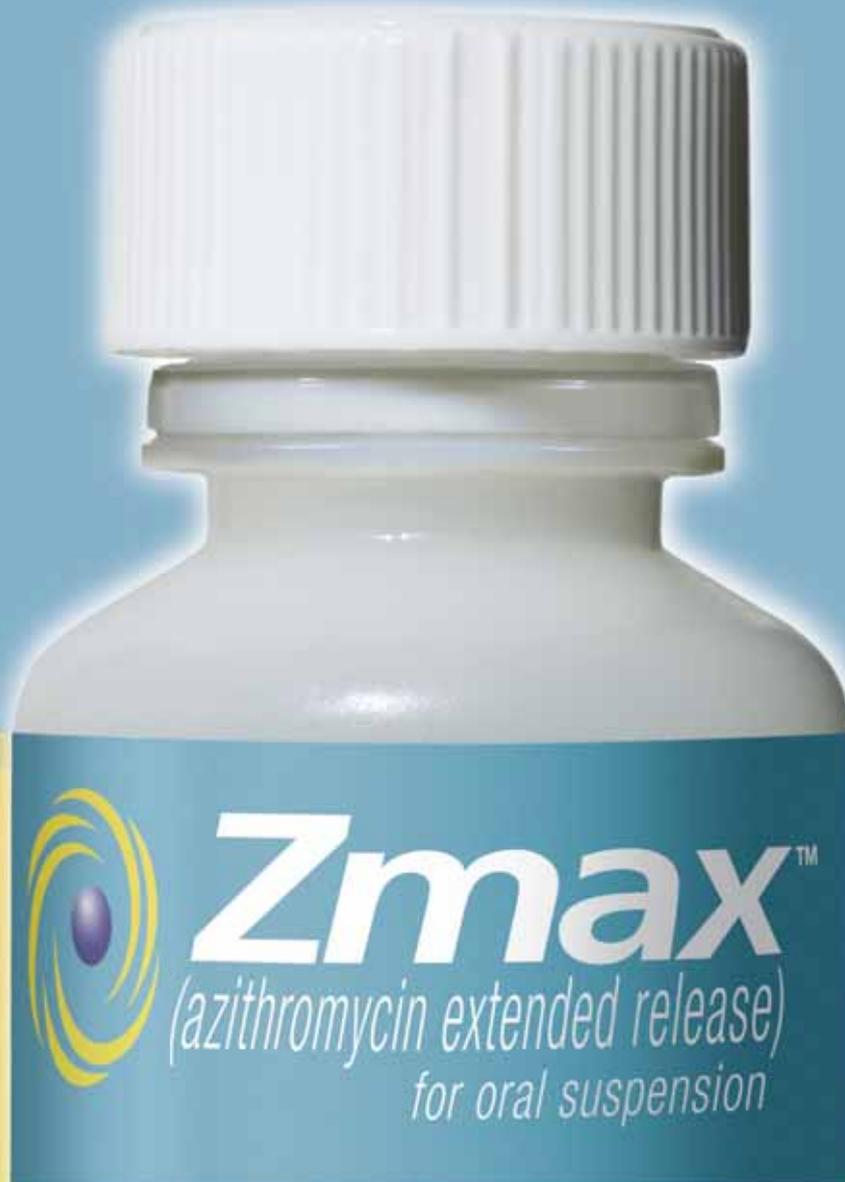
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COMING SOON



ZMAX ABBREVIATED PACKAGE INSERT

1. TRADE NAME: Zmax™ **2. PRESENTATION:** Zmax granules for oral suspension contains azithromycin dihydrate. Each bottle contains azithromycin dihydrate equivalent to 2.0 g of azithromycin, to be constituted with 60mL of water. **3. INDICATIONS:** Mild to moderate infections in adult patients appropriate for oral therapy. a) **Acute bacterial sinusitis** due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. b) **Community-acquired pneumonia** due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*. **4. DOSAGE:** Zmax should be taken as a single 2.0 g dose and provides a full course of antibacterial therapy in a single oral dose. It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal). **5. CONTRAINDICATIONS:** Zmax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic. **6. WARNINGS & PRECAUTIONS:** Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. If allergic reactions occur, appropriate symptomatic therapy should be instituted. However, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure, and prolonged periods of observation and symptomatic treatment of the allergic reactions are required. Pseudomembranous colitis has been reported and may range in severity from mild to life threatening. Diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents may be considered. Caution should be exercised with patients with impaired hepatic function; increased risk of prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes; In the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **7. INTERACTIONS:** Co-administration of neftinavir increases azithromycin serum concentration. Concurrent use of macrolides and warfarin has been associated with increased anticoagulant effects. Azithromycin had modest effect on the pharmacokinetics of atorvastatin, carbamazepine, ceftriaxone, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (IV and oral), triazolam, trimethoprim-sulfamethoxazole, zidovudine. Co-administration with efavirenz or fluconazole had modest effect of pharmacokinetics of azithromycin. **8. PREGNANCY AND LACTATION:** Teratogenic effects; should only be used during pregnancy if clearly needed. It is not known whether azithromycin is excreted in human milk. Caution should be exercised when administered to a nursing woman. **9. SIDE EFFECTS:** **Common:** Diarrhea/loose stools, nausea, abdominal pain, headache, vomiting. **Less common:** Palpitation and arrhythmias including ventricular tachycardia and hypotension, chest pain; constipation, dyspepsia, flatulence, gastritis, vaginitis, dizziness, vertigo, asthenia; rash, pruritus, urticaria; taste perversion. (Identifier number: AZIT0808)

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.



Pfizer Corporation Hong Kong Limited

16/F., Stanhope House, 738 King's Road, North Point, Hong Kong

Tel: (852) 2811 9711 Fax: (852) 2579 0599

Website: www.pfizer.com.hk

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