

# HONG KONG PHARMACEUTICAL *JOURNAL*

VOL 17 NO 2 Apr - Jun 2010 ISSN 1727-2874



## News & Short Communications

Evolution of Trainings in a Taiwan Pharmacy School during the Last Sixty Years

Evaluation of the Viability of *Lactobacillus bifidus* in Commercial Probiotic Supplements in Gastro-environment

News: Pharmacy Conference 2011

Newly elected General Committee/Council members of the three pharmacist societies/association

*THE IMPOSSIBLE DREAM*: Interview with Professor Kenneth LEE

攀摘星辰 - 李炯前教授訪問後記

Farewell to our Chief Pharmacist - Mr. Anthony Chan

The 1st Global Drug Safety Conference and Exposition Hong Kong 2010

Probiotics and Necrotizing Enterocolitis (2 CE Units)

Reflection on the Occurrence, Prevention and Management of Deviations in Pharmaceutical Manufacturing

Tredaptive®/ Synflorix™/ Dynastat



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

# Upgrading Hong Kong GMP Licensing Standards



The Pharmacy & Poisons Board of Hong Kong has increased the experience requirement for Authorized persons of local manufacturers from at least one year of

relevant working experience in GMP pharmaceutical manufacturing or quality control to at least three years. The requirements for heads of production or quality control are: for holders of a bachelor's degree in Pharmacy, the experience requirement should be increased from at least one year of relevant working experience in GMP pharmaceutical manufacturing or quality control to at least three years; for holders of the Higher Diploma in Pharmaceutical Technology or the Certificate in Dispensing Studies awarded by the Vocational Training Council of Hong Kong, the experience requirement should be increased from at least two years of relevant working experience in GMP pharmaceutical manufacturing or quality control to at least three years; and for holders of a bachelor's degree in a relevant science subject, there is no change to the three-year experience requirement (page 49).

It is reported in this issue that on 12 April 2010, the Pharmacy & Poisons Board of Hong Kong sent out a letter to local manufacturers on the new microbial requirements for pharmaceutical manufacturing (page 49). Local manufacturers are required to conduct microbiological tests on all batches of high risks raw materials prior to their use and then every six months thereafter. For in process granules, manufacturers are required to limit the holding time to not more than 48 hours before tableting. For finished products, manufacturers are required to conduct full microbial limit tests on every batch before release for sale, and if the test results of five successive batches of the products meet the in-house standards, manufacturers are allowed to reduce the test to every 5<sup>th</sup> batch. Manufacturers are also required to include microbial testing in the stability study programmes of all pharmaceutical products. This new microbial requirements stem from a series of medication incidents in 2009

in which five cancer patients developed gastrointestinal mucormycosis and subsequently died in public hospitals. Follow up investigations revealed that the allopurinol tablets, manufactured by a local manufacturer and administered to these patients were contaminated by *Rhizopus microsporus*. This step up requirement is good for Hong Kong to ensure the safety and quality of drugs.

The FDA also announced plans to revise the current good manufacturing practice regulations for component controls (page 51). Potential revisions include requiring pharmaceutical manufacturers to physically audit their suppliers, test containers in each shipment received, implement tamper-evidence packaging and security features, notify FDA of contaminated shipments and lots and to use only those components recognized as safe for their intended use. FDA noted the growing gaps in quality control caused by factors such as globalization, new technologies and processes, distribution challenges and increasing outsourcing of production.

On the other hand, microbials are not totally bad, some of them are actually useful and important to our lives. Probiotics of human origin and non-pathogenic, are live microorganisms which offer a health benefit to human including in diarrhoea, immunity, cancer and genitourinary disorders. Li Sin Man described the problem of neonatal necrotizing enterocolitis in new born baby which could be prevented by using non-pathogenic strains of *Lactobacillus* and *Bifidobacteria* (page 70). Mixture of these organisms, when orally taken, can colonize in the gut and eradicate or improve the enterocolitis. However the optimal probiotic supplement and the dosing regimen require further studies.

The use of probiotics is not simply strain dependent but also depends on the methods they are produced. Dr. Cheung's study on the acid resistance of the *Lactobacillus bifidus* in four commercial products reveals that even the same organisms can be many folds different in their performance (page 59). It was found that the same type of cells but formulated differently could have different impact on their performance. His study reflects that the method of microbial preparation and formulation should not be neglected.

Herman Leung points out the importance of reporting and proper documentation of the deviations of the parameters during manufacturing or operation (page 74). It is by analyzing the reason for the occurrence of the deviations and managing the deviations that continuous improvement can be made; it also enables management to evaluate the status of quality assurance and cost control. QA manager should review the deviations that occur frequently and request improvement in the manufacturing process to prevent future deviations. During product development, it is necessary for the manufacturing process to be validated and the product to go through a series of test. Manufacturers are encouraged to establish a product development protocol for quality improvement.

Because the requirements and expectation of each society and period are different, the training and practices of pharmacist are also changed. An article written by Chiang et al in this issue (page 53) describes the shift and emphasis of pharmacy trainings in National Defense Medical Center (NDMC) throughout the last sixty years. It may be a good example for pursuing excellent professionalism. In Hong Kong, DH is planning to upgrade Hong Kong's current GMP licensing standards by a phased approach to PIC/S standards, but where do we get the pharmacists with GMP training to be authorized persons, production or QA manager? It may be necessary for our local Pharmacy Schools to include courses in Industrial Pharmaceutics and Drug Manufacturing to train future competent pharmacists for the local pharmaceutical industry.

Leung Man Cho bid farewell to Prof Kenneth Lee who will be leaving the School of Pharmacy of the Chinese University of Hong Kong for the Malaysian branch of Monash University (page 68). A full report of the interview of Prof. Kenneth Lee is published in page 65. As announced in the Society news, the Hong Kong Pharmacy Conference is scheduled on 26-27 February 2011 at the Hong Kong Convention and Exhibition Centre. Please mark your calendar to attend this annual event.

*Cheng Mary Catherine*  
Managing Editor  
26<sup>th</sup> July 2010

# HONG KONG PHARMACEUTICAL JOURNAL

VOL 17 NO 2 Apr - Jun 2010 ISSN 1727-2874

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## INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drug & Therapeutics
- OTC & Health
- Pharmaceutical Technique & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

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

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

## Editorial

CHENG, Mary Catherine 46

## News & Short Communications

Serious adverse events related to medication errors/misuse of Exelon Patch (rivastigmine transdermal patch) reported by Health Canada	49
Minimum Requirements of Key Personnel in Pharmaceutical Manufacturer	49
Microbial Requirements in Pharmaceutical Manufacturer	49
Several Hundreds of Manufacturers of Proprietary Chinese Medicines not up to Standards	50
Proper Use of Proton Pump Inhibitors	50
Safe Use of Medicines Containing Orlistat	50
Commencement of the Relevant Legislative Provisions Relating to Mandatory Registration of pCm under the Chinese Medicine Ordinance (CMO)	51
FDA to Revise Current GMPs for Component Controls	51

## Pharmacy Education & Practice

Evolution of Trainings in a Taiwan Pharmacy School during the Last Sixty Years	53
--	----

CHIANG, Chiao-Hsi; LAM, Li-Wing Jason; CHEUNG, Hon-Yeung

## Over-the-Counter & Health

Evaluation of the Viability of <i>Lactobacillus bifidus</i> in Commercial Probiotic Supplements in Gastro-environment	59
---	----

CHEUNG, Hon-Yeung

## Society Activities

News: Pharmacy Conference 2011	64
Newly elected General Committee/Council members of the three pharmacist societies/association	64
<b>THE IMPOSSIBLE DREAM:</b> Interview with Professor Kenneth LEE WONG, Helen	65
攀摘星辰 - 李炯前教授訪問後記	68
Farewell to our Chief Pharmacist - Mr. Anthony Chan LEUNG, Peter	68
The 1st Global Drug Safety Conference and Exposition <i>Hong Kong 2010</i>	69

## Drug & Therapeutics

Probiotics and Necrotizing Enterocolitis (2 CE Units) LI, Sin Man	70
--	----

## Pharmaceutical Technique & Technology

Reflection on the Occurrence, Prevention and Management of Deviations in Pharmaceutical Manufacturing LEUNG, Herman	74
--	----

## New Products

Tredaptive® (MSD)	77
Synflorix™ (GSK)	78
Dynastat (Pfizer)	79



With risk coming from multiple directions, add on a multidimensional lipid therapy.

## New TREDAPTIVE<sup>®†</sup> sends lipids in the right direction.

Significant improvements with 2 g/40 mg when added to a statin ( $P < 0.001$ )<sup>1,a,b</sup>

LDL-C: -19%<sup>c</sup>

HDL-C: 20%<sup>c</sup>

TG: -25%<sup>d</sup>

n = 469  
Placebo-adjusted values

TREDAPTIVE<sup>®</sup> (ER Niacin/laropirant, MSD) tablets is indicated for patients with combined dyslipidemia (type IIa and IIb according to Frederickson) and primary hypercholesterolemia (heterozygous familial and non-familial), to reduce total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) when not controlled by diet and exercise alone. TREDAPTIVE can be used in combination with HMG-CoA reductase inhibitors (statins) or as monotherapy.

### Select Safety Information

TREDAPTIVE is contraindicated for use in patients with hypersensitivity to the active substances or to any of the excipients, in patients with significant or unexplained hepatic dysfunction, and in patients with active peptic ulcer disease or arterial bleeding.<sup>2</sup>

TREDAPTIVE was generally well tolerated in clinical studies. The most common side effect of TREDAPTIVE is flushing.<sup>2</sup>

### Please consult the full Prescribing Information before initiating therapy.

Data from a study of TREDAPTIVE 2 g/40 mg relative to placebo. The primary end point was safety and LDL-C percent change from baseline across weeks 12 to 24. Patients (N = 1,613; mean age: 58 years) were randomized to TREDAPTIVE 1 g/20 mg (n = 800), nicotinic acid 1 g (prolonged-release formulation) (n = 543), or placebo (n = 270) for 4 weeks; patients then advanced directly to TREDAPTIVE 2 g/40 mg, nicotinic acid 2 g, and placebo, respectively, for a total treatment duration of 24 weeks.<sup>1</sup>

<sup>a</sup> Each tablet of TREDAPTIVE contains 1 g of extended-release niacin and 20 mg of laropirant, a novel flushing pathway inhibitor.<sup>2</sup>

<sup>b</sup> Patients received the following statins: atorvastatin (29%), simvastatin (54%), other statins (pravastatin, fluvastatin, rosuvastatin, lovastatin, 17%). Nine percent of statin patients were taking ezetimibe. Baseline values for the entire cohort were: LDL-C, 113.5 mg/dL (2.9 mmol/L) (mean), HDL-C, 50.8 mg/dL (1.3 mmol/L) (mean), and TG, 127.0 mg/dL (1.4 mmol/L) (median).<sup>1</sup>

<sup>c</sup> Mean percent change from statin-treated baseline.

<sup>d</sup> Median percent change from statin-treated baseline.

References: 1. Maccubbin D, Bays HE, Olsson AC, et al. Lipid-modifying efficacy and tolerability of extended-release niacin/laropirant in patients with primary hypercholesterolaemia or mixed dyslipidaemia. *Int J Clin Pract.* 2008;62:1959-1970. 2. Hong Kong Product Circular (TREDAPTIVE, MSD)

The following are excerpts from the Prescribing Information. Please refer to the full Prescribing Information before initiating therapy.

#### Indication:

Therapy in patients with combined dyslipidemia (type IIa and IIb according to Frederickson) and primary hypercholesterolemia (heterozygous familial and non-familial), to reduce total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) when not controlled by diet and exercise alone. TREDAPTIVE can be used in combination with HMG-CoA reductase inhibitors (statins) or as monotherapy.

#### Dosage and Administration:

##### Dosage

The starting dose is one extended-release tablet (1 g niacin/20 mg laropirant) once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2 g/40 mg taken as two extended-release tablets (1 g/20 mg each) once daily. Daily doses greater than 2 g/40 mg have not been studied and therefore are not recommended.

If TREDAPTIVE is missed for less than 7 consecutive days, patients can resume therapy at the last administered dose. If TREDAPTIVE is missed for 7 or more consecutive days, therapy should be resumed at the 1 g/20 mg dose for 1 week, before advancing to the maintenance dose of 2 g/40 mg.

These patients switching from 2 g or more of prolonged-release niacin can initiate TREDAPTIVE at the 2 g/40 mg dose. Patients switching from less than 2 g of prolonged-release niacin should initiate therapy at the starting dose of 1 g/20 mg and advance to the 2 g/40 mg maintenance dose after four weeks. For patients switching from immediate-release niacin to TREDAPTIVE, therapy should be initiated at the 1 g/20 mg dose and advanced to the 2 g/40 mg maintenance dose after four weeks.

##### Method of administration

The tablets should be taken whole, with food, in the evening or at bedtime. To preserve the extended-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. To reduce the possibility of flushing, alcohol or hot drinks should be avoided at the time of ingestion of the medicinal product.

##### Use in the elderly

No dose adjustment is required for elderly patients.

#### Use in paediatric patients

Safety and effectiveness of TREDAPTIVE in paediatric patients have not been established. Therefore, treatment is not recommended in this age group.

#### Use in patients with hepatic or renal insufficiency

Use of TREDAPTIVE in patients with hepatic or renal insufficiency has not been studied. Like other niacin medicinal products, TREDAPTIVE is contraindicated in patients with significant or unexplained hepatic dysfunction. It should be used with caution in patients with renal insufficiency, because niacin and its metabolites are primarily excreted by the kidneys (see CONTRAINDICATIONS; PRECAUTIONS).

#### Concomitant therapy

Aspirin provides no additional reduction of flushing beyond that achieved by TREDAPTIVE. Therefore, treatment with aspirin to alleviate flushing symptoms is not necessary.

Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as niacin, it is recommended that TREDAPTIVE be administered > 1 hour before or > 4 hours after administration of a bile acid sequestrant.

#### Contraindications:

- Hypersensitivity to the active substances or to any of the excipients.
- Significant or unexplained hepatic dysfunction.
- Active peptic ulcer disease.
- Arterial bleeding.

#### Precautions:

##### Hepatic Effects:

Liver function tests are recommended before initiation, every 6 to 12 weeks for the first year, and periodically (e.g., semiannually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of > 3x ULN persist, reduction of dose or withdrawal of TREDAPTIVE is recommended.

#### Effect on Skeletal Muscle:

Because the incidence of myopathy is higher than expected in Chinese patients, caution should be used when treating Chinese patients with TREDAPTIVE coadministered with simvastatin or ezetimibe/simvastatin (particularly simvastatin doses of 40 mg or higher). Because the risk of myopathy with statins is dose-related, the use of TREDAPTIVE with simvastatin 80 mg or ezetimibe/simvastatin 10/80 mg is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy in other Asian patients treated with TREDAPTIVE coadministered with simvastatin or ezetimibe/simvastatin.

#### Effect on Glucose:

Diabetic or potentially diabetic patients should be observed closely. Adjustment of diet and/or hypoglycemic therapy may be necessary.

#### Side Effects:

TREDAPTIVE is generally well tolerated. Adverse reactions have usually been mild and transient. Flushing is the most common adverse reaction of TREDAPTIVE. Flushing is most prominent in the head, neck, and upper torso. In a pool of four active- or placebo-controlled clinical trials (N=2548), flushing was reported by the investigator as a possibly, probably, or definitely treatment-related adverse reaction in 12.3% of patients taking TREDAPTIVE. In these studies, the percentage of patients taking TREDAPTIVE, niacin (pooled prolonged-release formulations) or pooled placebo/simvastatin who discontinued due to any flushing-related symptom (redness, warmth, itching and tingling) was 7.2%, 16.6%, and 0.4%, respectively. Discontinuations due to other specific adverse reactions among patients taking TREDAPTIVE were infrequent (< 1%).

Reference: Hong Kong Product Circular (TREDAPTIVE, MSD).



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05-2011-CV1-10-HK-1010-1 (3-10 CV1-2008-W-1268801-1)

**NEW**  
**Tredaptive**<sup>®</sup>  
(ER niacin/laropirant, MSD) tablets  
Multidimensional Lipid Therapy

# Serious adverse events related to medication errors/ misuse of Exelon Patch (rivastigmine transdermal patch) reported by Health Canada

Date: 6 April 2010

Novartis Pharmaceuticals Canada Inc. ("Novartis"), in consultation with Health Canada, informed that serious adverse events including death, have occurred following rivastigmine overdose due to medication errors /misuse of Exelon Patch. Therefore, Novartis would like to remind the importance of the proper use and application of Exelon Patch (rivastigmine transdermal patch) and the need to instruct patients and caregivers on correct application techniques for the use of Exelon Patch. The Exelon Patch

Product Monograph is being revised to further emphasize the following safety information:

- Healthcare providers should inform patients and caregivers on the proper use of rivastigmine patch prior to initiating therapy, and advise them to strictly follow instructions on patch usage;
- Only one transdermal patch should be applied per day to healthy skin on one of the recommended locations: the upper or lower back, or upper arm or chest;
- The previous day's patch must be

removed before applying a new patch to a different skin location after 24 hours of use.

In Hong Kong, Exelon Patch is registered by Novartis Pharmaceuticals (HK) Ltd. The package insert regarding the emphasis on the proper use of Exelon Patch is being updated.

Source: [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2010/exelon\\_hpc-cps-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/exelon_hpc-cps-eng.php)

## Minimum Requirements of Key Personnel in Pharmaceutical Manufacturer

Date: 12 April 2010

On 12 April 2010, the Pharmacy & Poisons Board of Hong Kong sent out a letter to all local manufacturers on the change of minimum requirements of key personnel in pharmaceutical manufacturing. The Authorized person must be a pharmacist but the experience is increased from 1 year of relevant working experience in GMP pharmaceutical manufacturing or quality control to at least 3 years.

Regarding heads of production or quality control, for holders of a Bachelor's degree in Pharmacy, the experience is increased from 1 year of relevant working experience in GMP pharmaceutical manufacturing or quality control to at least 2 years; for holders of the Higher Diploma in Pharmaceutical Technology or of the Certificate in Dispensing Studies awarded by the Vocational Training

Council of Hong Kong, the experience requirement is increased from 2 years of relevant working experience in GMP pharmaceutical manufacturing or quality control to at least 3 years; for holders of a Bachelor's degree in a relevant science subject, there is no change to the 3 year experience requirement.

Source: Letter from DH to Holders of Licences for Manufacturer

## Microbial Requirements in Pharmaceutical Manufacturer

Date: 12 April 2010

On 12 April 2010, the Pharmacy & Poisons Board of Hong Kong sent out a letter to all local manufacturers on the new microbial requirements for pharmaceutical manufacturing.

**Raw materials** - Manufacturers should perform microbiological tests on all batches of high risk raw materials, which include but not limited to those from animal and plant origins, prior to the use of the batch, and every six months thereafter, until the batch is used up. If a manufacturer wishes to test in other time intervals, it has to provide justifications for approval.

**In-process granules** - Manufacturers are required to limit the holding time for in-process granules to not more than 48 hours before tableting. If a manufacturer intends to adopt a holding time beyond 48 hours for any product, it must first

seek approval with support of validation studies data.

**Finished products** - Manufacturers should set a more stringent in-house microbial alert level for microbial burden of each product to be two times one  $\log_{10}$  value lower than the pharmacopoeial limits, as compared with the common practice of one  $\log_{10}$  lower value. If a manufacturer intends to adopt other alert level, it must first seek approval with justifications. Manufacturers are required to conduct full microbial limit tests on every batch of every finished product before release for sale. If the test results of five successive batches of a product meet the in-house standards, manufacturers are allowed to reduce the testing to every 5<sup>th</sup> batch. However, at a minimum, manufacturer should still perform one batch test every six months. If any test result shows deviation

from the longitudinal trend of previous results, manufacturers must conduct investigation, record the investigation result in writing and take all necessary remedial measures to restore the test results within the in-house standards.

**Stability studies** - Manufacturers should include microbiological testing in the stability study programmes of all pharmaceutical products.

**Pharmacopoeial limits** - Pharmacopoeial limits referred to in the above only refers to the microbial limits set out in the current versions of the British Pharmacopoeia, the United States Pharmacopoeia and the National Formulary, the European Pharmacopoeia, the Japanese Pharmacopoeia or the Chinese Pharmacopoeia.

Source: Letter from DH to Holders of Licences for Manufacturer

# Several Hundreds of Manufacturers of Propriety Chinese Medicines not up to Standards

Date: 29 April 2010

After the detection of silbutramine & Phenolphthalein in the Li Chung Shing Tong Po Chai Pills Capsules, the Department of Health (DH) inspected the 500 local manufacturers of propriety Chinese medicines (pCm). Out of the 500, 350 of the manufacturers with the transitional

manufacturing licenses did not meet the required manufacturing standards. Of the 350, 70 were no longer in operation, 30 were, undesirably, in residential locations. The other 250 are required to improve in aspects such as prevention of cross contamination, documentation, technical

and personnel management. DH is giving the manufacturers 2 years to improve, if the manufacturers do not meet the required standards after 2 years, they would be required to close down.

Source: Metro Hong Kong April 29 2010

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## Proper Use of Proton Pump Inhibitors

Date: 27 May 2010

On 26 May 2010, the Department of Health (DH) drew the public's attention to the possible increased risk of fractures of the hip, wrist and spine with high doses or long-term use of a class of medications called proton pump inhibitors, which are used in the treatment of conditions such as gastroesophageal reflux disease, stomach and small intestine ulcers and inflammation of the esophagus. The USFDA issued a warning to consumers and healthcare

professionals on May 25 about a possible increased risk of bone fractures with high doses or long-term use of proton pump inhibitors. Changes in the product labels is required to describe this possible increased risk. Epidemiology studies reviewed by the USFDA suggest a possible increased risk of fractures of the hip, wrist and spine in patients using proton pump inhibitors for one year or longer, or at high doses. The majority of the studies evaluated

individuals 50 years of age or older and the increased risk of fracture primarily was observed in this age group. In Hong Kong, a total of 129 products containing proton pump inhibitors, including omeprazole, lansoprazole, pantoprazole, rabeprazole and esoprazole, are registered with the Pharmacy and Poisons Board (PPB).

Source: Department of Health, HKSAR Government

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## Safe Use of Medicines Containing Orlistat

Date: 28 May 2010

On 28 May 2010, the Department of Health (DH) drew the public's attention to the potential rare occurrences of severe liver injury in patients taking weight-loss medicines containing orlistat. The United States Food and Drug Administration (USFDA) advised consumers and healthcare professionals of the potential risk on May 26 (US time). Changes in product labels are required to reflect this rare occurrence. The USFDA reviewed cases of severe liver injury reported in individuals

taking orlistat and identified 13 cases. However at this time, a cause-and-effect relationship of severe liver injury with orlistat use has not been established. In Hong Kong, there are three registered products containing orlistat, namely Xenical, Zerocal and Alli. The former two which contain orlistat 120mg can be sold on a doctor's prescription and dispensed under the supervision of a pharmacist, while Alli which contains orlistat 60mg can be sold under the supervision of a pharmacist. Healthcare

professionals and consumers should be aware of the rare occurrence of severe liver injury in people taking orlistat products. Consumers taking these products should contact their healthcare professionals immediately if they present with signs and symptoms of liver injury, which include itching, yellow eyes or skin, dark urine, loss of appetite or light-colored stools.

Source: Department of Health, HKSAR Government

# Commencement of the Relevant Legislative Provisions Relating to Mandatory Registration of pCm under the Chinese Medicine Ordinance (CMO)

Date: 21 June 2010

According to the system of transitional registration of pCm under the CMO, where a pCm was, on 1 March 1999, manufactured or sold in Hong Kong, the relevant manufacturer, importer or local agent/representative of a manufacturer outside Hong Kong may apply for transitional registration of the pCm before 30 June 2004. The CMB has started to issue "Notice of confirmation of transitional registration of pCm" since 31 March 2008. As of end April 2010, the CMB received about 16540 applications for registration of pCm, of which about 14,100 also applied for transitional registration. The CMB has finished reviewing all the transitional registration applications and has already issued 9120 notices of confirmation of transitional

registration of pCm. CMB has also issued 2100 notices of confirmation of non transitional registration application of pCm if the basic safety and analytical reports of the products were received. CMC has rejected the registration of 4610 applications due to unacceptable reports or insufficient documents.

The Government has planned to put into full implementation the remaining provisions under the CMO related to mandatory registration of pCm starting from the end of this year. The proposed implementation plan is as follows –

(a) Starting July 2010 –mounting of various publicity activities and consulting the trade on the implementation plan of the proposed

commencement of the legislative provisions and;

- (b) July to November 2010 – submission of the commencement proposal to the Legislative Council and publication in Gazette;
- (c) 1 December 2010 – commencement of s119 and s129 and the sale, import or possession of unregistered pCm in Hong Kong will be an offence by then; and
- (d) 1 December 2011 – commencement of s143 and s144 to allow the trade to have adequate time to comply with the labelling and package insert requirements.

Source: [http://www.cmchk.org.hk/pcm/pdf/pcm100609\\_e.pdf](http://www.cmchk.org.hk/pcm/pdf/pcm100609_e.pdf)

## FDA to Revise Current GMPs for Component Controls

Date: 22 June 2010

The US Food and Drug Administration (FDA) announced plans to revise the current good manufacturing practice (GMP) regulations at a conference held jointly by the agency and Xavier University in Cincinnati, Ohio, June 13-16. Brian Hasselbalch, representing the Office of Compliance's Division for Manufacturing and Drug Product Quality within FDA's Center for Drug Evaluation and Research, was speaking as part of the first joint annual Global Outsourcing Conference at the school.

According to Haselbalch's presentation, a draft of new CGMP regulations focusing on component controls is expected before the year's end. Potential revisions include requiring pharmaceutical manufacturers to physically audit their suppliers (i.e., no more paper audits), test containers in each shipment received, implement tamper-evident packaging and security

features, notify FDA of contaminated shipments and lots, and to use only those components recognized as safe for their intended use or listed in an already approved application.

In addition to increased enforcement and information-sharing, FDA also plans to play a stronger "guiding role" in corporate responsibility. Hasselbalch offered some recent guidance documents as examples of FDA's role in encouraging corporate responsibility: process validation, pharmaceutical quality systems, and testing of glycerin for diethylene glycol. It seems the agency will go even further by issuing a second phase of revised CGMP regulations that focus specifically on corporate responsibility. These revisions might include requirements that management assures compliance, performs self-inspections, evaluates and investigates problems, implements change control, and documents training

and effectiveness. Hasselbalch's presentation noted growing gaps in quality control caused by factors such as globalization, new technologies and processes, distribution challenges, and increased outsourcing of production. Between 2001 and 2007, the number of products manufactured outside the United States and the number of manufacturing sites abroad doubled. Some of the new products being imported into the US come from countries with "less developed regulatory systems". Along with these more complex supply chains, there has been an increase in pharmaceutical cargo thefts and in drug counterfeiting. More preventative measures are therefore needed. Industry will have a chance to comment on the proposed revisions once they are issued.

Source: <http://pharmtech.findpharma.com/pharmtech/News/FDA-to-Revise-Current-GMPs-for-Component-Controls/ArticleStandard/Article/detail/675543>



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## Evolution of Trainings in a Taiwan Pharmacy School during the Last Sixty Years

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### ABSTRACT

The School of Pharmacy in the National Defense Medical Center, also known as NDMC, has been offering the professional pharmacy education to students for more than a century in China. Graduates of this school have advanced professional practices in modern pharmaceutical fields and knowledge in a variety of healthcare sectors. They have helped other institutes to setup courses and trainings in pharmacy. In the last sixty years, a variety of courses have been introduced and offered by the faculty in order to cope with the needs of society in Taiwan. More recently, a PharmD programme is being seriously considered by the school. The evolution of pharmacy courses in this school, therefore, could be a useful model for other institutes who may consider launching a professional degree programme in pharmacy.

**Keywords:** National Defense Medical Center; School of Pharmacy; Courses & trainings; BPharm; PharmD

### INTRODUCTION

The National Defense Medical Center, also known as NDMC, is the oldest military medical institute in China. It has a history of more than 110 years. The institute was originally setup in Tianjin 1902, then following relocation in several cities “ Beijing, Nanjing and Anshun, et al “ current name, NDMC was adopted in 1949 in Shanghai but evacuated and moved to Shuiyuen campus in Taipei in 1949. After half a century of operation on Shuiyuen campus, NDMC was given a block of land and relocated again to a new campus in Neihu in late 1999; just before the turn of the millennium. In 2008, the school of pharmacy of NDMC celebrated the Centennial Anniversary of its Establishment.<sup>(1)</sup> The contemporary training of the pharmacy programme has been derived and evolved from many

traditional training courses with different emphases in different periods of time. Understanding the evolutionary path of pharmacy training offered by this school in the last 60 years, perhaps, could assist people to correlate the replacement or evolution of some courses to the expectation of society at different periods. The information summarized in this investigational study, therefore, may be useful for those who are concerned and want to offer new training programmes in pharmaceutical fields for our next generation.

In this review article, the evolution of pharmacy courses offered by the school can be roughly divided into three stages. These three stages were the early day stage, the Shuiyuen stage and the Neihu stage. In the early day stage, a four year undergraduate programme was the only programme promoted in the pharmacy school of NDMC. Until 1986, there was no research school and no masters in pharmacy programme offered despite the fact that some postgraduate students were studying in NDMC, they were actually enrolled in other pharmacy schools. Modification of the programme structure and tuning of the curriculum in the pharmacy school of NDMC from 1957 to 1999 were regarded as the main achievements during the Shuiyuen stage while relocation to the permanent campus with further changes in curriculum from 2000 onwards at Neihu was regarded as the third stage.

Because of the uniqueness of each stage and some differences among the three stages of NDMC pharmacy courses, the courses offered in the last sixty years are listed and also compared. This article is not merely a review of the developmental history of pharmacy education in Taiwan, but also provides some inspiration and a blueprint for future reform of pharmacy education in other places.

### THE EARLY DAY STAGE

The 34<sup>th</sup> cohort of graduates (1951) finished their first and second academic years in mainland China. Because it was a long time ago, the details of programme structure and curriculum launched in the early day stage were not easily retrievable and spotted due to fragmentary records. However, the outline of the programme structure can be identified by studying the transcripts provided from the graduates. Courses offered in those days could be simply divided into some domains, including general education, military study, basic medical courses and professional pharmaceutical courses.

The credit units required for graduation was quite high in this period; it was about twice that of recent times. The main reason is that there were 4 semesters in the third year of the programme, it is equal to the addition of a one year study period. Some courses setup were more than ten credit units, including English (29), physics (10), medicinal botany (15), advanced organic chemistry (13.5), pharmaceuticals (14) and the administration of medical devices (10.3). The distribution of the credit hours revealed that the school of pharmacy put a lot of emphasis on education in foreign languages, medicinal dispensing and preparation. As the source of medicine mainly depended on natural herbal sources and artificial synthesis via organic chemical approaches, some related courses, namely medicinal synthetic chemistry, industrial pharmaceutical chemistry and drug identification, were introduced. Most of the graduates had taken responsibility to provide medical support in the army. Consequently, the administration of medical devices was indispensable for students in that period.

After re-establishment in Taiwan, the curriculum of pharmacy programme was modified to some extent. The curriculum of the 39<sup>th</sup> graduation (1957) was a typical example (Table 1). The programme structure of the 39<sup>th</sup> graduation was more or less the same as that of the 34<sup>th</sup>. However, the courses required

less credit hours than before, the total number of credit unit requirements for graduation was reduced to 231.5 units. On the other hand, the credit units in the military domain were expanded from 26 to 39.5. However, some new professional courses were introduced, for example, pharmacology, forensic ethics, forensic law and pharmaceutical research project, were introduced. This indicated that the coverage of the programme was expanding gradually from the field of professional dispensing with a chemistry approach to pharmacists possessing professional knowledge in working mechanisms and functions of various medicines. Apart from possessing professional skills and knowledge, it is also crucial that pharmacists practise legally and morally. Professional research projects mainly required presentation of a thesis. The students were supervised by the teaching staff, they learnt some analytical and data collecting skills, and also running various research projects in the laboratories. Then, the students had to compose the research reports and essays according to the instructions provided. Students were able to benefit by those types of learning experience after they had solved related problems independently, and then their critical thinking skills were nurtured. The effect of those approaches was not reflected completely, since the majority of graduates were financially supported by the military. Nevertheless, the graduates, who continued their post-graduate education in Europe and America, performed well in research projects and were highly appreciated. It showed the adequate practical training and sufficient opportunities to participate in research projects in the undergraduate programme benefited students' development and prospects.

### THE SHUIYUEN CAMPUS STAGE

The curricula were arranged according to the previous stage and the requirements for graduation and courses were modified to catch up with the needs of society. Five years is considered as an appropriate interval to monitor the reformation so as to obtain a clearer image of the change of the programme (Table 2). From the 39<sup>th</sup> to 59<sup>th</sup> graduation (1957-1976), in these 20 years, on basic medical domains, in 44<sup>th</sup>, 54<sup>th</sup> and 59<sup>th</sup> years, anatomy, public health and biostatistics were the newly introduced courses, respectively. Studying anatomy was to consolidate the understanding of human body structure, organs and various systems. Hence, it built a solid foundation for learning physiology. The other two mentioned courses, public

Table 1. Courses and credits assigned to pharmacy students from cohort 34<sup>th</sup> (1951) to 39<sup>th</sup> (1957)

CATEGORY	COURSES	YEAR OF GRADUATION		Remark
		1951	1957	
General Education	Chinese Literature	6	8	(+2)
	English	29	16	(-13)
	Calculus	9	4	(-5)
	Physics	10	8	(-2)
	Biology	6	6	
	General Chemistry	3	6	(+3)
	Introductory Laws	1	1	
	General Politics	3	1	(-2)
	General Economy	2	1	(-1)
	Economical Study of China	2	0.5	(-1.5)
	Contemporary Chinese History	2		
	Music	1		
	Chinese Civilization History		2	
	Sociology		2	
	Logic		1	
Military Courses	Introductory Philosophy		1	
	Chinese Philosophy		1	
	Physical Exercises	8	3	(-5)
	Military Science	1		
	Military Education	13		
	Land Policies in China	2		
	Soviet Political & Economy	2		
	Martial Art		8	
	Strategies for National Development		2	
	Virtue Lessons from President		2	
	Spiritual & Political Education		3	
	Contemporary International Development		1.5	
	Military Education		3	
	Critical Study of Communism		1	
	Russian Invasion of China		1	
	Personal Hygiene		2	
	Fate of China		1	
	Military Geography		2	
	Political Duties of Army		0.5	
	Hygienic Monitoring		4	
Speech Deeds of Leader		1		
Revolutionary Leadership		0.5		
Thinking of National Father		0.5		
Six Lectures of Premier		1		
Biographical Study of National Heroes		1		
Management of Battle Fields		0.5		
Latest International Development		1		
Basic Biomedical Courses	Analytical Chemistry	13	6	(-7)
	Organic Chemistry	8.5	5	(-3.5)
	Physiological Chemistry	7.5	6	(-1.5)
	Physiology	12	4	(-8)
	Mineralogy	2		
	Zoology	2		
Professional Courses	Bacteriology	3	1.5	(-1.5)
	Medicinal Botany	15	8	(-7)
	Pharmacognosy	7.5	6	(-1.5)
	Advance Organic Chemistry	13.5	6	(-7.5)
	Hygienic Chemistry	6	7	(+1)
	Pharmaceutics	14	10	(-4)
	Medicinal Chemistry	9	8	(-1)
	Pure Chemistry	4	3	(-1)
	Forensic Sciences	7	8.5	(+1.5)
	Synthetic Drug Chemistry	8	6	(-2)
	Industrial Pharmaceutics	6	3	(-3)
	Toxicology	8	5	(-3)
	Management in Medical Devices	10.3	2	(-8.3)
	Dispensing	6.7	3	(-3.7)
	Dispensing Internship	8.5	3	(-5.5)
	Drug Manufacturing Internship	0	10	(+10)
	Extraction and Analysis of Phytomedicines		6	
	Analytical Organic Chemistry		4.5	
	Forensic Ethic		1	
	Pharmacology		4	
Forensic Laws		1		
Project		6		
<b>Total Accumulated Credits(總計學分)</b>		<b>271.5</b>	<b>231.5</b>	

health and biostatistics, are professional studies of the relation between environment and social activities, and aid the development of preventative approaches against infectious diseases. Moreover, to strengthen the reading ability of professional theses, statistics and data collection skills for related research fields are the other emphasis of those courses.

There was no significant change of the courses in the professional pharmaceutical domains. The bacteriology course has been changed and renamed as microbiology twice, the syllabus was revised to cover studies of a wider variety of pathogens. It was also closely related to the former research project about parasitology. In 1978, both Director King Ming-Lu (金明儒) and Professor FAN Pingchin (范秉真) led a research team to formulate and dispense Hetrazan salt (diethylcarbamazine) which is applicable for the treatment and the prevention of bancroftian filariasis in Kinmen. The effect of the treatment was outstanding. The threat of bancroftian filariasis was completely eradicated in Kinmen. Advanced organic chemistry focuses on learning the synthetic pathways and chemical reactions among heterocyclic chemical species; it was combined with organic chemistry in the 54<sup>th</sup> cohort. Health chemistry was revised as food chemistry in the 59<sup>th</sup> cohort and students were taught to determine the ingredients in food. Hence, training on various testing methods for food samples were the main focuses at this period. Medicinal industrial chemistry was replaced by industrial pharmacy for the 44<sup>th</sup> cohort. Beside the traditional classes and lectures, the students had to pay some visits or conduct surveys in food factories and pharmaceutical plants. All students were given opportunities to acquaint the manufacturing process and the preparation methods of pharmaceutical products. For example, the students were arranged to visit and to write reports on the preparation process of Hetrazan salt, which was part of the manufacturing setup in Synpac-Kingdom Pharmaceutical Company Ltd. Students were instructed to observe the coating process of table salt with hetrazan in a sugar coating pan followed by packaging them as a salt product in bag. Through this type of in-situ learning exercises, students were able to link pharmaceuticals with parasitic disease without difficulty. Hence, it may be one of the good learning examples designed for the practical classes in medicinal manufacturing.

Before the admission of the 59<sup>th</sup> cohort, the final score of any courses was based on the summation of assessments on both practical exercises and academic

**Table 2. Courses and credits assigned to pharmacy students from cohort 39<sup>th</sup> (1957) to 59<sup>th</sup> (1976)**

CATEGORY	COURSES	YEAR OF GRADUATION				
		1957	1962	1967	1971	1976
<b>Basic Biomedical Courses</b>	Analytical Chemistry	6	6	6	8	7
	Organic Chemistry	5	5	6	10	6
	Physiological Chemistry	6	7	6	6	7
	Physiology	4	4	4	4	5
	Anatomy	---	4.5	3	3.5	3
	Public Health	---	---	---	2	2
	Biostatistics	---	---	---	---	2
<b>Professional Courses</b>	Bacteriology	1.5	2	2	4.5	4
	Parasitology	---	---	2	---	2
	Medicinal Botany	8	5	5	5	4
	Pharmacognosy	6	6	6	6	5
	Advance Organic Chemistry	6	6	4	---	---
	Hygienic Chemistry	7	6	6	6	4
	Pharmaceutics	10	8.5	7	9	8
	Medicinal Chemistry	8	6.5	12	12	9
	Pure Chemistry	3	---	4	4	3
	Forensic Sciences	8.5	7	7	7	7
	Synthetic Drug Chemistry	6	---	---	---	---
	Industrial Pharmaceutics	3	3	3	3	3
	Toxicology	5	5	5	5	5
	Management in Medical Devices	2	4	4	4	2
	Dispensing	3	5	5	5	4
	Dispensing Internship	3	---	---	---	---
	Drug Manufacturing Internship	10	12	12	12	0
	Extraction and Analysis of Phytomedicines	6	---	---	---	---
	Analytical Organic Chemistry	4.5	4	4	---	---
	Forensic Ethic	1	---	---	---	---
	Pharmacology	4	4	4	4	5
	Forensic Laws	1	2	2	2	2
	Project	6	4.5	5.5	8.5	8.5
Introductory Pharmacy	---	2	2	2	1	
<b>Total Accumulated Credits (總計學分)</b>		<b>133.5</b>	<b>119</b>	<b>126.5</b>	<b>132.5</b>	<b>108.5</b>

evaluations without any restriction. Consequently, these two parts of assessment could be complementary to each other. However, the scores of these two parts were calculated separately afterwards. Therefore, failure of a course could be due to a failure of either one part and student, whoever failed a particular part of the course, might be asked to repeat the whole year of courses and face deferment. These requirements of the academic and practical performance maintained a very high standard for all NDMC graduates.

From cohorts of the 59<sup>th</sup> to 79<sup>th</sup> (1976-1996, Table 3), two courses, namely biostatistics and public health, were phased out as the core basic medical courses for the students. The main reason was that students of these batches had been given too many courses to do. Moreover, a public health programme, which led to a four-year undergraduate degree, was already approved and launched by the institute in 1979. Hence, the responsibility and duty in the area of public health were taken by those graduates instead of pharmacy graduates. Since then these courses lost their importance for pharmacy students. In the professional pharmaceutical domain, contents of the course of medicinal identification were redesigned as medicine and toxin identification for

the 64<sup>th</sup> cohort. Toxicological chemistry was incorporated as a new component of the course. The course was subsequently further revised for the 74<sup>th</sup> cohort; it was revised to cover medicinal analysis.

During the same period, various Chinese medicine courses were also introduced; including introductory course to Chinese medicines, Chinese medicinal dispensing, Chinese medicinal processing and herbal studies. According to the instruction provided by the Department of Health of Taiwan, all pharmacists have to take 16 credit units of courses relevant to Chinese medicine before being entitled to work on Chinese medicinal dispensing and supplying. After finishing the four Chinese medicine courses mentioned above, and also pharmacognosy and medicinal botany, the person was regarded as meeting the minimal requirements to manage Chinese medicines.

At about the same time, various courses relevant to clinical diagnosis and medicinal effects were offered in order to improve the standard of graduates in the clinical pharmacy field. These courses included internal medicine, introduction to pathology, pharmacodynamics, clinical and therapeutic pharmacy, nuclear medicinal studies and clinical biochemistry. Beside pharmacodynamics, which was renamed

Table 3. Courses and credits assigned to pharmacy students from cohort 59<sup>th</sup>(1976) to 79<sup>th</sup> (1996)

CATEGORY	COURSES	YEAR OF GRADUATION				
		1976	1981	1986	1991	1996
Basic Biomedical Courses	Analytical Chemistry	7	8	8	3	3
	Organic Chemistry	6	9	7	4	5
	Biochemistry	7	6	6	5	5
	Physiology	5	5	5	5	5
	Anatomy	3	8	3	3	3
	Introductory Public Health	2	2	2	---	---
	Biostatistics	2	---	---	---	---
Professional Courses	Microbiology	4	4	4	4	4
	Parasitology	2	---	---	---	---
	Medical Botany	4	4	2	2	2
	Pharmacognosy	5	5	5	4	5
	Food Chemistry	4	---	---	---	---
	Pharmaceutics	8	7	7	7	7
	Medicinal Chemistry	9	8	8	8	8
	Physical Chemistry	3	4	4	3	3
	Drug Identifications	7	10	10	7	7
	Industrial Pharmacy	3	3	2	1	1
	Toxicology	5	---	---	---	---
	Management in medical devices	2	---	---	---	---
	Dispensing	4	5	5	5	5
	Internship Training in Drug Store & Manufacturing Plants	0	0	0	4	4
	Logic	5	6	6	6	6
	Forensic Laws	2	2	2	---	1
	Project	8.5	2	---	---	---
	Introductory Pharmacy	1	1	1	---	---
	Fundamental of Chinese Medicines	---	1	1	1	1
	Herbal Medicines	---	---	---	---	2
	Herbal Processing	---	---	---	---	3
	Herbal Dispensing	---	---	---	---	3
	Introductory Internal Medicines	---	---	---	---	2
	Introductory Pathology	---	---	---	2	2
	Nucleus Medicines	---	2	3	---	---
	Biopharmacology	---	2	2	3	3
	Forensic Ethics	---	1	1	1	---
	Clinical Pharmacy & Therapeutics	---	2	2	3	3
	Clinical Biochemistry	---	4	---	---	---
	<b>Total Accumulated Credits(總計學分)</b>		<b>108.5</b>	<b>111</b>	<b>96</b>	<b>81</b>

recently as biopharmaceutics, was taught by staff from NDMC. Teaching of these courses as mentioned above were assisted by doctors and clinical pharmacists who were working in Tri-Service General Hospital.

From the 69<sup>th</sup> cohort onwards, the study hours of military courses and training were not counted as credit units for graduation. Hence, the total credit units displaced on their academic transcript decreased tremendously after this change. For example, the credit units for the graduation in the 59<sup>th</sup> cohort and that of the 69<sup>th</sup> cohort were 206.5 and 169, respectively.

### THE NEIHU STAGE

In 1999, NDMC was relocated to the Neihu International Medical Center. NDMC was re-organized and has been affiliated to the National Defense University, which also includes the ChungZheng Technical Institute and the National Defense Management Institute. The new campus of the National Defense Medical Center is quite large; a 40 hectare area was given to the institute to establish its new campus. Many modernized buildings on

this new campus are attached directly to the Tri-Service General Hospital, which is the ideal place for both teaching and practical trainings. Advanced equipment and facilities are installed to provide a better teaching and learning environment. Numerous scholars and professionals in biomedical science pay their visits or short term study in the Neihu International Medical center every year. Academic conferences of biomedical science are organized and held more than ever in the center. Moreover, a research laboratory has been setup in the National Health Research Institute for conducting some front edge researches relating to the discovery of innovative medicines which could be used for curing cancer yet still belong to a stage classified as investigative drug. Canteens, restaurants and a small shopping mall are also setup in the main building of the center so that students and staffs are not necessary to go out for meal and for shopping of daily necessity. They can save more time for learning, writing thesis, participating in practical training and revision etc. Although a lot of new facilities have been installed, residential halls or accommodation for staff are not covered.

In this stage, there were no

significant modifications or changes of the programme and alteration of credit units of the curriculum up to the 84<sup>th</sup> (1995) cohort (Table 4). As the idea of flexible tertiary education become more popular in verywhere, some core courses have been changed to electives so that students are given the freedom to choose some courses that they like. Due to the philosophical change in education, the credit units required for graduation of a student are further trimmed. For example, the credit units required for graduation of the 95<sup>th</sup> cohort was only 131. As a result, the successful rate of graduation has been increased; while it was very common in the past that more than a quarter of students were unable to graduate on time. This phenomenon does not occur anymore in this day.

Nowadays, some specific features of learning can be found in the NDMC pharmacy programme. These include integration of courses, problem-based teaching and learning approaches and strong emphasis in pharmaceutical practice. With regard to the integration of courses, both pharmacology and medicinal chemistry are taught during the second semester of year two and the first semester of year three. The arrangement of these two courses could be arranged by the teaching staffs involved after some discussions among themselves in order to achieve the best order of integrated teaching and learning for all enrolled students. Similarly, a systematic approach for learning pharmaceutical preparations is designed for student taking both pharmacognosy and medicinal chemistry. They are given chances to practise the extraction skills on botanical medicinal materials and apply the knowledge of chemical synthesis for medicinal compounds by integrating the practical section of both courses in laboratory exercise. To enhance the efficiency of learning on both clinical pharmacy and therapeutics, staffs of NDMC designed and revised their own new teaching materials derived from real examples and cases of therapeutic treatments of patients in hospital. Some courses are delivered using a problem-base teaching and learning approach. As a result of these modifications and changes, students have plenty opportunities to discuss with clinical pharmacists on practical problems. Their ability to apply knowledge on therapeutics, clinical pharmacy and other professional fields is significantly improved. In order to cope with the flexibility of learning, a great number of electives has been added. Some courses relating to pharmaceutical practice are setup; for instance, pharmaceutical information, clinical pharmacy practices, pharmacoeconomics and pharmacy

Table 4. Courses and credits taken by pharmacy students from cohort 79<sup>th</sup> (1996) to 95<sup>th</sup> (2011)

CATEGORY	COURSES	YEAR OF GRADUATION			
		1996	2001	2006	2011
Basic Biomedical Courses	Analytical Chemistry	3	3	3	3
	Organic Chemistry	5	5	5	4
	Biochemistry	5	5	5	5
	Physiology	5	5	5	4
	Anatomy	3	3	3	3
	Biostatistics	---	---	---	2
	Molecular Biology	---	---	---	2
Professional Courses	Microbiology & Immunology	4	4	4	4
	Medicinal Botany	2	2	2	2
	Pharmacognosy	5	5	5	3
	Pharmaceutics	7	7	7	6
	Medicinal Chemistry	8	8	8	6
	Practical in Pharmacognosy & Medicinal Chemistry	---	---	---	2
	Medicinal Physical Chemistry	3	4	4	4
	Drug Analysis	7	7	7	6
	Drug Manufacturing	1	---	---	1
	Dispensing	5	5	5	5
	Internship	4	4	4	6
	Pharmacology	6	6	6	5
	Drug Administration and Laws	1	1	2	4
	Project	---	---	1	3
	Introductory Pharmacy	---	---	1	1
	Introductory Pathology	2	2	2	2
	Biopharmaceutics	3	3	3	4
	Forensic Ethics	---	---	1	1
	Clinical Pharmacy & Therapy	3	3	2	8
	Directed Study in Clinical Pharmacy & Therapy	---	---	---	2
	OTC Drug & Therapy	---	---	---	2
	Introductory Chinese Medicines	1	1	1	1
	Herbal Medicine	2	3	3	3
	Herbal Processing	3	3	3	3
	Herbal Dispensing	3	3	3	3
	Internal Medicine	2	2	2	2
	Pharmaceutical Information	---	2	2	2
	Management of Community Proagation	---	2	2	2
	Drug Management in Hospitals	---	---	1	1
	Clinical Pharmacy Practices	---	---	---	2
	Pharmacoeconomics	---	---	---	2
	Introductory Military Medicines	---	---	---	1
	Radiopharmaceutics	---	---	---	2
Special Study of Pharmaceutics	---	---	---	4	
Heterorganic Chemistry	---	---	---	2	
<b>Total Credits of courses offered</b>		<b>93</b>	<b>98</b>	<b>102</b>	<b>130</b>

management and administration. Student can choose subjects according to their preferences and studying plans (Table 4). Starting from July 2008, the National Examination Ministry has implemented a higher examination requirement for some subjects such as dispensing, clinical pharmacy and pharmaceutical therapeutics in the National Professional Examination for candidature wants to become a qualified Pharmacist. Because the assessment of each subject has been raised to 100 scores, all relevant courses taught in NDMC have been modified and extended in response to the change of the professional examination.

## CONCLUSION

The Pharmacy school of NDMC was setup in the Ching Dynasty. In 2008, faculty members, alumni and students celebrated the Centennial Anniversary of Establishment of the pharmacy school. They have also witnessed the

development and the reformation of pharmacy education. In the last sixty years, graduates of this school not only successfully established themselves in Taiwan but also spread their influences to the nearby countries along the Western Pacific region. The syllabus of pharmacy education has been modified a lot from nurturing professionals for medicinal manufactory in the early days, to professional pharmacists with sufficient knowledge on handling drugs and ability of dispensing and management. Nowadays, pharmacists have become a vital force in the medical professional crews in the healthcare system of society. They take heavy responsibility for providing medicinal support. Consequently, pharmacists are expected not only to possess professional knowledge of medicinal manufactory, but also need various knowledge and skills, including clinical pharmacy, pharmaceutical therapeutics, pharmacoeconomics and management. However, the four-year programme

may not be adequate to nurture "modern pharmacists" who possess integrated professional skills and knowledge. Nowadays, most developed countries, such as the USA, Japan and Korea, promote six-year pharmacy programmes. Another Asian country, Thailand, has changed the pharmacy programme from four-year to become a six-year programme. In addition, the University of Taiwan has started a six-year pharmacy programme in 2009 as well; the person who is able to finish the six-year programme will be considered as a PharmD holder. Promoting a six-year PharmD programme will be a trend in worldwide pharmacy education, as a consequence this trend will influence new inspiration for further reformation of the pharmacy programme of NDMC.

It is quite well known that students who want to pursue a pharmacy career in the USA have to complete the two-year pre-pharmacy courses with outstanding performance prior to be admitted to the pharmacy training programme. The quality of students, therefore, is guaranteed by this specific admission policy. As the pharmacy school of NDMC is envisaged to nurture young people for providing medical support in the army, the admission model of the pharmacy programme of the USA may be appropriate for training a pharmacist. After studying a medical science programme for two years, the students will be permitted to continue their study in the pharmacy programme in NDMC. After a four-year study programme the graduate will take possession of PharmD. This programme structure is designed similar to the current structure, but the time required for study of foundation courses will be saved. It will be expected that new courses, programme structure and admissions policy will be planned and carried out so that more talented graduates will be nurtured, and then the public and the army will have service and support provided from professional pharmacists.

### Author's background

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# Evaluation of the Viability of *Lactobacillus bifidus* in Commercial Probiotic Supplements in Gastro-environment

CHEUNG, Hon-Yeung\*

Research Group for Bioactive Products, Department of Biology and Chemistry, City University of Hong Kong, 83 Tat Chee Aveune, Hong Kong SAR, China (\*Email: [bhhonyun@cityu.edu.hk](mailto:bhhonyun@cityu.edu.hk))

**ABSTRACT**

The ability of a lactic acid bacterium to survive passage through the stomach is essential for it to function as a probiotics. Four commercially available supplements of *Lactobacillus bifidus* were suspended in broth and buffer at pH 2.5, 3.5 and 7.0 and incubated at 37°C for 1 hr and 3 hr. In buffer at pH 2.5 and 3.5, viable cell numbers decreased rapidly. The viability of *Lactobacillus bifidus* dropped as pH became more acidic in all samples. One sample outperformed all other samples by 3.8 to 13.1 times in pH 2.5. A more significant result was found in pH 3.5, it outperformed all other samples by 2.9 to 26 times when it was exposed for 3 hours. It was found that the formulation of a probiotic could also have some effects on the viability of the organism.

**Keywords:** Probiotics, pH, *Lactobacillus bifidus*, Viability, Gastro-environment.

**INTRODUCTION**

The word probiotics is used to describe a food or microbial cell preparation that, when consumed, has a beneficial effect on health. These preparations contain live microorganisms to help the host to improve health. According to the definition by FAO/WHO, probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host".<sup>(1)</sup> Etymologically, the term "probiotics" is made of the prefix, "pro" and root "biotics". In Latin, "pro" means "for" and "biotics" is evolved from the Greek βιωτικός, means "life".<sup>(2)</sup> The term "probiotics" was first introduced in 1953 by Kollath.<sup>(2)</sup> In constrast to antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other microorganisms. In 1989 Roy Fuller suggested a definition of probiotics which has been widely used: "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance".<sup>(2)</sup> Probiotic effects are shown mainly by lactic acid bacteria,

including *Lactobacillus acidophilus*, *Bifidobacterium bifidus*, *Lactobacillus casei*, which are commonly used in probiotic yoghurt known as nicknamed, ABC, as well as selected strains of the yeast *Saccharomyces cerevisiae* and *Escherichia coli*.

Some benefits to health were reported after consumption of probiotics.<sup>(3)</sup> These benefits include controlling of intestinal infections, lowering of serum cholesterol levels, synthesis of B vitamins, lowering of blood ammonia levels, beneficially influencing the immune system, and improvement of lactose utilization.<sup>(4-6)</sup> Also, colonization in the human gut of the bifidobacteria is postulated to increase mineral absorption, prevent hypercholesterolemia, and even provide anticarcinogenic activity.<sup>(7-8)</sup> Figure 1 summarizes the possible health benefits of consuming probiotic foods and preparations. All health benefits reported so far are attributed either to immunomodulation, metabolism or normalization of intestinal microbial composition.

benefits of probiotics has grown, there has been a trend to incorporation of probiotic bacteria into a wide range of food products including milk, yoghurts, cheese, and dietary supplements.<sup>(9-10)</sup> A daily consumption of high levels of probiotic bacteria is required to confer health benefits (Table 1). To achieve the maximum benefits, the concentration of live probiotic bacteria is required to be at the level of approximately 10<sup>7</sup> CFU/mL of the product at the time of consumption.<sup>(11-13)</sup> Moreover, probiotic bacteria should withstand the adverse conditions of digestion including the acidic environment encountered in the host's stomach and bile in the duodenum. However, many probiotic bacteria lack the ability to survive the harsh acidity.<sup>(14-17)</sup> Therefore, the study of viability of microorganisms in an acidic environment is essential.

Marteau conducted a study on validation of a dynamic model of the stomach to quantify the survival of different species of lactic acid bacteria (*Bifidobacterium bifidus*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*).<sup>(18)</sup>

As awareness of the therapeutic

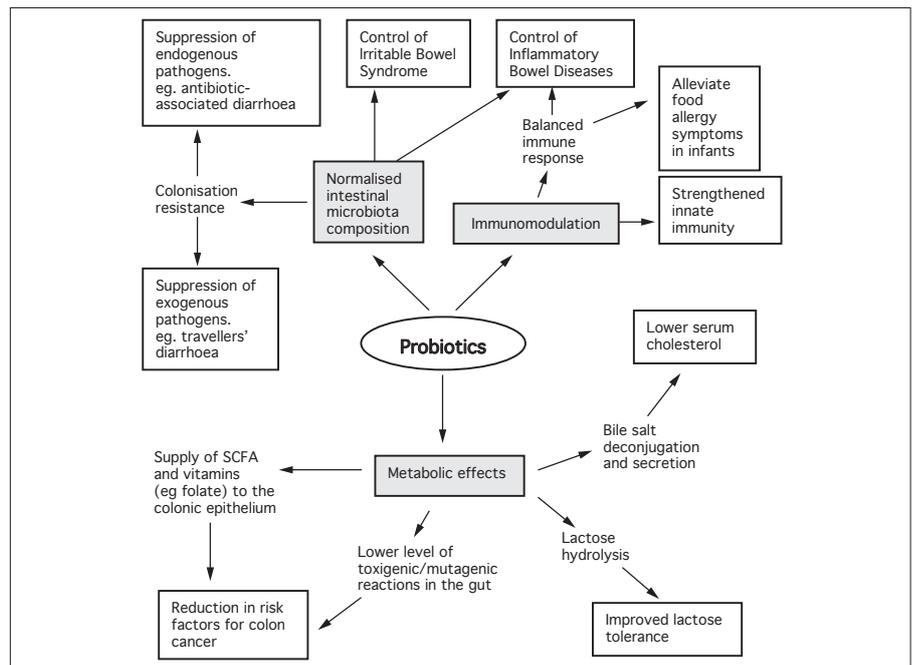


Figure 1. Possible health benefits of probiotic consumption

**Table 1. Reported Clinical Effects of some Probiotic Microorganisms**

Clinical effect	Probiotic Microorganisms
Immune stimulation	<i>Lactobacillus acidophilus</i> , <i>L. casei</i> , <i>L. rhamnosus</i> , <i>L. plantarum</i> , <i>L. delbrueckii</i> , <i>L. johnsonii</i> , <i>Bifidobacterium bifidum</i>
Antibiotic-associated diarrhoea	<i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>Saccharomyces cerevisiae</i> (str. Boulardii), <i>B. longum</i> , <i>Enterococcus faecium</i>
Travellers diarrhoea	<i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>B. bifidum</i> , <i>Streptococcus thermophilus</i> , <i>L. johnsonii</i> , <i>S. cerevisiae</i> (str. Boulardii)
Recurrent <i>C. difficile</i> colitis	<i>L. rhamnosus</i> , <i>S. boulardii</i>
Anti-tumour	<i>L. acidophilus</i> , <i>L. casei</i> , <i>L. plantarum</i> , <i>L. delbrueckii</i> , <i>L. gasseri</i> , <i>B. longum</i> , <i>B. bifidum</i> , <i>B. adolescentis</i> , <i>B. infantis</i>
Rotavirus diarrhoea	<i>L. rhamnosus</i> , <i>B. bifidum</i> , <i>S. thermophilus</i>
Acute diarrhoea	<i>B. bifidum</i> , <i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. acidophilus</i> , <i>E. faecium</i> , <i>L. rhamnosus</i> , <i>L. reuteri</i>
Balancing of intestinal microbiota	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i> , <i>L. plantarum</i>
Lactose intolerance	<i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. rhamnosus</i> , <i>L. johnsonii</i>
Lowering faecal enzyme activities	<i>L. rhamnosus</i> , <i>L. casei</i> , <i>L. gasseri</i> , <i>L. delbrueckii</i> , <i>L. acidophilus</i>

A study on the commercially available *Lactobacillus bifidus* supplements, however, has never been reported. In this report, the viability of *Lactobacillus bifidus* in four different brands of products from the market after treatment with artificial stomach solution was studied and examined. When one of the products was reformulated, the viability of the microorganism in different pH was found different. Our results indicate that preparation and formulation of a probiotic preparation could have significant impact on the resistance of *L. bifidus* to the acidic environment.

**EXPERIMENTAL**

**Samples**

Samples of four commercial probiotics products were purchased from the market. The details of these products are tabulated in Table 2.

Table 2. Sample of probiotics products used in this study			
Sample	Brand	Lot No.	Origin
A	KOLON KXX	01/93692	USA
B	PrXXX 7	6534015	France
C	BXXX + FIBER	Unknown	Japan
D	BISXXX 100	HS BI 9906	Japan

**Methods**

Artificial stomach solutions at pH 2.5 and 3.5 were prepared and used for serial dilution of the provided samples of bifidus products. The diluted samples were kept in the artificial stomach solutions for one hour or for three hours with regular shaking before their pH were adjusted 6.5. The number of cells per gram of the tested samples was derived from viable count after an aliquot of diluted samples was spread onto reinforced Clostridial medium agar plates. The plates were incubated at 37°C from 1-3 days under anaerobic conditions. Samples diluted in distilled water were treated as controls. The number of colonies formed on each agar plate was counted from three plates

and were presented as percentage of bacterial colonies after each treatment compared to the control.

The sample D was reformulated and named as D'. The viability of *Lactobacillus bifidus* in pH 2.5 and 3.5 and 7.0 was studied using the method as described above.

**RESULTS AND DISCUSSION**

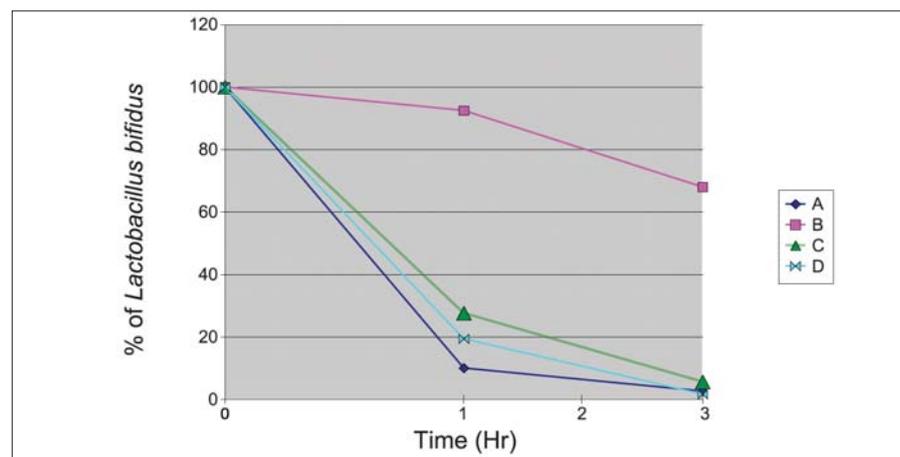
**Effect of pH on the viability of cells**

The effect of pH on the viability of cells was summarized in Figure 1-3.

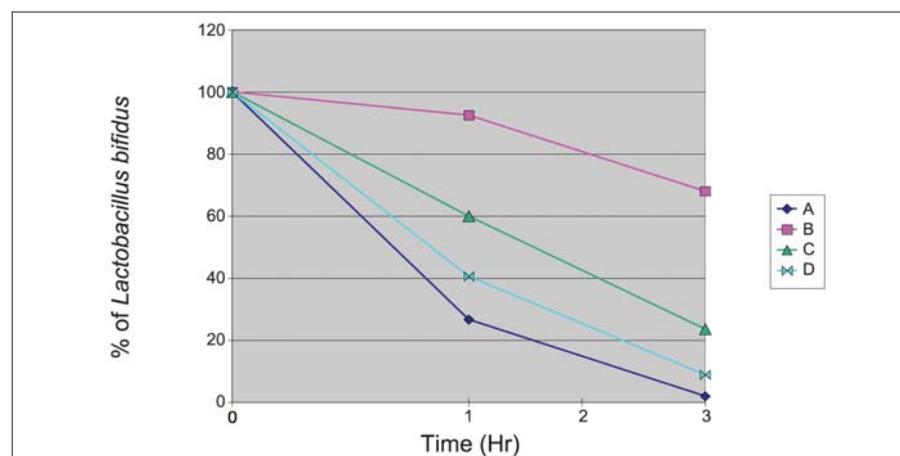
In all samples, the viability of *Lactobacillus bifidus* dropped as pH became more acidic. Sample B exhibited the greatest stability while sample A showed the weakest stability in the different pH levels. In the simulation of acidic environment in the stomach (pH 2.5 and pH 3.5), the degree of stability is summarized as follows: B>C>D>A. In acidic environment of pH 2.5 for 3 hours, sample B outperformed all other samples by 3.8 to 13.1 times. A more significant result was found in pH 3.5, sample B outperformed all other samples by 2.9 to 26 times when it was exposed for 3 hours.

It was observed that the viability of *Lactobacillus bifidus* dropped as pH became more acidic. It is expected, since pH could change the hydrogen-ion equilibrium at the active center or alter the active structure of *Lactobacillus bifidus*.

Among all samples, sample B was found to have the greatest performance in terms of viability. It is postulated that sample B contains the greatest range and number of lactobacilli that could less alter the active structure of *Lactobacillus bifidus*. While the microbial ingredients of sample A, C and D remained commercially confidential, it was claimed of sample B that it contained 7 species of lactic acid



**Figure 1.** Viability of *Lactobacillus bifidus* in pH 2.5.



**Figure 2.** Viability of *Lactobacillus bifidus* in pH 3.5.

**Author's background**  
**CHEUNG Hon-Yeung** is an Associate Professor of Pharmaceutical Microbiology & Biotechnology of Department of Biology & Chemistry, City University of Hong Kong.

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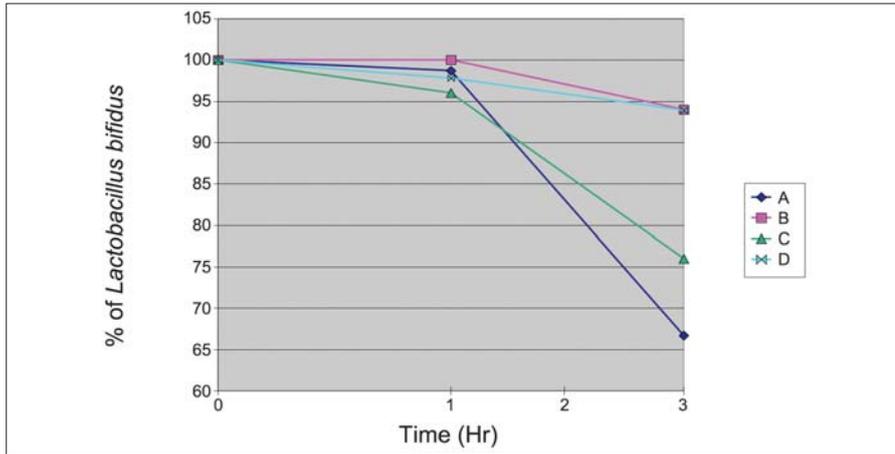


Figure 3. Viability of *Lactobacillus bifidus* in pH 7.0

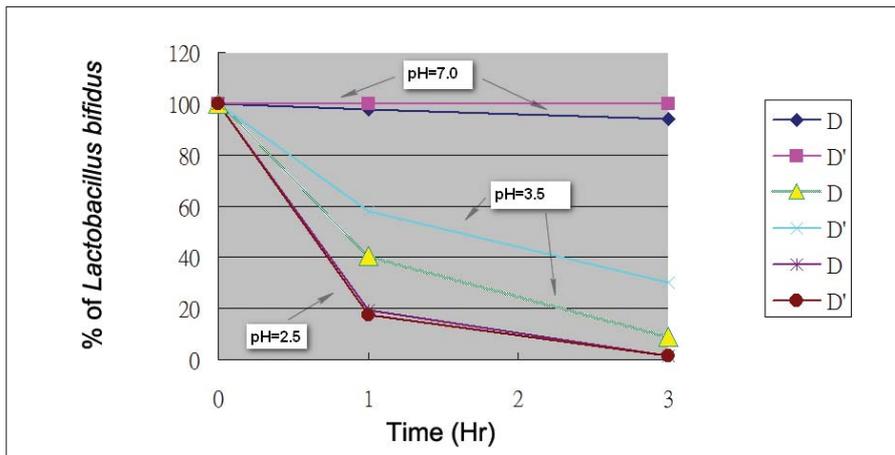


Figure 4. Viability of *Lactobacillus bifidus* in pH 7.0, 3.5 and 2.5 after reformulation.

bacteria, including *Lactobacillus bifidus*, *Lactobacillus bulgaricus*, *Lactococcus lactis*, *Streptococcus thermophilus*, *Lactobacillus casei*, *Lactobacillus acidophilus*.

**Effect of formulation on the viability of cells**

The effect of pH on the viability of cells after reformulation of sample D, is summarized in Figure 4.

The performance of sample D' in terms of its viability after reformulation was generally improved. In pH 7.0, the stability of sample D' was significantly improved. No loss of *Lactobacillus bifidus* was found in sample D when it was compared to the sample without reformulation. Sample D' was 1.9 times better than the original sample D after exposure in pH 3.5 for 3 hours. However, in a more acidic environment in pH 2.5, sample D' performed equally as its original sample D.

The performance of sample D' in terms of its viability after reformulation was significantly improved. As the reformulation is commercially confidential, some common methods could be postulated to explain its improvement on

the viability. F varo-Trindade reported the microencapsulation of *Lactobacillus* could improve the viability of cells.<sup>(19)</sup> DING conducted research in microcapsules made of alginate, xanthan gum, and carrageenan gum and greatly improved the survival of probiotic bacteria when exposed to acidic conditions.<sup>(20)</sup>

Antioxidants also perform an important role in enhancing the viability of probiotic bacteria. Shah reported that the juice containing vitamin C, an antioxidant, have a protective effect on probiotic cells during storage, presumably because it is an oxygen scavenger.<sup>(21)</sup>

**CONCLUSION**

Acidic pH conditions in the stomach could weaken the viability of *Lactobacillus bifidus* and hence reduce its beneficial effects. Sample B demonstrated the greatest performance in terms of viability in the acidic pH environment. Besides, reformulation of probiotic supplement could significantly strengthen the viability of *Lactobacillus bifidus* in acidic environment. Consumers were advised to purchase suitable supplements with the greatest strengthen in viability to obtain the maximum effect of probiotics.

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## News: Pharmacy Conference 2011

While you are still recalling having fun in the Pharmacy Conference early this year, the organisation work of Conference 2011 has been started.

The Organisational Committee has just

formed (as shown in the table below). A few positions are pending but will be confirmed very soon.

The Hong Kong Pharmacy Conference 2011 will be held as follows:

**Date:** 26-27, February, 2011

**Venue:** Hong Kong Convention and Exhibition Centre, 1 Expo Drive, Wanchai, Hong Kong.

**Mark your calendar for the event!  
Stay tuned for further news of Pharmacy Conference 2011!**

Subcommittees	Post	Appointed Person			
<b>Organizing</b>	Chairperson	Iris Chang			
	Vice-Chairperson	Godfrey Lui			
<b>Secretarial</b>	Secretary	Tracy Lee			
<b>Programme</b>	Coordinator	Vivian Lee	Gloria Hung	Keary Zhou	Michael Ling
		Teresa Ngan	Elaine Lo	Ritchie Kwok	
<b>Finance</b>	Coordinator	Eric Wong	Patrick Liu		
<b>PR and Liaison</b>	Coordinator	Benjamin Kwong			
<b>Site &amp; Dinner / Gimmick</b>	Coordinator	Jacky Chan	Michael Yim	Michael Lau	Ng Ting Fung
<b>Registration</b>	Coordinator	Judy Kwok	Heidi Chan	Vincent Tsui	
<b>Publication</b>	Coordinator	Amy Chu	Joe Leung	Sylvania Ho	Karen Wong
<b>Account</b>	Treasurer	<i>To-be-confirmed</i>			
<b>Intern/ Poster Presentations</b>	Coordinator	Susan Ho			
<b>Photography</b>	Coordinator	---			
<b>IT</b>	Coordinator	Tom Chan			
<b>Master of Ceremony</b>	Master of Ceremony	<i>To-be-confirmed</i>			

## Newly elected General Committee/Council members of the three pharmacist societies/association

### The 39<sup>th</sup> G.C. of Practising Pharmacists Association of Hong Kong (PPA) 2010 - 2011:

President:	Ms. Iris Chang			
Vice-President:	Mr. Godfrey Lui			
Vice-President:	Dr. Yanji Leung			
Hon. Treasurer:	Mr. Bernard Tang			
Hon. Secretary:	Dr. Yan Chung			
GC:	Mr. Kevin Cheung	Mr. Tom Chan	Mr. Jacky Chan	
	Mr. Gordon Lee	Dr. Christy Sung	Mr. James Ho	
	Mr. Foster Cheung	Mr. Ng Hei (Wu Hsi)		

### The general committee members and office bearers of the Pharmaceutical Society of Hong Kong (PS) 2010:

President:	KWONG Benjamin		
Vice President:	CHENG Mary Catherine		
Treasurer:	LAM Anson		
Secretary:	LEUNG Peter		
General Committee Members:	CHAN Shirley	CHIANG Sau Chu	LAM Daisy
	LEE Vivian	LEUNG Kenneth	NG Brian
	SUEN Peter	TAI Candy	TSANG Warren
	YAU Rico	YIU William	

### The general committee members and office bearers of Society of Hospital Pharmacists of Hong Kong (SHP) 2010:

President:	SO Yiu Wah		
Vice President:	CHUI Chun Ming William		
Treasurer:	LAI Oi Lun Ellen		
Secretary:	NG Long Yee Stephanie		
General Committee Members:	CHAN Man Chi, Sarah	CHAN Wing Lam Phoebe	CHEUNG Ka Lung Kenneth
	CHUNG Wing Fai Kenneth	HUI Hoi Yun, Helen	KWOK Ching Chi, Ritchie
	LAM Po Yu Daisy	LO Cheuk Hang Charles	NG Man Keung
	PANG Ying Ho, Bobby	WONG Sze Ho, Johnny	

# THE IMPOSSIBLE DREAM: Interview with Professor Kenneth LEE

**WONG, Helen**  
MSD(HK) Sigma Manager

## ABSTRACT

Professor Kenneth Kwing-Chin Lee is a world-renowned scholar in pharmaceutical science, particularly in pharmacoconomics which is his area of interest. Besides being actively involved in outcomes research, he has been highly devoted to pharmacy education. One of his well-recognized achievements is the establishment of the first pharmacy school in Hong Kong, and subsequently the production of batches of local passionate pharmacists. This article summarizes an interview with this scholar when he recently decided to leave Hong Kong and seek a greater opportunity to contribute to the pharmaceutical universe.

**Keywords:** education, profession, pharmacy, student, Chinese University of Hong Kong (CUHK), Monash University

It was a scorcher in July. I could really feel the heat of the sun on my back as I was walking in the campus of the Chinese University of Hong Kong (CUHK). Not even having the foggiest idea of the way to the School of Pharmacy, I finally managed to arrive at the place with sweat dripping off the body.

An important appointment with Professor Kenneth Lee (Ken) was in fact the passion that drove my way. Accompanying me for the interview included Dr. CHEUNG

Hon-Yeung, the Chief Editor of Hong Kong Pharmaceutical Journal (HKPJ), and Mr. Joe LEUNG, a pharmacy intern.

First and foremost, Ken is a pivotal contributor to the Hong Kong pharmacy profession. Throughout the years, he had been proactively participating and contributing in lots of pharmacy professional activities. His enthusiastic dedication to pharmaceutical education deserved him a renowned reputation in this field. Ken was one of the founding members of the pharmacy technical course at Vocational Training Council [which was later transformed into Pharmaceutical Technology Program at The Hong Kong Institute of Vocational Education (IVE)], as well as the Pharmacy degree program in CUHK (See Table 1).

Nevertheless, such an influential and reputable talent will soon leave us for the next challenge in his life – Ken has accepted an offer at the Monash School of Medicine and Health Sciences, Sunway Campus, Malaysia, as a Professor of Pharmacy and the Head of Pharmacy Programme. That's why three of us were willing to grasp this valuable chance to meet him up before his departure regardless of the need to experience a tough walk under the sun.

## A DIFFICULT DECISION

'Can you tell us why you decide to leave

CUHK for Malaysia after having served the School for 18 years?' I asked directly and unambiguously. It should not be an easy decision to him.

'It is definitely not an easy decision for me. When I was approached for this opportunity, it was difficult to decide. I struggled and hesitated. Finally I asked myself "if I let the opportunity go, would I regret?"' At that point, Ken had a decisive answer to the question. He knew what he should do.

'Besides, you know my personality. I don't like to be "restricted".' He added. Nodding with a smile, I recalled how he thought of different alternatives and proactively made suggestions to solve problems with the clerkship partners, when the Pharmacy Clerkship Programme was initiated years ago. 'More importantly, it is a golden chance for me to test myself. It seems that I just have some little achievements in HK. I'd like to see if I can also achieve something at the international level,' he spilled out the last but probably the most critical reason. To him, Monash University is a well-known academic institution where he could take a step forward to approach and contribute to a bigger pharmaceutical universe at large.

Ken said the Pharmacy Programme at CUHK had been running maturely on the right track. All the teaching staff had a strong consensus on how to continue and further develop it. Even with his departure, he told us he expected nothing but an upgrading of the overall academic and professional standard. As for the change of curriculum from 3 years to 4 years in 2012, the School had actually completed the essential foundation work. He expressed these were the reasons behind which made him feel comfortable to leave the School of Pharmacy at this moment in time.

Ken will keep serving as an adjunct professor in CUHK basically for research purpose. He will continue to take care of the remaining on-going research projects in HK. He is also willing to consider any new research projects in the future, whether as a project supervisor or a consultant, to share his expertise in the areas of study design, data analysis and scientific reporting.

## THE MONASH UNIVERSITY SUNWAY CAMPUS

Ken will leave HK in early August 2010 and formally report duty to the Monash University Sunway Campus, Malaysia.

Monash University (Monash) is a public university based in Melbourne, Australia. It was founded in 1958 and is the second oldest university in the Victoria State. Each year, Monash enrolls approximately 39,000 undergraduate and 16,000 graduate students from Australia and across the globe, making it the largest university in Australia.<sup>(1)</sup> Monash has an entrepreneurial strategy that Ken

Table 1: Prof. Kenneth Lee's mini-file	
<b>FULL NAME</b>	LEE, KWING CHIN KENNETH BSc (Pharm) MPhil PhD Reg Pharm (HK)
<b>ACADEMIC QUALIFICATIONS</b>	University of Oxford The Chinese University of HK The Chinese University of HK University of Washington, Seattle (Awarded with the University of Washington School of Pharmacy Dean's List in 76-77 and 75-76)
<b>EMPLOYMENT HISTORY</b>	Professor of Pharmacy and Head of Pharmacy Programme Monash School of Medicine and Health Sciences, Sunway Campus, Malaysia Associate Director (External Affairs), School of Pharmacy, CUHK Professor, School of Pharmacy, CUHK Associate Professor, School of Pharmacy, CUHK Assistant Professor, School of Pharmacy, CUHK Lecturer, School of Pharmacy, CUHK Senior Lecturer, Vocational Training Council, Hong Kong Director of Pharmacy Service, Tsuen Wan Adventist Hospital, Hong Kong
<b>HONOURS</b>	Appointed Justice of the Peace, Hong Kong
<b>MAJOR AREA OF RESEARCH INTEREST</b>	Health Economics/Pharmacoconomics
<b>CURRENT SERVICES TO HONG KONG GOVERNMENT COMMITTEES</b>	1. Member, Pharmacy Internship Training Committee, Pharmacy & Poisons Board of HK 2. Examiner, Examination Committee, Pharmacy & Poisons Board of HK 3. Member, Review Committee on Regulation of Pharmaceutical Products in Hong Kong 4. Member, Research Advisory Group, Action Committee Against Narcotics (ACAN)
<b>CONTRIBUTIONS TO THE PHARMACY PROFESSION</b>	1. Vice-Chairman and CUHK liaison person, Pharmacy Central Continuing Education Committee (3/00-1/01) 2. Convenor, Working Group on CE programmes for Practising pharmacists of Hong Kong (10/98-3/99) 3. Supervisor and Advisor, exhibition on "Pharmacists and Public Health" organised by the student Pharmacy Society of CUHK (8/96) 4. Chairman, Ad Hoc Committee for the campaign of CUHK Pharmacy course (88-90) 5. Member, Organising Committee of Exhibition on "Labelling of Dispensed Medicines" (11/89) 6. Member, Organising Committee of Exhibition on "Gastrointestinal Drugs and You" (12/85) 7. Editor, The Journal of Practising Pharmacists of HK (85-89) 8. President, The Pharmaceutical Society of HK (89-93, 94-95) 9. President, The Practising Pharmacists Association of HK (87-88, 88-89, 89-90)

admired. It has eight campuses scattered worldwide: six in Australia, one in Malaysia and one in South Africa. Monash has a research and teaching centre in Italy, as well as a graduate research school in India.

Monash's Sunway Campus is located close to Kuala Lumpur. It has six schools, in which the School of Medicine and Health Sciences offers a Bachelor degree of Pharmacy. Monash has a long history in offering medical and pharmacy degree courses in Australia. The Sunway Campus is positioned as a private university and mainly targets for local students. (See Table 2)

**Table 2: Monash University and the Sunway Campus**

**Facts about Monash University and the Sunway Campus**

Monash has a history of providing medical, surgical and health sciences training that is recognized and respected worldwide for its excellence. In the 2009 rankings of universities worldwide carried out by the THES (Times Higher Education Supplement) in Britain, Monash has been ranked 25th with respect to the life sciences and biomedicine.

On 23 February, 1998, the Malaysian Ministry of Education forwarded Monash University an invitation to set up a campus in Malaysia jointly with Sunway Group. Monash University Sunway Campus was established in 1998 and is the first offshore campus of Monash University outside Australia. As one of eight Monash campuses around the world, it shares the same status as every Monash campus and is subject to the same rigorous standards that govern the University's academic development, teaching and support, admission requirements, curriculum and assessment. The doors were opened for the first time to 261 students in July 1998. In 2007, Monash University officially opened its new Sunway campus, marking a major milestone for the university's presence in Malaysia.

The current Sunway campus was purpose-built in 2007 at a cost of some RM200m. At present there are about 4,500 students and 500 staff, with growth projected to lead to over 6,000 students and 600 staff. About one quarter of the student body is international. Its degrees in Medicine and Surgery (MBBS) are the first medical degrees outside Australia and New Zealand to be accredited by the Australian Medical Council.

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Per the estimation announced by the Minister of Health of Malaysia, the country currently lacked sufficient pharmacists to serve the community. Malaysia needed at least two to three times the existing number of pharmacists to fulfill the pharmacist-to-population ratio as recommended by the World Health Organization (WHO). The Universities and Pharmacy Programmes offered in Malaysia are listed in Table 3. It is not surprising to see that the School of Medicine and Health Sciences has a direction to fill the country gap. The Programme has just started for one and a half year with about 40 students in total. Ken is given a task to increase the yearly intake of students to 120 over the next three to four years, or even sooner.

The BPharm Programme in the Sunway Campus is designed with a focus on "Drug Safety" through various disciplines, not limiting itself to drug delivery, pharmacy practices and clinical pharmacy.

**Table 3: Pharmacy Programmes in Malaysia**

*How many universities in Malaysia offer pharmacy programs?*

Pharmacy programs, no matter BPharm, MPharm, MPhil or PhD in Pharmacy, have been getting hot in Malaysia in recent years. They are offered through various kinds of arrangements, ranging from pure local universities, collaborations between local & overseas universities to foreign universities with campuses established in Malaysia locally.

Below is a glance of those universities offering pharmacy programs in Malaysia. Yet, it may not represent a full list.

- University of Malaya
- University Kebangsaan Malaysia
- Universiti Sains Malaysia
- International Islamic University Malaysia
- Universiti Teknologi MARA
- Island College of Technology
- Cyberjaya University College of Medical Sciences
- UCSI University
- Segi University College<sup>1</sup>
- International Medical University<sup>2</sup>
- University of Nottingham (Malaysia Campus)<sup>3</sup>
- University of Monash (Sunway campus)

<sup>1</sup> MPharm is awarded by University of Sunderland, UK

<sup>2</sup> MPharm is offered in collaboration with the University of Strathclyde in Scotland.

<sup>3</sup> A UK based university which is listed as the best school of pharmacy in UK in most of the recent years.

Ken's most important aim is to have the BPharm Programme accredited by both Australian and Malaysian Pharmacy Boards. That means the pharmacy graduates from the Sunway Campus can directly register as pharmacists in both Australia and Malaysia. It is logical to have the qualification recognized by the Malaysian Board, but why is there a will to have the programme recognized by the Australian government also?

Ken explained, 'That is all because of the close resemblance of the courses itself. The curriculum of BPharm courses offered in the Sunway Campus is exactly the same as that of the BPharm course in Monash Melbourne. Since the Monash Melbourne Pharmacy programme has a long established reputation in the Australian society, the Pharmacy Board of Australia is willing to consider an accreditation for the Pharmacy course in Sunway Campus.' He then added, 'the reason why I must arrive in Malaysia in early August is the first accreditation visit by Australian Pharmacy Board. The visit has been scheduled on 2<sup>nd</sup> and 3<sup>rd</sup> of August. You know...Although I don't know the course details at this stage, I still need to be present in their visit.'

As a matter of fact, the Sunway Campus has just received an accreditation from the Australian Medical Council for medical practitioners. Students who successfully complete the MBBS (Bachelor of Medicine, Bachelor of Surgery) Programme in Sunway Campus are now eligible for direct registration in both Malaysia and Australia as practicing physicians.

Another top item in Ken's priority list is the recruitment of teaching staff. To prepare for development of the Pharmacy Programme in Sunway Campus, he needs to recruit more senior staff to reach a target teacher-to-student ratio of 1:9 to 1:10.

**THE UNFORGETTABLE ORIENTAL DAILY NEWS**

'Looking back your years at CUHK, what impressed you the most?' I tried to pick bits and pieces from his memory.

After thinking for a moment, Ken slightly raised his head and replied, 'I remember a news report from the Oriental Daily in around 1998. In fact, I still keep the newspaper clipping to continuously remind myself that "we must make the [CUHK] Pharmacy programme better".'

If you are old enough, you may recall the difficulties that Hong Kong pharmacy graduates faced in the late 1990's. At that time, there were very limited pharmacist vacancies in the hospitals, Department of Health and retail pharmacies. Some CUHK pharmacy graduates, although quite unwilling, worked in non-pharmacist positions. There were also complaints within the profession saying that new graduates had an adverse impact to the salary level of community pharmacists. The Oriental Daily news used a sarcastic tone to report the difficult employment situation at that time with some exaggerations. The School was blamed to have caused a waste of young talents in Hong Kong.

Ken supplemented, half-laughed and half-seriously, "Since that Oriental Daily news, CUHK Pharmacy had a tough period for about 5 years. In those 5 years, the public could merely remember "graduates' unemployment" when talking about the School of Pharmacy at CUHK. The situation only started to change gradually after the SARS outbreak in 2003. General public appreciated the services and assistance provided by pharmacists during the hardship. They later on realize what pharmacists could help them in their normal daily life. Coupled with the rapid expansion of the two community pharmacy chain stores, pharmacists' professional image and reputation have been uplifted in the mind of the general public. With all these, the demand for pharmacy graduates increases continuously in recent years.'

Yes, I agree that the toughest time for CUHK School of Pharmacy has passed. All of our pharmacists are pleased to witness this. Today, the majority of the pharmacy graduates can work for a career they are interested in. Even though a few of them may not choose to work in the traditional pharmacy profession, these are merely attributable to their choices to pursue dreams elsewhere. This improvement is not only because of the employment market or the two chain drug stores, but also because of the uninterrupted efforts inputted by each party in the profession, including CUHK School of Pharmacy itself, various pharmacy professional societies and associations.

**PHARMACY PROFESSION IN HONG KONG**

Another interesting topic that we asked Ken to comment was about the issue of Separation of Prescribing from Dispensing (SPD). This is currently a controversial topic in the society. Despite several government healthcare/health reform consultation papers suggesting the implementation of SPD over the past two decades, there is still little consensus in the local context. The Hong Kong Government also does not show a tendency to implement SPD in the near future.

Ken's non-traditional view towards this issue caused surprised me a little bit. Nevertheless, I think it is consistent with his personality: he does not like to be 'restricted' to 'the way'.

Ken said, 'I personally think that the Singapore model may work for Hong Kong. I believe Hong Kong will have SPD sooner or later in terms of practice, but may not come with a change in the regulations. Singapore used a rather soft and native approach to execute SPD. This is more sustainable and acceptable in my opinion. It won't jeopardize the cooperation among professionals.'

'I have doubt in using legislative approach for SPD. This would likely lead to conflicts between medical and pharmacy professions, and also within our own profession.' He clearly indicated there were objection voices toward SPD from within the profession several years ago. This could probably be the biggest obstacle for the legislative approach.

As indicated by Ken, Singapore has no regulation mandating SPD. Her situation was similar to Hong Kong few years ago. However there had been an obvious elevation of pharmacists' social status and reputation there in the recent years. The small group of Singaporean pharmacists was very united. They behaved professionally and consistently demonstrated their values to the general public throughout the years. Notwithstanding a lack of SPD regulation, the actual practice in Singapore today is not too far from SPD. The public respect pharmacists. They recognize their knowledge. They are used to go to community pharmacies to seek for consultation on minor illnesses or health problems.

Another difficult question for Ken in the meeting arose from the troublesome interviewers: why does CUHK not offer a Master of Pharmacy (MPharm) or PharmD which are getting popular overseas?

Ken told HKPJ, 'The School is actually looking at PharmD as an option for students, rather than a must.' He explained, as a responsible public university, CUHK could not open a new course because of the popularity. The way they looked at it was the demand for the 'product' from the society in the foreseeable years. The students' affordability is another issue. If the new course is not subsidized by the government, there may be three to four academic years requiring full tuition fees from the students. If the demand gets much more certain in the future, the School would definitely work on it.

## PHARAMCY STUDENTS

As one of the founding members of the CUHK School of Pharmacy, Ken is looking at the development of the School as well as his students. He has undetectable feelings towards his students. Every time when you ask him how he thinks about the students, he will tell you they are great. This time, not an exception, 'Oh, the students, they are great! They have outstanding academic results. They are very proactive in their study. You don't need to push them. At the same time, they are not only good at studying. CUHK Pharmacy students are truly exemplifying the motto "Work hard, Play hard." They...'

he replied to my question in a proud tone. I found that I could not stop him on this topic. Ken passionately gave us different examples. One can certainly tell how much he likes his students.

However, he suddenly slowed down the rhythm of the conversation, "But I do see a trend in the recent two to three years. This is not something unique to pharmacy students. The whole society is having this common problem. Although the students still have outstanding academic results, their level of maturity is dropping. This is not only from my observation but also consistently from the feedback provided by the hospitals and pharmaceutical industry."

"This phenomenon is definitely associated with the way the children grown up nowadays. They face the computers, a virtual world, more than the real world. In the virtual world, there is no need to handle human relationships and interactions with people. There is no such thing as EQ [emotional quotient]. They tend to be more self-centered. I think this is also significantly related to the secondary education in Hong Kong."

'The School is worried about this, particularly because pharmacy profession is at the initiation phase in Hong Kong. If our students cannot give a right presentation to the public, it will adversely affect the development of this profession. This is not an easy task for us. Our staff is thinking of better ways to strengthen students in this area before they graduate.'

At the moment, apart from the General Education curriculum mandated by CUHK for all students, School of Pharmacy offers student consultation and relationship management services to assist students in closing the gap. HKPJ was told by the School that they plan to launch a mentorship programme next year with the [CUHK Pharmacy] Alumni. The School strives to bring in senior graduates as mentors to the juniors. Hopefully the mentorship programme can bring in value for the students.

## REACH THE IMPOSSIBLE DREAM – EVERYONE CAN DO IT!

'How about your cello? Will you take it with you?' I asked. Many fellow pharmacists should remember Ken likes music very much and he can play several musical instruments. Among those instruments, he likes cello the most and he is a good cellist. 'I will leave it in Hong Kong for my son who is now studying music and who can play cello really well. The cello is heavy too. I don't want to damage it during shipment. Moreover, the flight from Malaysia to Hong Kong is about three hours only. I can come back very often,' Ken replied.

Ken said to HKPJ the most challenging thing for his move is actually the weather in Malaysia. He does not like hot weather and somewhat wonder how himself can survive in the heat. Apart from that, almost everything has been settled there such as accommodation. Ken added, 'but there is one last item I need to arrange. I need to get myself a car as soon as possible. Otherwise I can't go anywhere!' We laughed and chatted about the life in Malaysia.

Time flew. The interview time was over. We must let Ken go. Just before leaving, Ken

seriously handed a piece of paper to us. That was the song 'The Impossible Dream' (see Table 4).

Table 4: The Impossible Dream

**"The Impossible Dream"**  
*from MAN OF LA MANCHA (1972)*  
*music by Mitch Leigh and lyrics by Joe Darion*

**To dream the impossible dream**  
**To fight the unbeatable foe**  
 To bear with unbearable sorrow  
 To run where the brave dare not go

To right the unrightable wrong  
 To love pure and chaste from afar  
 To try when your arms are too weary  
 To reach the unreachable star

This is my quest  
 To follow that star  
 No matter how hopeless  
 No matter how far

To fight for the right  
 Without question or pause  
 To be willing to march into Hell  
 For a heavenly cause

And I know if I'll only be true  
 To this glorious quest  
 That my heart will lie peaceful and calm  
 When I'm laid to my rest

And the world will be better for this  
 That one man, scorned and covered with scars  
 Still strove with his last ounce of courage  
**To reach the unreachable star**

Ken looked at Joe and said, 'It is something I want to share to the younger generation and may be your juniors in the future. If you think I have some achievements in my life. I can tell you, throughout my life, there were obstacles and challenges. Every time when I faced a difficulty, I reminded myself with this song. It has very meaningful lyrics: "To dream the impossible dream; To fight the unbearable foe". But the set of words inspired me the most is "To reach the unreachable star". This is one of my favorite songs.'

The difficult times were condensed by Ken in just a few statements. He pointed to the lyrics and continued in a firm but sincere voice, 'they strengthened me and helped me to pursue my dreams.' In the whole interview, this was the only thing he urged the HKPJ to publish.

I have to say thanks to Ken, on behalf of HKPJ and the younger generation. Firstly, I asked for the interview at a short notice. His flexibility and kind cooperation is highly appreciated. More importantly, I think he accepted the invitation because he would like to use himself as an example. He wants to encourage the pillars of our future to pursue their dreams, regardless of the barriers in front of them. We all know life is never easy, especially in today's fast-moving world.

### Author's background

**Ms. Helen Wong** graduated from the University of Sydney and she is currently working for MSD(HK) as a Sigma Manager. She has a wide spectrum of experience in the industry, ranging from Regulatory Affairs to Clinical Research. During her spare time, she also spends a lot of time in helping the Pharmaceutical Journal as the Section Editor of the Pharmacy Practice. E-mail address of the author: helen\_wong@merck.com

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## 攀摘星辰 - 李炯前教授訪問後記

知道了李炯前教授即將離開中大，前往馬來西亞赴任 Monash University 藥劑部開山祖師的消息；當下便向HKPJ的編輯自薦一同前往採訪這位認識了五年的學者。也許，這是作為學生的我可以送別他的一種方式。

訪問前，我試著搜集了李教授的背景資料，這才慢慢領略到他一路走來的足跡：當年遠赴美國唸藥劑；回流後考牌所要克服的困難；為當時在港還不成氣候的藥劑業不斷爭取應有的地位；在中大扎根與同道中人一起打造了全港第一所藥劑學院，教育出數以百計貢獻社會的藥劑師；屈指一算，李教授把數十年的時光奉獻了給藥劑業。成功，除了需要不斷堅持，還有賴他對醫藥所抱持著的熱誠與追求。

回望學生時代對李教授的認識，很淺。印象最深刻的一次是上Dispensing課的時候；我們都在吃力地製作著油油膩膩的suppository，全班很多同學（當然包括我）的成品總是失敗，李教授於是親身示範。‘很久沒做這個，試試還成不成功’

他邊用沉實敦厚的聲線說著，邊乾淨俐落地造出一粒粒製成品，靈活而又不失紳士風範；那自信的動作至今難忘，當下就讓所有同學深深佩服他的真材實學。李教授認真的教學態度和逗趣幽默的作風到了現在仍為大家所敬重。

這次見到李教授，很想知道離開進駐了十八年的中大藥劑系，他有了怎樣的感悟？又是甚麼信念讓他拿出這麼大的勇氣？

在訪問的過程中，李教授謙遜地表示中大藥劑已經上了軌道，也有很多充滿熱情與理念的同事留守陣地繼續作戰，所以即使自己離開，中大藥劑亦能好好發展下去。輕描淡寫的話語中蘊含著十八年的心血，其中的感情與不捨，溢於言表。今天中大藥劑能茁壯成長李教授功不可沒。是多年來的灌溉，才成就了今天盛放了繁花；是他在任時跟其他教授一同努力不懈的打穩地基，才得以讓後人蓋建高樓。身為中大的學生，作為藥劑業的後輩；我無限感謝李炯前教授悉心的栽培。

李教授是少數為廣大市民所認識的藥劑師；多年來他憑藉無容置疑的深厚藥物知識亮相人前，好讓藥劑師的專業形象得以彰顯，一步一步為我們的行業建立領地。今天，他決定離開，是為了追尋更遠大的理想、更具意義的嚮往。李教授說很想將自己現在的得著放諸大舞台，讓世界來評價。也許每個人所追求的生活模式不一樣，但李教授從開始到現在對藥劑業的堅持如此耀目，已然贏取同行的敬仰。

離開中大，讓我們跟李教授好好道別，祝您一路順風。相信只要大家仍為了藥劑業的發展而努力前進，終於會在某地再次相遇。到了那一天，希望您悠揚的大提琴聲中一起詠唱您最愛的歌：

**實現一個不可能的幻夢。攀摘一顆不能觸碰的星辰。**

梁文藻  
二零一零年七月十六日

## Farewell to our Chief Pharmacist - Mr. Anthony Chan

**LEUNG, Peter**

*Pharmaceutical Society of Hong Kong (PSHK), Hon. Secretary*

On behalf of PSHK, I would like to congratulate to Anthony for his happy retirement.

We like to express our sincerely thanks to Anthony for his invaluable support to our pharmacy profession & PSHK in the

past, especially his tremendous support in our yearly event on hosting forensic lecture series for the overseas' pharmacy graduates.

Apart from the words of wisdom and pharmaceutical knowledge that you

have generously tendered at different occasions, we will also miss your sense of humour which made an otherwise frigid process lively and interesting.

Wishes you all the best & take good care! Goodbye!



Participants at Farewell dinner of Anthony Chan organized by P&PB Licensing Committee



Participants at Farewell dinner of Anthony Chan organized by PSHK

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## Probiotics and Necrotizing Enterocolitis

LI, Sin Man

United Christian Hospital, Kwun Tong, Hong Kong SAR, China

### ABSTRACT

**Necrotizing enterocolitis is a gastrointestinal emergency; commonly occurred in preterm infants. It has high mortality and morbidity. Current clinical management is primarily targeted at limiting the disease progression. Since abnormal colonization of intestinal tract is believed to play a major role in the cause of disease, probiotics have been used for the prevention. Probiotics are live microorganisms which offer a health benefit on human. Their applications have been associated with a number of health benefits including in diarrhoea, cancer and genitourinary disorders. Randomized controlled studies have shown that probiotics reduce the incidence of necrotizing enterocolitis and death in preterm neonates. Probiotics are generally considered safe to be used in children. These results support the use of probiotics on the prevention of necrotizing enterocolitis in preterm infants, particularly those of very low birth weight (<1500g). However, the optimal prophylactic probiotic regimen is not well known and further studies are needed before incorporating into routine practice.**

**Keywords:** Probiotic agents; Necrotizing enterocolitis; *Bifidobacteria*; *Lactobacillus*; Health benefits

### INTRODUCTION

In 1907, Metchnikoff conducted the first scientific assessment of probiotics. He stated that “the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes”.<sup>(1,2)</sup> However, the word “probiotics” was only devised in 1960. In 2001, joint Food and Agriculture Organization of the United Nations and World Health Organization expert panel gave a universal definition for probiotics, which is “live microorganisms which when administered in adequate amounts confer a health benefit on the host”.<sup>(3)</sup>

Not all microorganisms can be considered as probiotics. They must be of human origin and non-pathogenic. Probiotics are usually given orally. Stability in gastric acid and bile would allow them to preserve the benefits until the delivery to the target site. Probiotics should be able to persist in the gastrointestinal tract and attach to the target epithelial tissue. They should have the ability to produce antimicrobial substances, modulate the immune system and influence metabolic activities.<sup>(4)</sup> *Lactobacillus*, gram-positive bacteria and *Bifidobacteria* are commonly used probiotics in human.

The use of probiotics is associated with a number of health benefits including in diarrhoea, immunity, cancer and genitourinary disorders.<sup>(2)</sup> There are various paediatric uses of probiotics including alleviating lactulose tolerance and management of allergic diseases.<sup>(5,6)</sup> Among them, the applications in gastrointestinal diseases have been most extensively studied and their efficacy in the treatment and prevention of diarrheal diseases is well-established.<sup>(6,7)</sup>

In this article, we are going to review the application of probiotics in neonatal necrotizing enterocolitis and the safety of probiotics for use in paediatrics.

### NECROTIZING ENTEROCOLITIS

Neonatal necrotizing enterocolitis is the most common gastrointestinal emergency in neonates. In every 1000 live newborn infants, there are about 1 – 3 of them experience necrotizing enterocolitis.<sup>(8)</sup> Mortality rate ranges from 15 – 30%.<sup>(9)</sup> Prematurity and low birth weight are the most important risk factors of the disease. Preterm neonates account for 90% of all cases. The risk for necrotizing enterocolitis is inversely proportional to birth weight and gestational age. With the improvement in obstetric and neonatal care, there are more very low birth weight (<1500g) preterm infants who survive and this at-risk population for necrotizing enterocolitis continues to rise.<sup>(9)</sup>

The pathophysiology of neonatal necrotizing enterocolitis is not well-defined and is believed to be multifactorial. Physiological immaturity of gastrointestinal tract, hypoxic-ischaemic injury and abnormal colonization of intestinal tract have been proposed to be the possible contributing factors.<sup>(9-12)</sup> The onset of necrotizing enterocolitis usually occurs within the first 10 – 14 days of life.<sup>(10)</sup> Necrotizing enterocolitis is presented with both gastrointestinal and systemic signs and symptoms. Feeding intolerance, abdominal distension, bloody diarrhoea, apnoea, bradycardia, lethargy and temperature instability are commonly seen in neonates with necrotizing enterocolitis. Laboratory abnormalities such as metabolic acidosis, thrombocytopenia and leukopenia are also observed.<sup>(9-12)</sup> However, these clinical presentations are non-specific and common in other neonatal diseases. Based on the signs & symptoms, laboratory results and radiographic evidence, the degree of severity can be classified into three stages according to modified Bell's criteria.<sup>(13)</sup>

When necrotizing enterocolitis is suspected, the initial management strategies are aimed at limiting the progression of the disease. Affected infants are given bowel rest and total parenteral nutrition is given for nutritional support. Broad-spectrum antibiotics will be initiated as soon as possible after cultures are obtained. Radiographic evaluation and laboratory studies should be performed to confirm the diagnosis and aid the management. Once the diagnosis of necrotizing enterocolitis is confirmed, the antibiotic treatment should be continued for 7 – 14 days. Surgical management may be sometimes needed in cases unresponsive to medical treatment or with poor prognosis.<sup>(9-11)</sup>

Survivors of necrotizing enterocolitis are at great risk of morbidity. About 10 – 30% of the infants with necrotizing enterocolitis have significant morbidity.<sup>(12)</sup> Postoperative complications, such as wound dehiscence and intra-abdominal

abscess, can occur in infants who have undergone surgery.<sup>(14)</sup> Gastrointestinal morbidities can be both short- and long-term, including malabsorption, failure to thrive and short bowel syndrome.<sup>(11)</sup> Neonates surviving necrotizing enterocolitis are also increased risk for adverse neurodevelopmental outcomes. Neurodevelopment impairment, cerebral palsy, visual and hearing impairment and psychomotor impairment are more likely to be observed in neonates with necrotizing enterocolitis than those without.<sup>(15)</sup>

In view of high mortality and morbidity rates, effective prophylaxis can help to reduce the incidence rate of necrotizing enterocolitis and improve the outcome of the high-risk population. Different prevention strategies aimed at the proposed aetiology of the disease have been evaluated. They include breast feeding, trophic feeding, antenatal steroids and probiotics.<sup>(10-12,14)</sup>

## ROLE OF PROBIOTICS IN NECROTIZING ENTEROCOLITIS

Abnormal intestinal colonization is one of the possible contributing factors for the development of necrotizing enterocolitis.<sup>(9-12)</sup> The gastrointestinal tract is sterile at birth. Once the intestine is exposed to environment and the ingestion of bacteria takes place during the birthing process, the intestine is quickly colonized with various bacterial species.<sup>(5,16)</sup> Colonization of intestine in preterm infants is different from that in term infants. Bacterial composition in the intestine of preterm infants is predominated by pathogenic bacteria such as enterococci, *Klebsiella*, *Clostridium* and *Bacteroides* instead of non-pathogenic bacteria such as *Lactobacillus* and *Bifidobacteria*. Normal intestinal flora offers immunologic protection against invading bacteria. Changing the composition of intestinal microflora, together with immaturity of gastrointestinal tract, would predispose the preterm infants to developing necrotizing enterocolitis.<sup>(17)</sup> Therefore, normalizing the abnormal intestinal colonization patterns with probiotics may help to prevent the development of necrotizing enterocolitis.

Several randomized controlled studies have evaluated the efficacy of various probiotics for the prevention of necrotizing enterocolitis. Dani *et al.* evaluated the efficacy of *Lactobacillus* GG supplement in reducing the incidence of urinary tract infections, bacterial

sepsis and necrotizing enterocolitis in preterm infants. In this multicentre study, 585 neonates with gestational age of <33 weeks or birth weight <1500g were recruited. They were randomized to receive either standard milk formula supplemented with *Lactobacillus* GG at a dose of  $6 \times 10^9$  colony forming units (CFUs) or placebo. Necrotizing enterocolitis occurred less frequently in the probiotic group (1.4 vs 2.7%), but this result did not reach statistical significance.<sup>(18)</sup>

Bin-Nun *et al.* studied the impact of a probiotic mixture on the incidence and severity of necrotizing enterocolitis. 145 infants with birth weight  $\leq 1500$ g were randomized to receive daily probiotic supplement of  $10^9$  CFUs or placebo, until 36 weeks postconceptual age. The probiotic mixture consisted of *Bifidobacteria infantis*, *Streptococcus thermophilus* and *Bifidobacteria bifidus*. It was found that infants in the probiotic group were less likely to develop necrotizing enterocolitis as compared with the control group (4% vs 16.4%,  $p=0.03$ ). Using the Bell's criteria, the severity of necrotizing enterocolitis was milder in the probiotic recipients ( $p=0.005$ ). Mortality due to necrotizing enterocolitis was observed in the control group alone.<sup>(16)</sup>

Lin *et al.* evaluated the effect of probiotic prophylaxis for necrotizing enterocolitis using a different probiotic mixture and in a larger sample. They recruited 367 very low birth weight infants and randomized them to be fed with mixture of *Lactobacillus acidophilus* and *Bifidobacterium infantis* of placebo until discharge. Significantly lower incidence of death or necrotizing enterocolitis was observed in the probiotic group (5% vs 12.8%,  $p=0.009$ ). The incidence of necrotizing enterocolitis alone was also significantly higher in control group (5.3% vs 1.1%,  $p=0.04$ ). Severe necrotizing enterocolitis (Bell's criteria stage 3) was only reported from the control group.<sup>(19)</sup> Later on, Lin *et al.* repeated the study in 7 different centres and 434 infants. Again, they found that probiotics significantly reduced the incidence of necrotizing enterocolitis or death in very low birth weight preterm infants ( $p=0.002$ ).<sup>(20)</sup>

Similar findings were reported by Samanta and coworkers. They studied 186 very low birth weight preterm infants using a probiotic mixture of *Bifidobacteria infantis*, *Bifidobacteria bifidum*, *Bifidobacteria longum* and *Lactobacillus acidophilus*. The probiotic mixture

significantly reduced the occurrence of necrotizing enterocolitis ( $p=0.042$ ), however, the severity observed in the probiotic group and control group was similar.<sup>(21)</sup>

In 2007, Deshpande *et al.* systematically reviewed 7 randomized controlled studies to determine the effectiveness of probiotics in prevention of necrotizing enterocolitis in very low birth weight preterm infants. Both necrotizing enterocolitis and death were decreased in probiotic group. The number needed to treat with probiotics to prevent one case of necrotizing enterocolitis and one death due to all causes were 25 and 20, respectively.<sup>(22)</sup>

Recently, Cochrane review published their recommendation on probiotics for prevention of necrotizing enterocolitis in preterm neonates. Since oral probiotic supplementation was shown to significantly decrease the incidence of severe necrotizing enterocolitis and death in premature infants >1000g at birth, their clinical use in daily practice was supported. However, more evidence is needed for the use in extremely low birth weight infants (<1000g).<sup>(23)</sup>

The prophylactic use of probiotics offers a promising approach in prevention of necrotizing enterocolitis. However, several practical issues remain to be answered. First of all, it is the choice of the appropriate probiotic supplement to use. Different probiotic preparations, either in single strain or in a mixture of strains, were evaluated in previous studies. Single strain preparation has yielded non-significant findings, while mixture of strains has yielded significant results.<sup>(16,18-21)</sup> There may be synergistic effect between different strains and probiotic mixture may offer a better protective effect than single strain. Nevertheless, it is difficult to decide which probiotic mixture offers the optimal probiotic prophylaxis for necrotizing enterocolitis. Besides, there are issues regarding the vehicle of administration, the timing of administration and the duration of use.

## SAFETY OF PROBIOTICS

Probiotics of *Lactobacillus* and *Bifidobacteria* groups are generally considered to be well-tolerated and suitable for use in infants and children. Reported adverse drug reactions in clinical studies are usually mild.<sup>(24)</sup> In 2004, Saavedra *et al.* evaluated the

tolerance and safety of probiotics after long-term consumption. 118 infants were randomly assigned to consume either normal infant formula or infant formula supplemented with *Bifidobacteria lactis* Bb 12 and *Streptococcus thermophilus* (low concentration or high concentration) for a mean period of 210 days. It was found that the probiotic group had a lower incidence of colic or irritability ( $p < 0.001$ ) and a lower frequency of antibiotic use ( $p < 0.001$ ). They concluded that probiotics were safe and well-tolerated in long-term consumption.<sup>(25)</sup>

However, there were several reported cases of probiotics related-bacteraemia or fungemia. Cases of fungemia associated with *Saccharomyces boulardii* were documented in children.<sup>(26-31)</sup> Fungemia occurred not only in immunocompromised patients, but also happened in patients without receiving probiotics via airborne or interpersonal colonization.<sup>(26)</sup> It was recommended that *Saccharomyces boulardii* be prepared under aseptic condition in order to prevent indwelling catheter contamination.<sup>(24,28)</sup> *Lactobacillus* associated bacteraemia was also documented in children. Three cases of bacteraemia were reported after consuming *Lactobacillus* GG.<sup>(32,33)</sup> Since all three cases were immunocompetent, this suggests that bacteraemia associated with *Lactobacillus* does not only occur in immunocompromised patients. Impaired gut integrity was proposed as one of the risk factors, which might allow translocation of bacteria into the blood streams.<sup>(32,33)</sup> However, more studies are warranted to determine the exact mechanism. Besides bacteraemia, *Lactobacillus* was also associated with D-lactic acidosis, particularly in patients with short bowel syndrome.<sup>(24,34)</sup> Though no specific case report was found, probiotics used in infants were usually restricted to L-lactic acid producing probiotics.<sup>(24,35,36)</sup>

## CONCLUSIONS

Probiotics are generally safe and well-tolerated. Studies of probiotics on the prevention of necrotizing enterocolitis have demonstrated their efficacy and this supports the prophylactic use in very low birth weight preterm infants. However, a number of issues need to be addressed. These include the optimal probiotic supplement and the dosing regimen to choose, and the safety and efficacy in extremely low birth weight infants. Further studies are still required before adopting it as our routine practice.

### Author's background

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# Questions for Pharmacy Central Continuing Education Committee Program

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

## 1. Which of the following statement concerning probiotics is incorrect?

- The first scientific evaluation of probiotics was conducted in 1907.
- The use of probiotics in human began in 1960.
- Joint Food and Agriculture Organization of the United Nations and World Health Organization expert panel standardized the definition of probiotics.
- Lactobacillus* and *Bifidobacteria* are the probiotics commonly used in human.
- The beneficial effects of probiotics in the treatment and prevention of diarrhoea have been demonstrated.

## 2. Which of the followings are the properties of probiotics?

- Living microbes
  - Non-pathogen and human origin
  - Readily absorbed by intestinal tract
  - Able to produce antimicrobial substances
- i
  - i & ii
  - ii & iv
  - i, ii & iv
  - All of above

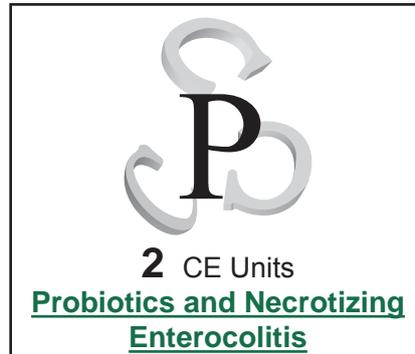
## 3. Which of the following bacteria is predominated in the intestine of term infants?

- Klebsiella*
- Lactobacillus*
- Clostridium*
- Enterococci
- Bacteroides*

## 4. Which of the following are the possible pathophysiology of neonatal necrotizing enterocolitis?

- Physiological immaturity of gastrointestinal tract
  - Hypoxic-ischaemic injury
  - Abnormal colonization of intestinal tract
- i
  - ii
  - i & ii
  - ii & iii
  - All of above

## 5. Which of the following statement concerning neonatal necrotizing enterocolitis is correct?



- Low birth weight is not a risk factor of neonatal necrotizing enterocolitis.
- Infants with necrotizing enterocolitis only present with gastrointestinal signs and symptoms.
- Enteral nutritional support had a role in the initial management of neonatal necrotizing enterocolitis.
- The initial management of necrotizing enterocolitis is aimed at limiting the disease progression.
- Affected infants should be given broad-spectrum antibiotics before cultures are obtained.

## 6. Which of the followings are the complications of neonatal necrotizing enterocolitis?

- Short bowel syndrome
  - Wound dehiscence
  - Malabsorption
  - Visual and hearing impairment
- i & ii
  - i, ii & iii
  - i, ii & iv
  - ii, iii & iv
  - All of above

## 7. Which of the following statement is correct?

- Probiotics have been studied for the treatment of neonatal necrotizing enterocolitis.
- It has been proven that probiotic preparation of single strain is less efficacious than that with mixture of strains.
- All the randomized controlled studies have shown that the severity of necrotizing enterocolitis was less in probiotic recipients.
- Cochrane review supports the routine clinical use of probiotics for the prevention of necrotizing enterocolitis in premature infants < 1000g at birth.

- It has been proposed that probiotics prevent the development of necrotizing enterocolitis by normalizing the abnormal intestinal colonization patterns in preterm infants.

## 8. Which of the following statement concerning the clinical trial of probiotics is incorrect?

- According to Desphande *et al.*, 25 preterm infants were needed to treat with probiotics to prevent one case of necrotizing enterocolitis.
- Dani *et al.* found that the incidence of necrotizing enterocolitis was lower in probiotic group, but it did not reach statistical significance.
- Lin *et al.* showed that probiotics could relatively lower the incidence of death or necrotizing enterocolitis by 7.8%.
- Bin-Nun *et al.* showed that probiotics reduced the absolute risk of neonatal necrotizing enterocolitis by 12.4%.
- Lin *et al.* found that probiotics significantly reduced the incidence of necrotizing enterocolitis in very low birth weight preterm infants.

## 9. Regarding the application of probiotics in neonatal necrotizing enterocolitis, which of the following areas should be further evaluated?

- Efficacy in premature infants >1000g at birth
  - Vehicle of administration
  - Duration of use
  - Choice of probiotic
- i & ii
  - ii & iii
  - i, iii & iv
  - ii, iii & iv
  - All of above

## 10. Which of the following concerning the safety of probiotics is incorrect?

- Saccharomyces boulardii*-related fungemia can be caused by catheter contamination.
- Lactobacillus* associated bacteraemia has been reported in both immunocompetent and immunocompromised patients.
- Lactobacillus* was not associated with risk of D-lactic acidosis.
- The long-term safety of *Bifidobacteria* has been evaluated in randomized trial.
- Probiotics of *Lactobacillus* and *Bifidobacteria* groups are generally considered to be well-tolerated

Answers will be released in the next issue of HKPJ.

## 製藥過程中「生產偏差」的發生，預防，處理及反思 Reflection on the Occurrence, Prevention and Management of Deviations in Pharmaceutical Manufacturing

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### 摘要

偏差偶然會在藥物生產時發生，但基於多種原因，偏差通常均會被忽視。不過，沒有正確地管理或記錄偏差，亦是違反GMP的一種行為。本文透過討論，希望為業界建立一個正確的偏差管理概念。

### ABSTRACT

Deviations happen occasionally in the pharmaceutical industry but they are always deliberately ignored because of many reasons. However, not managing nor reporting deviations are also considered as a GMP infringement. This article discusses the proper approach about the management of deviations.

**Keywords:** GMP, Manufacture deviations, Out of specification, Out of range, Out of trend, Rework, Reprocess

### 引言

在藥物的生產過程中，偶然會發生一些意外，我們統稱這些意外為「生產偏差Manufacture Deviations」。本文主要是描述「偏差」的管理及討論在「偏差」管理過程中的一些反思。

### 「生產偏差」的定義

「生產偏差」，是指在一個已經驗證的生產過程中，出現一些不正常的情況。

### 「偏差」的分類

在生產中，「偏差」可能在幾個情況下發生，因此可以劃分成不同的種類。

- (1) 一切生產情況正常，但半成品或成品卻出現不符合規格；例如顆粒的水份含量偏高；顆粒粒狀不符要求；試壓的藥片硬度不足、或崩解或溶出度不符規定；pH偏高或低，粘度不符規定，糖份(比重)不符規定；含量不符規定；均勻不符規定等等；這些均是在半成品或成品的內控檢查時發現的。
- (2) 生產的過程中出現問題；例如設備在使用中突然停電或發生故障，空調故障致使生產環境偏離規定範圍；在設定設備或調機時發覺需要將設備設定至超出已驗證的範圍才可生產出符合規定的半成品或成品（時間，溫度，壓力等等）；
- (3) 在生產過程中出現一些錯誤，例如投料次序出錯；設備的某一些設定出錯；使用了一些未及時通過驗證的設備；使用了未經驗證的生產程序；使用了錯誤的物料；使用了不合格的

物料等等；使用了未經培訓或認可的操作人員；或好像近來發生最多的情況 - 顆粒存放超過了48小時。

另一種「偏差」的分類方法，是按「偏差」的嚴重性來劃分，而嚴重的定義，通常是在考慮了產品的安全性，效能及質量的幾個因數來界定的。

- (1) 嚴重：指產品的安全性，效能及質量已因為「偏差」而受到了極嚴重的破壞，產品有可能對使用者引起了嚴重的後果，甚至死亡。
- (2) 可接受：指產品的安全性及效能均未有受到「偏差」影響，但產品的質量已受到一定程序的破壞，甚至可能不能符合規格。
- (3) 輕微：產品不論在安全性，效能及質量均不受「偏差」的影響。

### OOS, OOR及OOT等等與「偏差」的分別

OOS, OOR 及OOT, 均是QA管理中經常遇到的問題，OOS (Out of Specification) 是指結果超出規定；OOR (Out of Range) 是指結果超出範圍；OOT (Out of Trend) 是指結果超出趨勢。三者均可能是生產出現「偏差」後引起的情況。但是，OOS, OOR及OOT並不是造成「偏差」的原因，如果在出現OOS, OOR及OOT的情況下，不

能自動引用「偏差管理」來應付這情況；OOS，OOR及OOT必須首先使用OOS，OOR及OOT的管理程序，在完成了OOS，OOR及OOT的調查後，才能考慮是否使用「偏差管理」來完成後續的工作。

### **Marginal Pass, 超出 Alert Limit 及 Marginal Fail**

Marginal Fail 已經是OOS，必須立即啟動OOS管理程序；但是，Marginal Pass及超出Alert Limit (OOL) 則可以使用「偏差管理」來評估及處理後續的工作。

### **「偏差」的管理**

GMP的條文中，未有對「偏差」提出一個較全面的規定。而另一方面，因為生產的既定程序已經「充分地」通過驗證，所以有一個誤解認為偏差是不可能發生，如果發生了「偏差」，便是違反了GMP，所以「偏差」便經常性的「被忽略」，或用其他方式「隱藏」起來；而更多時候，生產發生「偏差」後，產品只會被「廢置」掉，而「批生產記錄 PBR」只會填寫上「不合格」或「作廢」後便被存放入檔案中。

實際上，「偏差」是需要管理的，因為「偏差」的調查，可以用作產品的「Continue Improvement 持續性改進」的依據，甚至是GMP的「Continue Improvement 持續性改進」的依據。「偏差」的管理，亦能夠讓管理人員明白評估公司的「質量管理QA」狀態，及成本的控制；或更進一步說，是一個量度「浪費 Waste」的工具 (6 Sigma)，從而用來為公司制定指標，控制好質量及成本。

「偏差管理」首要的工作，當然是制定一套管理程序，以便規範化的對「偏差」作出報告，記錄，調查，風險評估，後續的處理，建立防治計劃等等。

「偏差」的報告，這是一個非常重要的環節，QA需要為「偏

差」訂立報告的機制，報告需要及時及準確，前線的工作人員應該清楚在發生「偏差」是如何立即處理在生產中的產品及設備等等。現場的緊急處理程序中，除了需要確保產品的質量外，更要考慮如何避免繼續有受影響的產品繼續生產出來，又或混入未受影響的產品的部份中，當然，工場中的安全亦是一個需要關注的項目。在未有對個別不同的「偏差」作出詳細的現場處理守則前，建議QA先暫定所有「偏差」均需要立即停止生產，並且最小要向「生產經理」報告，如果「生產經理」不在，則需要改向「QA經理」報告，報告的方式，除了即時的現場口頭通知外，亦可以包括電話的聯絡方式，務求所有「偏差」，不會因為未能接觸到有關的「Key Persons」下，變成不受控制地繼續下去，成為一個「run away process」。

「偏差」的記錄，根據規定，QA部需要為「偏差」成立 Log Book，按時間順記錄「偏差」，除此之外，QA部亦需要為「偏差」制定一套標準表格，表格應容許記錄「偏差」的詳細資料，包括日期，時間，產品資料，批號，「偏差」事故的詳細內容，操作人員，有關設備，報告人，接受通知的人員資料，即時的處理方法詳情，現場主管的確認等等。跟著，報告亦要附上有關的「偏差」的調查內容，評估的分級，後續的處理方案，QA的確認，處理跟進的報告，可能需要的防治方案，總結等等。

「偏差」的調查，根據報告，QA必須聯同其他部門對報告作出調查，同時對收到報告的內容作出確定，調查應該從多方面考慮，例如發生「偏差」的原因，「偏差」對產品可能引起的影響，「偏差」覆蓋的範圍(只是局部影響一個生產程序，或範圍比較大，影響一個產品，甚至一個劑型或一整個工廠?)，「偏差」影響的深度(只是一次性的影響，或是可能對生產一個時段有影響，或甚至是否會繼續影響將來的所有生產?)。

「偏差」的風險評估 - 如果生產出現了「偏差」，即意味著產品已經不是根據一個既定已驗證的程序下生產出來，質量已經失去保證。但是，在質量並未能保證的情況下，半成品或成品存在了多大的風險？產品的安全性，效能及質量是否受到影響？如果容許產品繼續完成生產程序並放行出市場上，是否會對公眾構成風險？這些風險情況，均是需要考慮，並且需要構成一個文字的報告記錄在案。風險評估應該是科學化的，要有數據的依據，如果有必要，甚至需要一些某一些專業領域的專家來協助評估，例如微生物專家、藥學專家、臨床專家、藥物化學專家等等，如果是中成藥產品，或基因工程產品，更可能需要中藥專家及生物科技專家的協助。風險評估的總結應由一個小組共同完成。

### **返工 (Rework)，返處理 (Reprocess) 或作廢?**

Rework 是指使用非常規，而且未有驗證的方法/程序，將一批或一部份的小批的不合格物料/半成品，重新處理至令其達符規格。

Reprocess是指重覆使用一個已驗證的方法/程序，將一批或一部份的小批的不合格物料/半成品，重新處理至令其達符規格。

在完成風險評估後，QA 可以考慮如何處理有關的半成品或成品。當然，最簡單的處理方法是將整批半成品或成品作廢。但是，基於多方考慮及成本的問題，公司可能需要考慮保留該有關的半成品及成品，在此情況下，QA應根據風險評估的結論，穩定性數據，產品開發時收集的數據及實際的化驗報告等等，決定是否重新處理或返工產品。

不論是決定了「返工」或「返處理」半成品或成品，至而最後產品完全達符規格，QA仍需要考慮這些批已經合格的產品是否仍然存在不明朗的安全性，效能及質量風險，而需要作出一些相應的措施，

例如取更多的樣品化驗，增加取樣數量以便加大化驗結果的代表性，收緊規程，縮短有效期，收緊儲存條件，留更多的樣品並且定期進行質量覆核等等。

在「返工」中，算重新處理的程序是曾經驗證過，但我們應該知道我們是未有對重覆處理過的產品做過任何「穩定性」試驗的，所以我們是不知道究竟產品在重新處理過後，雖然產品出廠時是合格，但長期儲存下是否能夠保持穩定，試舉一個例子說，烘箱在晚間烘乾顆粒的過程中出現故障停下來，需要重新烘焗顆粒，因為顆粒已經通過烘焗一段時間，停下來又重新烘焗，雖然重新「返工」的工序是一個已經驗證的程序，但我們卻從來沒有對重覆烘焗的顆粒做成的產品進行過穩定性實驗，產品化驗時是合格的，但QC卻留意到HPLC圖譜，某一些雜峰比以往的正常生產的產品偏高，對於此批產品，QA是完全可以進行「「偏差」管理」及「風險評估」後，決定將產品放行，但將有效期相應地縮短，縮短多少時間則需要按產品的「穩定性實驗」的數據來決定。

「返處理」是一個非常敏感的工作，如果是從事中藥提取，基因工程藥品等等的生產會比較容易遇到這種情況。因為處理的程序及方法是未經驗證的，例如重新投入物料，增加一個過濾程序，加大壓片壓力（超過已驗證的壓片壓力），延長烘焗時間等等，增加消毒程序等等。在此情況下，「返處理」必須是首先通過「風險評估」，返處理的方式亦需要有科學根據，甚至事先必須作出一些全面性的試驗，取得足夠的數據來支持，再經過QA評估方可進行。在這裡有需要提到的，根據歐美及中國的規定，在返處理過程中添加物料是容許的（例如 magnesium stearate, PVP 等等），但可以添加甚麼物料及多少數量，卻有一定的規矩限制，這主要是要看產品在「開

發 development」過程中做過甚麼實驗及有何種數據來證明，這是一個非常敏感的工作，在未有足夠的實驗及數據支持下添加物料，可能會被認為是一個非法行為生產未經註冊的藥品。

### 「偏差」的回顧及防治行動

QA部應定期對「偏差」作出回顧及總結，及提出有效的防治計劃。例如在回顧中，發覺某一產品經常出現一些特定的「偏差」，例如顆粒水份含量經常性偏高，又或許可能是某產品壓片時經常性出現裂片的情況，又或許某一軟膏粘度經常性偏低等。QA部便需要發起對這些產品作出「改良要求」，這些「要求」必須是書面的，而且應該有記錄，「要求」需要有關的部門跟進及作出回應，「要求」是需要有時限的規定。

另一些「偏差」，可能是因為員工的錯誤操作引起的，例如投料次序，錯誤使用設備等等，QA部應因應這些情況要求有關部門重新培訓員工，並作出考核。

有些時候，「偏差」是因為設備的故障產生的，例如停電，設備超負荷停機，溫度感應器或計時器故障而致令生產程序出錯，密封圈破損等等；QA部應該提出評估設備是否適合用作該生產用途？設備是否需要安裝「不斷電裝置」？電力負荷是否符合設備的要求？感應器及控制器是否需要更換？設備的維護計劃是否需要修改？是否需要再驗證？

### 從「偏差」管理中引發的反思

「偏差」在GMP規模中只是一個很小提及的環接，亦沒有詳細規定制藥商如何處理「偏差」。這有極大的可能是因為國外藥廠的產品開發及生產條件比香港好，配方亦比較成熟。偏偏，「生產偏差」卻是香港這些「半途GMP藥廠」的經常遇到的問題，這是

因為香港的藥廠沒有建立一個完善的產品開發系統，對本身的產品配方及生產工藝(GMP角度)仍然未有完全理解。當然，另一些原因是工人的制藥水平偏低及設備不完全適合有關。「生產偏差」一直是香港的藥廠的一個「死穴」，沒有人願意了解，願意提及，願意處理，在不聞不問不面對的情況下，甚至做成一些違反GMP規定的事件。

其實，如果藥廠QA部願意面對問題，為「偏差」建立管理制度，完善風險評估的機制，容許「偏差」明正言順的記錄下來，並作出合理及合法的處理措施，那麼藥廠已經可以避免絕大部份的做假行為。

查在歐美地區，產品的開發是通過一系列，有組織性的實驗來完成。就算是比較「低技術水平」的非專利藥物的開發過程中，不單只是配方的穩定性及QC方法及其驗證是研究對象，現在本地藥廠已經開始加上藥物的生物利用度作為產品開發的考慮因數，歐美國家亦會在配方及生產條件(工藝)上在產品開發過程中進行驗證，務求在產品開發的同時，已經取得足夠的資料以備將來如果需要進行「偏差管理」及「風險評估」時有更多的數據來決定如何處理半成品。本人在此希望藥廠在制定「偏差管理」的系統時，亦同時建立一套「產品開發規範 Product Development Protocol」，將質量管理向前推進。

#### 作者背景

梁靄明 (LEUNG, Herman) 於1986年在英國 Bath 大學藥劑系畢業，專科制藥科技，並且在1991年在香港成立自己的制藥廠，公司在1999年與德國默克合併，組成默克香港有限公司。梁靄明在中國成立的默克中國有限公司的藥廠是中國首批取得GMP認證的制藥企業。同時，在1999年至2002年間，該藥廠更被默克公司評為集團內最佳藥廠，直至默克的新工廠2003年完成才被取代。默克及梁靄明在2005年將「生產公司」出售，梁靄明亦離開默克成為顧問。梁靄明在2009年4月加入萬輝藥業，主力公司重組質量管理系統及建立產品開發部。他的電郵: herman@i-otc.com

## NEW PRODUCTS

**Tredaptive®**  
(MSD)

### Active ingredient:

Niacin and Laropiprant

### Presentation:

Extended release tablet containing 1 g of ER niacin (nicotinic acid) and 20 mg of immediate release laropiprant.

### Pharmacological Properties:

**Niacin:** ER niacin at therapeutic doses is a lipid-modifying agent.

**Laropiprant:** Laropiprant is a potent, selective antagonist of the prostaglandin D2 (PGD2) receptor, DP1. Laropiprant suppresses PGD2 mediated flushing associated with administration of niacin.

### Indications:

Therapy in patients with combined dyslipidemia (type II a and IIb according to Frederickson) and primary hypercholesterolemia (heterocyeous familial and non-familial), to reduce total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) when not controlled by diet and exercise alone. TREDAPTIVE can be used in combination with HMG-CoA reductase inhibitors (statins) or as monotherapy.

### Dosage and Administration

The starting dose is one extended-release tablet (1 g niacin/20 mg laropiprant) once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2 g/40 mg taken as two tablets (1 g/20 mg each) once daily. Daily doses greater than 2 g/40 mg have not been studied and therefore are not recommended.

If the medication is missed for less than 7 consecutive days, patients can resume therapy at the last administered dose. If medication is missed for 7 or more consecutive days, therapy should be resumed at the 1 g/20 mg dose for 1 week, before advancing to the maintenance dose of 2 g/40 mg.

Those patients switching from 2 g or more of prolonged-release niacin can initiate TREDAPTIVE at the 2 g/40 mg dose. Patients switching from less than 2 g of prolonged-release niacin should initiate therapy at the starting dose of 1 g/20 mg and advance to the 2 g/40 mg maintenance dose after four weeks. For patients switching from immediate-release niacin to TREDAPTIVE, therapy should be initiated at the 1 g/20 mg dose and advanced to the 2 g/40 mg maintenance dose after four weeks.

The tablets should be taken whole, with food, in the evening or at bedtime. To preserve the extended-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. To reduce the possibility of flushing, alcohol or hot drinks should be avoided at the time of ingestion of the medicinal product.

### Use in patients with hepatic or renal insufficiency

Use in patients with hepatic or renal insufficiency has not been studied. Like other niacin medicinal products, TREDAPTIVE is contraindicated in patients with significant or unexplained hepatic dysfunction. It should be used with caution in patients with renal insufficiency, because niacin and its metabolites are primarily excreted by the kidneys.

### Concomitant therapy

Aspirin provides no additional reduction of flushing beyond that achieved by TREDAPTIVE. Therefore, treatment with aspirin to alleviate flushing symptoms is not necessary. Because co-administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as niacin, it is recommended that TREDAPTIVE be administered > 1 hour before or > 4 hours after administration of a bile acid sequestrant.

### Contraindications

Hypersensitivity to the active substances or to any of the excipients  
Significant or unexplained hepatic dysfunction  
Active peptic ulcer disease  
Arterial bleeding

### Precautions

#### Hepatic Effects

Switching from immediate-release (crystalline) niacin to TREDAPTIVE has not been studied. However, cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have switched from immediate-release niacin to long-acting niacin at equivalent doses. Therefore, patients switching from immediate-release niacin to TREDAPTIVE should be initiated at the 1 g/20 mg dose. Should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Significant or unexplained hepatic dysfunction is a contraindication.

Like other lipid-lowering therapies, niacin medicinal products have been associated with abnormal liver function tests. Transaminase elevations were reversible upon discontinuation of TREDAPTIVE. Liver function tests are recommended before initiation, every 6

to 12 weeks for the first year, and periodically (e.g., semiannually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of  $\geq 3X$  ULN persist, reduction of dose or withdrawal of Tredaptive is recommended.

### Effect on Skeletal Muscle

Rare cases of rhabdomyolysis have been associated with concomitant administration of lipid-altering doses ( $\geq 1$  g/day) of niacin and HMG-CoA reductase inhibitors (statins). Patients should be monitored carefully when used with statins for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dosage of either drug is increased. If muscle pain, weakness or cramps occur while a patient is receiving TREDAPTIVE with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated ( $> 5 \times$  ULN), treatment should be stopped.

TREDAPTIVE should be used with caution in patients with renal dysfunction, diabetes, acute coronary syndrome, hematologic conditions, gout, hypophosphatemia and peptic ulcers.

### Pregnancy

There are no data from the combined use of niacin and laropiprant in pregnant women. The combination has not been tested in reproductive toxicity studies. The potential risk for humans is unknown. Therefore, TREDAPTIVE should not be used during pregnancy unless clearly necessary. Niacin is excreted in human breast milk. It is unknown whether laropiprant

is excreted in human breast milk. Animal studies have shown excretion of laropiprant in milk.

### Drug Interactions

Simultaneous use of alcohol or hot drinks can enhance the effects of flushing and should therefore be avoided around the time of ingestion of TREDAPTIVE. Niacin may potentiate the effects of ganglionic blocking agents and vasoactive medicinal products such as nitrates, calcium channel blockers, and adrenergic receptor blocking agents, resulting in postural hypotension. Multiple doses of laropiprant 40 mg did not affect the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Therefore, laropiprant is not an inducer or inhibitor of CYP3A4. However, the plasma concentration of a metabolite of midazolam, 1'-hydroxymidazolam, was increased approximately 2-fold with multiple doses of laropiprant. Because 1'-hydroxymidazolam is an active metabolite, the sedative effect of midazolam may be increased and caution should be used when laropiprant is co-administered with midazolam.

### Side Effects

Flushing is the most common adverse reaction of TREDAPTIVE. Flushing is most prominent in the head, neck, and upper torso. Common were elevations in ALT, AST, fasting glucose, uric acid, dizziness, headache, diarrhoea, dyspepsia, vomiting, erythema, pruritus, rash, urticaria, paraesthesia and feeling hot.

### Forensic Classification:

P1S1S3

**Synflorix™**  
(GSK)

### Active ingredient:

Pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine, adsorbed.

### Presentation:

1 dose (0.5 ml) of Synflorix suspension for injection contains:

Pneumococcal polysaccharide serotype 1 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 4 <sup>1,2</sup>	3 micrograms
Pneumococcal polysaccharide serotype 5 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 6B <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 7F <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 9V <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 14 <sup>1,2</sup>	1 microgram
Pneumococcal polysaccharide serotype 18C <sup>1,3</sup>	3 micrograms
Pneumococcal polysaccharide serotype 19F <sup>1,4</sup>	3 micrograms
Pneumococcal polysaccharide serotype 23F <sup>1,2</sup>	1 microgram

<sup>1</sup> adsorbed on aluminium phosphate  
0.5 milligram Al<sup>3+</sup>

<sup>2</sup> conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein  
9-16 micrograms

<sup>3</sup> conjugated to tetanus toxoid carrier protein  
5-10 micrograms

<sup>4</sup> conjugated to diphtheria toxoid carrier protein  
3-6 micrograms

### Pharmacological Properties:

SYNFLORIX is a pneumococcal polysaccharide conjugate vaccine using protein D as the main carrier protein. Protein D is a highly conserved surface protein from Non-Typeable *Haemophilus influenzae* (NTHi). The vaccine contains 10 *Streptococcus pneumoniae* serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F).

Protection against the *Streptococcus pneumoniae* bacterium is triggered by antibodies, directed against its polysaccharide capsule, which can mediate bacterial killing.

### Vaccine Efficacy

It has been demonstrated that SYNFLORIX induces an appropriate immune response to protect against IPD caused by serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

6A	ELISA (≥0.2µg/ml)	44.2-52.7%	72.8-84.4%
	OPA (≥8)	70.4-85.6%	68.6-85.0%
19A	ELISA (>0.2µg/ml)	45.0-86.8%	83.0-83.8%
	OPA (≥8)	19.8-32.4%	46.6-48.8%

† Primary immunisation results is the range obtained from 2 separate studies using a 2-4-6 schedule (Total N ~600, although number of subjects may vary for each serotype)

\* Results expressed reflect immunological responses seen following booster vaccination across all primary immunisation schedules (Total N = ~500 (ELISA and OPA))

A plain polysaccharide challenge at 12 months of age elicited an anamnestic antibody response for the 10 pneumococcal serotypes included in the vaccine, which is considered indicative for the induction of immune memory following the primary series with SYNFLORIX.

### Efficacy against Acute Otitis Media (AOM)

In a large randomised double-blind Pneumococcal Otitis Media Efficacy Trial (POET) conducted in the Czech Republic and in Slovakia 2,489 infants received an 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of SYNFLORIX along with serotype 3 for which efficacy was not demonstrated according to a 3, 4, 5 and 12-15 months vaccination schedule.

The vaccine efficacy against AOM episodes observed during this study is presented below in Table 3.

### Indications:

Active immunisation of infants and children from the age of 6 weeks up to 2 years against disease caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (including invasive disease, pneumonia and acute otitis media). The use of SYNFLORIX should be determined on the basis

of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different areas.

### Dosage and Administration:

**Method of administration**  
The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in children under 12 months of age or the deltoid muscle of the upper arm in children over 12 months of age. SYNFLORIX syringe is for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

### Dosage

*Infants from 6 weeks to 6 months of age*

The primary vaccination schedule consists of three doses of 0.5 ml with an interval of at least 1 month between doses. A booster dose is recommended at least 6 months after the last priming dose.

### Previously unvaccinated older infants and children

- infants aged 7-11 months: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 1 month between doses. A third dose is recommended in the second year of life with an interval of at least 2 months between doses.
- children aged 12-23 months: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses. The need for a booster dose after this immunisation schedule has not been established.

### Immunisation schedules:

Official recommendations should be taken into account when immunising with SYNFLORIX. It is recommended that subjects who receive a first dose of SYNFLORIX complete the full vaccination course with SYNFLORIX.

### Contraindications:

SYNFLORIX should not be

administered to subjects with known hypersensitivity to any component of the vaccine (see *Qualitative and Quantitative Composition* and *List of excipients*).

#### Precautions:

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

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

As with other vaccines, the administration of SYNFLORIX should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

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

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

SYNFLORIX will not protect against pneumococcal serogroups other than those included in the vaccine. Although antibody response to diphtheria toxoid, tetanus toxoid and Protein D (protein D is highly conserved in all *Haemophilus influenzae* strains including NTHi) occurs, immunization with SYNFLORIX does not substitute routine immunization with diphtheria, tetanus or *Haemophilus influenzae* type b vaccines. Official recommendations for the immunisations against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Safety and immunogenicity data in children with increased risk for pneumococcal infections (sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.

For children at high-risk for pneumococcal disease (such as children with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised),

- the appropriate-for-age SYNFLORIX vaccination series should be given below 2 years of age (see Dosage and Administration)
- a 23-valent pneumococcal polysaccharide vaccine should be given  $\geq 2$  years of age.

Prophylactic administration of antipyretics before or immediately after vaccine administration can reduce the incidence and intensity of post-vaccination febrile reactions. However, data suggest that the prophylactic use of paracetamol might reduce the immune response to SYNFLORIX. The clinical relevance of this observation, as well as the impact of antipyretics other than paracetamol on the immune response to SYNFLORIX remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born  $\leq 28$  weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

#### Side effects:

##### *Nervous system disorder*

Very common: drowsiness

Rare: febrile and non-febrile convulsions

*Respiratory, thoracic and*

##### *mediastinal disorder*

Uncommon: apnoea in very premature infants ( $\leq 28$  weeks of gestation)

##### *Gastro-intestinal disorders*

Uncommon: diarrhoea, vomiting

##### *Skin and subcutaneous tissue disorders*

Rare: rash, urticaria

#### Drug Interactions:

##### *Use with other vaccines*

SYNFLORIX can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine (V), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), oral polio vaccine (OPV) and oral rotavirus vaccine. Different injectable vaccines should always be given at different injection sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known. No negative interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM<sub>197</sub> and TT conjugates). Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed.

##### *Use with systemic immunosuppressive medicinal products*

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

#### Forensic Classification:

P1S1S3

NEW PRESENTATION

Dynastat  
(Pfizer)

**Active Ingredient:**  
Parecoxib

#### Presentation:

DYNASTAT 40 mg powder and solvent for solution for injection

#### Pharmacological Properties:

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

#### Indications:

For the short-term treatment of postoperative pain.

#### Dosage & Administration:

The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle

#### Forensic Classification:

P1S1S3

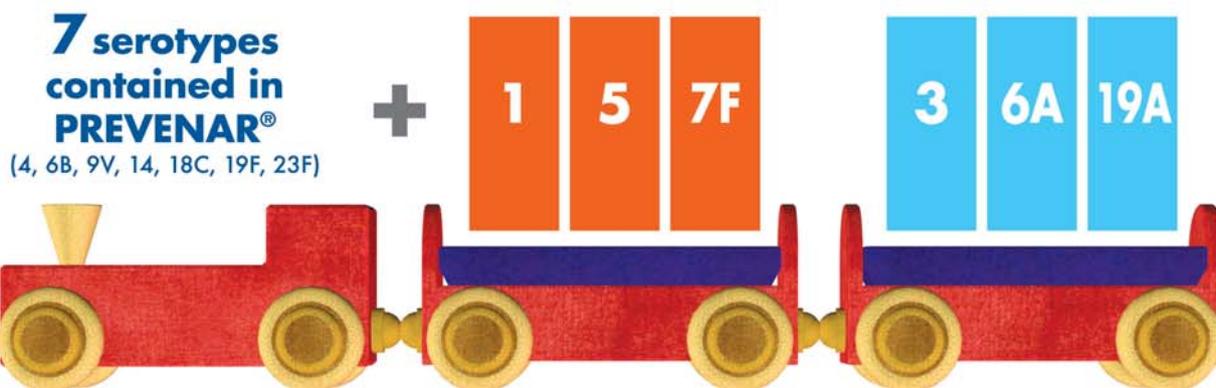
**NOW**

**Prevenar 13**<sup>®</sup>

Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)



## PREVENAR 13 – Broadest coverage of any pneumococcal conjugate vaccine



### BUILT ON THE SCIENTIFIC FOUNDATION OF PREVENAR

#### INDICATIONS<sup>1</sup>

- Prevention of **invasive disease, pneumonia and acute otitis media (AOM)** caused by *Streptococcus Pneumoniae*.
- For use in infants and children from **6 weeks to 5 years of age**.

The use of PREVENAR 13 should be determined on the basis of official recommendations, taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographic areas.



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Website: [www.pfizer.com.hk](http://www.pfizer.com.hk)

Reference: 1. Hong Kong Prescribing Information, version: October 2009.

**PREVENAR 13<sup>®</sup> ABBREVIATED PRESCRIBING INFORMATION :** 1. **TRADE NAME:** PREVENAR 13<sup>®</sup> 2. **PRESENTATION:** A homogeneous white suspension for injection. 3. **INDICATIONS:** Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age. 4. **DOSAGE:** I.M. only. For more dosage information, please refer to the full package insert. 5. **CONTRAINDICATIONS:** Hypersensitivity to the active substances, to any of the excipients or to diphtheria toxoid. As with other vaccines, the administration should be postponed in subjects suffering from acute, severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination. 6. **WARNINGS & PRECAUTIONS:** Not for intravascular administration; should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration; only protect against *S. pneumoniae* serotypes included in the vaccine, and not for protecting against other microorganisms that cause invasive disease, pneumonia, or otitis media; may not protect all individuals receiving the vaccine from pneumococcal disease. Children with impaired immune responsiveness may have reduced antibody response to active immunisation. Limited data have demonstrated that Prevenar 7 valent (three-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non high-risk groups. Safety and immunogenicity data are not yet available for children in other specific high-risk groups for invasive pneumococcal disease (e.g., children with another congenital or acquired splenic dysfunction, HIV infected, malignancy, nephrotic syndrome). Vaccination in high-risk groups should be considered on an individual basis. Specific data are not yet available for Prevenar 13. Children younger than 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born  $\leq 28$  weeks of gestation), and particularly for those with a previous history of respiratory immaturity. For vaccine serotypes, protection against otitis media is expected to be lower than protection against invasive disease. Antipyretic treatment should be initiated according to local treatment guidelines for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis. 7. **INTERACTIONS:** Can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella; Different injectable vaccines should always be given at different injection sites. 8. **PREGNANCY AND LACTATION:** Not intended for use in adults. 9. **SIDE EFFECTS:** Decreased appetite; pyrexia; irritability; any injection-site erythema, induration/swelling or pain/tenderness; somnolence; poor quality sleep; injection-site movement impairment (due to pain); apnoea in very premature infants ( $\leq 28$  weeks of gestation). Reference: HK LPD version CDS 4.0 Oct 2009. Date of preparation: MAY2010 Identifier number: PR13-0510.

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.