

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

Updates on Setting up and Operating a Community (Retail) Pharmacy in Hong Kong in Professional, Legal and Business Perspective

Makes Everything He Does As His Interest – An Interview with Mr. Michael Ling

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Utilities and Limitations of Polymerase Chain Reaction in Pharmaceutical and Food Analysis

Discussion Forums for consultation of the establishment of Pharmacy Council – with the students of the two Pharmacy schools in Hong Kong

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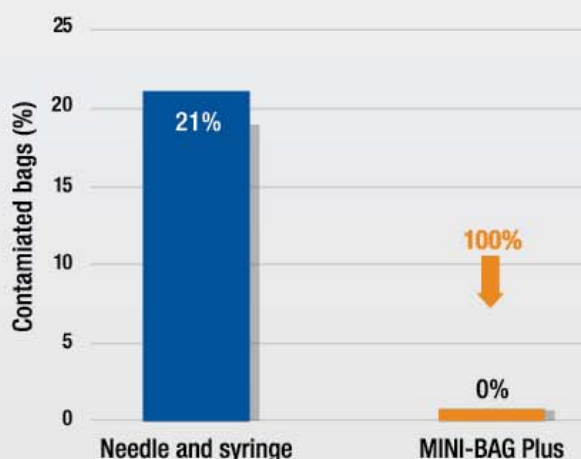
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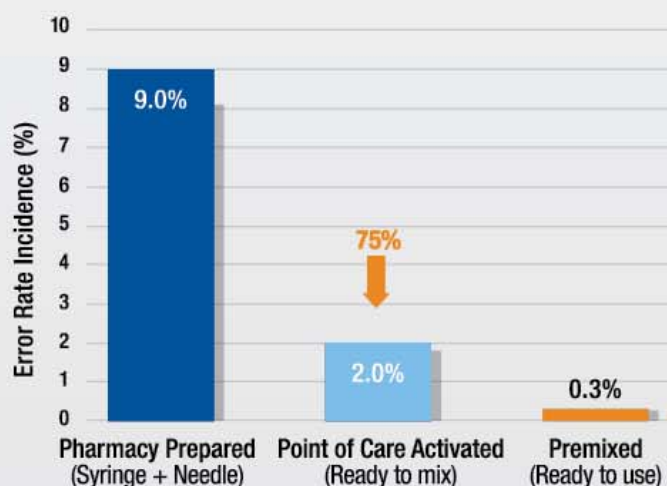
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¹ Nichols S, et al. Evaluation of the Baxter MINI-BAG Plus for ward preparation of cefuroxime / metronidazole infusion mixtures. Hospital Pharmacy. 2003; 10: 127-30

² Flynn EA, Pearson RE, Barker KN. Observational study of accuracy in compounding i.v. admixtures at five hospitals. American Journal of Health-System Pharmacy. 1997; 54: 904-12

³ Ortega A, et al. Economic evaluation of Vialflex with vial adapter in a unit-dose distribution system. Pharmacy World & Science. 1999 Dec; 21(6): 278-80.

* On ward comparison of reconstitution methods in a British Hospital

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- New Products

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Editorial

CHEUNG, Hon-Yeung

128

News & Short Communications

Study Doubts Acetaminophen Treatment in Acute Infections	129
Nivolumab: Better Alternative in Advanced Non-squamous Non-Small-Cell Lung Cancer	129
Similar Effect for Second Generation Antidepressants and Cognitive Behavioural Therapies, either Alone or in Combination	129
Nitrates May Not Be Effective in Heart Failure Management	130
Liraglutide Could Be Used To Combat Fatty Liver Disease, Study Finds	130
Benefits of Empagliflozin in Prevention of Heart Failure	130
On-Demand Pre-exposure Prophylaxis in Men at High Risk for HIV-1 Infection	131
Venetoclax: Alternative Therapy for Relapsed Chronic Lymphocytic Leukaemia	131
Flu Vaccine is Safe for Egg-Allergic and Asthmatic Children, Study Reassures	131

Pharmacy Education & Practice

Updates on Setting up and Operating a Community (Retail) Pharmacy in Hong Kong in Professional, Legal and Business Perspective	132
KWONG, Suk Fan Phyllis	
Makes Everything He Does As His Interest – An Interview with Mr. Michael Ling	139
CHAN, PH Andrew; WONG, KS Kalson	

Drug & Therapeutics

Biosimilar Pharmaceutical Products of Recombinant Human Growth Hormone (rhGH) Currently Available on Market (2 CE Units)	142
WONG, Ho Sze Hersey; WONG, Lok Sze; CHEUNG, Hon-Yeung	

Pharmaceutical Techniques & Technology

Utilities and Limitations of Polymerase Chain Reaction in Pharmaceutical and Food Analysis	149
LIU, Jing-Yi; CHEUNG, Hon-Yeung	

Society Activities

Discussion Forums for consultation of the establishment of Pharmacy Council – with the students of the two Pharmacy schools in Hong Kong	155
General Council of the Pharmaceutical Society of Hong Kong 2016	155

New Products

Aubagio (Sanofi-Aventis)	156
STRIVERDI® RESPIMAT® (Boehringer Ingelheim)	158

Professional with Strong Sense of Responsibility, Positive Mindset and Principle



It is time for yet another issue of the Hong Kong Pharmaceutical Journal. Upon launching this latest one, it signifies completion of volume 22 and demonstrates that the mission, which was initiated by the Pharmaceutical Society of Hong Kong some 22 years ago, to provide a platform of sharing, servicing and educating to its members on pharmaceutical knowledge remains unchanged. The Society should be proud of having

such a journal published regularly throughout these years even though it does not have a large number of membership nor a global distribution network; yet Hong Kong pharmacists are capable to make it realized.

The pharmaceutical society can achieve these goals because we continuously have people, like Mr. Michael Ling, who wholeheartedly devoted at different time to the pharmaceutical healthcare sector. In this issue, Mr. Ling was interviewed by two junior pharmacists and he told us how things could be done once he identified them as his interest from the very first day. With this attitude and approach, he has transformed his limited strength and resources to fruitful results; he has made many possible from impossible in many occasions. Readers should find out this secret and the details of his success by taking a closer look of this interview in pages 139-141. We hope that all our colleagues could follow his footsteps and make contributions to our society.

Because distribution of pharmaceuticals may affect people's life, this duty requires professional trainings and has been assigned to pharmacist in our society. On top of this, regulatory control is introduced to safeguard their practice. Being a pharmacist, who is an expert on drugs, regular continuing education should be a compulsory training for every pharmacist who wants to renew his license so that his pharmaceutical knowledge could be kept up-to-date. Meanwhile, regulatory laws may have to be revised according to new developments or technologies in our society. In an article written by Kwong,⁽¹⁾ we are reminded that new regulatory requirements have been introduced and implemented in 2015 for setting up and operating a community pharmacy. Her updated information is useful as it provides a step by step guideline for whoever interested to set up a retail pharmacy store in Hong Kong.

Twenty-fifteen was not an easy year for people who work in global healthcare. Looking back, the year began with the continue threat from Ebola viral infection followed by another dangerous outbreak called Middle-East Respiratory Syndrome (MERS) during last summer; both of them were viral epidemics killing thousands of people in Africa and infecting hundreds of people in South Korea, respectively. To recapture the spread of the Ebola disease and methods of cure, readers can find the relevant information in an earlier article written by Lee & Cheung.⁽²⁾ Fortunately, these two epidemics slowly ebbed and finally receded in mid of 2015.

On the other hand, with the approval of Sandoz's Zarxio by US Food and Drug Administration in 2015, it reflects that

FDA is taking a "much more engaged approach" to biosimilar development. It also signifies biosimilar drugs can finally enter the US market and have the potential to be as disruptive as generic drugs following the Hatch-Waxman Act of 1984 although it is almost a decade behind the European Community. Nevertheless, this is really a gospel for many patients because biosimilars are expected to bring significant price discounts compared with branded versions of biologics. Before the Biologics Price Competition and Innovation (BPCI) Act was passed as part of the Affordable Care Act (ACA) or colloquially, Obamacare,⁽³⁾ there was no established regulatory pathway for biosimilar drugs. But now a path has been laid down and at least four biosimilar applications are pending FDA review in 2016, with another 50 in the FDA review process. A review article written by Wong et al on biosimilar products of the recombinant human growth hormone (p.142) provides a glimpse of this trend although this biopharmaceutical is not regarded as a top 10 selling biotech drugs.

New discoveries are always a driving force for the advancement of our society. Some of these discoveries receive immediate recognitions, such as the Polymerase Chain Reaction (PCR) for amplifying DNA molecules were awarded the Nobel Prize two years after its report; while other discoveries may not be so lucky; for example the discovery and application of artemisinin, a drug that was discovered and isolated by Tu Youyou for *Plasmodium falciparum* malaria therapies took nearly 35 years to be recognized and awarded the Nobel Prize.⁽⁴⁾ It doesn't mean that the former is much important than the latter. Indeed, some of our new discoveries and applications have been over disseminated by some people while the others are not. For example, for some years, people in the molecular biology frequently claims that PCR could be used for both qualitative and quantitative determination of DNA molecules. It may be true in the real-time biological analysis but not the processed one; yet limitation of this technique has not been properly deal with and disclosed to people. Consequently, its application may mislead people, in particular, in quantitative determination of food or drug. In Liu & Cheung's article (p. 149-154), they address this problem and provide us a real picture of this technique. Certainly there are still many other similar cases in the application of sciences and technologies, which may be abused by some people for certain purposes. This phenomenon indicates that being an analytical chemist or a public serviceman handling the problem should have the ability, critical and fair mind to assess whether a method or a pieces of equipment is suitable for uses in order to drawing our final judgement.

Cheung Hon-Young
Editor-in-Chief
26th January, 2016.

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Prepared by William Kwan, Brian Leung, Janet Wong, Raymond Wong, Bryan Kan, Dilys Chow, Ivan Leung Kelvin Cheng, Matthew Ho, Peony Lau, Sally Tsang

Study Doubts Acetaminophen Treatment in Acute Infections

Date: October 5, 2015

Acetaminophen treatment is common for patients with fever due to probable infection in the intensive care unit (ICU). However, this practice is challenged by studies showing that fever might be beneficial to the treatment of infection.

A multicenter, blinded, randomized, controlled trial was done to evaluate the hypothesis that intravenous acetaminophen administration to treat fever would worsen outcomes. Seven hundred patients were enrolled in twenty three adult medical-surgical ICUs in Australia and New Zealand. Patients of 16 years old or above with a temperature of 38°C or higher within 12 hours before enrolment and who were receiving antimicrobial therapy for a known or suspected infection, were randomly assigned to receive an infusion containing either 1 g of intravenous acetaminophen or 5% dextrose in water, every 6 hours. The primary outcome measure was ICU-free days to day 28, calculated by 28 minus the number of days or part-days in ICU during the first 28 days after randomisation.

There was no significant difference in the number of ICU-free days to day 28 between the acetaminophen group (median = 23) and the

placebo group (median = 22). Other secondary outcomes, including 28-day mortality, 90-day mortality, and survival time to day 90, also did not differ greatly between the two groups. It was observed that in the acetaminophen group, the hospital and ICU length of stay were shorter among patients who survived and longer among patients who died, when compared with those taking placebo. Nonetheless, this was not the major area of interest in this study; thus the observation should be regarded as hypothesis-generating rather than a conclusion on the efficacy of acetaminophen, and cautious interpretation is required.

Since the median duration of acetaminophen administration was short, it is concluded from this study that an early administration of acetaminophen in treating fever due to suspected infection would neither increase nor reduce the number of ICU-free days. Further studies are required to investigate whether prolonged acetaminophen administration would show greater influence on patient-centered outcomes.

Source: www.nejm.org

Nivolumab: Better Alternative in Advanced Non-squamous Non-Small-Cell Lung Cancer

Date: October 22, 2015

Effective treatment options are limited for patients with non-squamous non-small-cell lung cancer (NSCLC) whose disease progresses after first-line chemotherapy. Docetaxel has been approved for second-line treatment in advanced NSCLC. Current research did not report superiority of newer agents, such as pemetrexed and erlotinib, to docetaxel in terms of overall survival.

A randomized, open-label, international phase 3 study was conducted to compare nivolumab, a fully human IgG4 programmed death-1 (PD-1) immune check point inhibitor antibody, with docetaxel in previously treated patients with advanced non-squamous NSCLC. Patients with NSCLC that had progressed during or after platinum-based doublet chemotherapy were randomly assigned to receive either nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks, or docetaxel at a dose of 75 mg per square meter of body-surface area every 3 weeks. The primary end point was overall survival.

Overall survival was longer in the nivolumab treatment group than the docetaxel treatment group. The median overall survival was 12.2 months among 292 patients receiving nivolumab and 9.4 months among 290 patients receiving docetaxel. At 1 year, the overall survival rate was higher with nivolumab (51%) than with docetaxel (39%). With additional follow-up, the overall survival rate at 18 months was 39% with nivolumab versus 23% with docetaxel. The response rate of nivolumab was higher than that of docetaxel (19% with versus 12%, $P=0.02$). Treatment-related adverse events of grade 3 or 4 were reported in 10% of the patients in the nivolumab group, much lower than the docetaxel group (54%).

In conclusion, nivolumab has shown statistically superiority in terms of survival over docetaxel in unselected patients with advanced and previously treated non-squamous NSCLC.

Source: www.nejm.org

Similar Effect for Second Generation Antidepressants and Cognitive Behavioural Therapies, either Alone or in Combination

Date: October 24, 2015

Major depressive disorder (MDD) is the most prevalent and disabling form of depression. Second generation antidepressants including selective serotonin reuptake inhibitor (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are most commonly prescribed. Despite different mechanisms of action, they share similar benefit. However, frequency and severity of side effects lead to lack of adherence to these medications. In light of the situation, studies were carried out and psychotherapy was suggested as an additional

option for patients. Cognitive behavioural therapy (CBT) is one form of psychotherapy that helps patients reduce distress and improve mood.

A systemic review was conducted to investigate the comparative benefits and harms of using the second generation antidepressants and CBT in treating MDD. Randomized controlled trials between 1990 and 2015 were searched from six databases to compare the effectiveness of using second generation antidepressant and CBT, either alone or in combination.

Meta-analyses found no statistically significant difference in the effectiveness between second generation antidepressants and CBT for response, remission, or change in 17 item Hamilton Rating Scale for Depression score. Similarly, no significant difference was found in rates of overall study discontinuation or discontinuation due to lack of efficacy.

Since both therapies had no significant difference in effectiveness, it was believed that both treatments should be made accessible, either alone or in combination. The freedom of treatment choice might improve compliance and treatment outcomes in patients with MDD.

Source: www.bmj.com

Nitrates May Not Be Effective in Heart Failure Management

Date: November 8, 2015

Exercise intolerance is a feature in patients with heart failure with a preserved ejection fraction (HFpEF), and nitrates are commonly prescribed to enhance activity tolerance. While early studies have proved the efficacy of long-acting nitrates for patients with heart failure and a reduced ejection fraction, related studies on HFpEF are limited.

A study funded by the U.S. National Heart, Lung, and Blood Institute has been conducted between April and October 2014 to test whether extended-release isosorbide mononitrate could enhance the daily activity level of patients with HFpEF. A total of 110 patients with HFpEF were randomly assigned to a six-week dose-escalation regimen of isosorbide mononitrate or placebo (from 30 mg to 60 mg to 120 mg once daily), with subsequent crossover for another six weeks. Patient-worn accelerometers were used to provide a continuous measurement of physical activity during daily life, thus reflecting the activity tolerance of patients.

Results showed that isosorbide mononitrate did not improve the daily activity level of participants. Patients receiving isosorbide

mononitrate showed lower average daily accelerometer units, including both 120-mg dose phase and the combination of three dose phases, compared to patients receiving placebo. The former in contrast showed a dose-dependent decrease in daily activity levels. Of patients receiving isosorbide mononitrate during the 120-mg phase, the number of hours of activity per day, determined by the number of fifteen-minute cumulative accelerometer units greater than 50 (activity threshold), were eighteen minutes less than those receiving placebo. No significant differences were shown in submaximal exercise capacity, quality-of life scores, and N-terminal pro-brain natriuretic peptide levels between the two groups.

In conclusion, the administration of isosorbide mononitrate would decrease the daily activity levels of patients with HFpEF, when compared with placebo. However, limitations of this study were noted, including a rapid dose escalation, and the use of organic nitrates instead of inorganic nitrates or nitrates, which might have enhanced bioavailability during exercise.

Source: www.nejm.org

Liraglutide Could Be Used To Combat Fatty Liver Disease, Study Finds

Date: November 19, 2015

It was noted from *The Lancet* on 19 November 2015 that liraglutide, a glucagon-like peptide-1 (GLP-1) analogue for treating type II diabetes was found to be effective in the histological resolution of non-alcoholic steatohepatitis (NASH), a form of non-alcoholic fatty liver disease (NAFLD) which can increase the risk of liver failure, in addition to reducing hepatic steatosis, concentrations of liver enzymes, and insulin resistance in murine models of fatty liver disease.

This double-blinded, randomized, placebo-controlled phase 2 trial was conducted in four UK medical centers to assess the effects of subcutaneous injections of liraglutide (1- 8 mg daily) compared with placebo on overweight patients with NASH. After 48 weeks, 9 out of

23 patients (39%) in the liraglutide treatment group demonstrated clearing evidence of NASH from their livers, compared to 2 of 22 (9%) patients in the placebo group. Moreover, patients in the active treatment group had a higher level of weight loss (over 5 kg) upon receiving the medication.

Promisingly, this study gives hope in developing drugs to cope with the large clinical needs, stemmed from the absence of licensed treatments for non-alcoholic fatty liver disease, and the growing incidences of fatty liver disease and obesity.

Source: www.thelancet.com

Benefits of Empagliflozin in Prevention of Heart Failure

Date: November 26, 2015

A research showed that empagliflozin, an inhibitor of sodium-glucose cotransporter 2, as compared with placebo, can reduce both cardiovascular morbidity and mortality in patients with type 2 diabetes who were at a high risk for cardiovascular events and receiving standard care.

In this randomized, double-blind, placebo-controlled trial, patients with type 2 diabetes and risk factors for heart disease were randomly assigned to receive once-daily doses of either empagliflozin (10 mg or 25 mg), or a placebo. The drug or placebo was given in addition to standard care.

At the end of the trial, patients treated with empagliflozin, as compared with placebo, showed reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood

pressure with no increase in heart rate, as well as small increases in both LDL and HDL cholesterol. There were also significant reductions in the rates of death from cardiovascular causes (3.7% versus 5.9% in the placebo group); and of hospitalization for heart failure (2.7% and 4.1%, respectively).

The outcomes for subgroups of patients who had heart failure at the beginning of the trial and those who did not were analyzed - reductions in the hospitalization outcomes were similar between the two subgroups. Therefore, it might be possible that empagliflozin might not only prevent deterioration in patients who already had heart failure, but also may prevent patients who never had heart failure before from developing the condition.

Source: www.nejm.org

On-Demand Pre-exposure Prophylaxis in Men at High Risk for HIV-1 Infection

Date: December 1, 2015

Prevention of HIV-1 and HIV-2 has been a longstanding challenge in public health. Without effective vaccine, biomedical interventions are particularly crucial in prevention. Among all the reliable interventions, pre-exposure prophylaxis, which refers to the prescription of antiretroviral drugs to HIV-negative patients before virus exposure, is recently recognized and adopted.

In a multicentre study, namely IPERGAY, the efficacy and safety of sexual activity-dependent pre-exposure prophylaxis with TDF-FTC were assessed. Randomization was performed in the study together with the use of placebo due to previous inconsistent efficacy of pre-exposure prophylaxis. TDF-FTC was a fixed-dose combination of 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC) per pill. From 2012 to 2014, 445 participants were screened at seven study sites.

Participants took a median number of 15 pills per month during the study period. Overall sexual practices did not change among them. The relative risk of HIV-1 infection was significantly reduced by 86% in patients taking TDF-FTC. In the intention-to-treat analysis, the reduction rate was 42%, but it escalated to 92% in a case-control subgroup with detectable levels of tenofovir in blood. Nevertheless, there were occasional drug-related gastrointestinal adverse events (14%).

In conclusion, pre-exposure prophylaxis with TDF-FTC was effective in reducing the incidence of HIV-1 infection. However, the results of this study cannot be extrapolated to homosexual men with less frequent sexual intercourse.

Source: www.nejm.org

Venetoclax: Alternative Therapy for Relapsed Chronic Lymphocytic Leukaemia

Date: December 6, 2015

Conventionally, Ibrutinib monotherapy and idelalisib in combination with rituximab are prescribed indefinitely for patients with relapsed Chronic Lymphocytic Leukaemia (CLL). However, this treatment is likely to induce resistance and the outcome remains unsatisfactory. Venetoclax, a highly selective inhibitor of BCL2, was investigated under phase 1 study in patients with relapsed CLL or small lymphocytic lymphoma (SLL). The objectives were to determine safety and pharmacokinetic profile, as well as assessing the response rates and efficacy.

The study was an open-label, multicentre, dose-escalation trial of venetoclax for 116 patients with relapsed CLL or SLL. In the dose-escalation phase, 56 patients received active treatment ranging from 150 to 1200 mg per day. In the expansion cohort, 60 additional patients were treated with a weekly stepwise doses as high as 400 mg per day.

In the pharmacokinetic profile, peak venetoclax levels were attained 6 to 8 hours after the first dose and terminal half-life was approximately 19 hours. Venetoclax was proven to be active at all doses, with overall response rate as high as 79%. In the dose-escalation cohort, the most significant toxic effect was tumour lysis syndrome (18%). Another notable toxic effect was grade 3 or 4 neutropenia, which was developed in 41% of patients during the trial.

In conclusion, selective targeting of BCL2 with venetoclax had substantiated anti-tumour activity, improved survival and a manageable safety profile in patients with relapsed CLL or SLL. However, maximum tolerated dose of venetoclax has yet to be investigated.

Source: www.nejm.org

Flu Vaccine is Safe for Egg-Allergic and Asthmatic Children, Study Reassures

Date: December 9, 2015

Research attests that the children's flu vaccine is safe for children with egg allergy and/or asthma, while there have been warnings about using live attenuated influenza vaccine (LAIV) in them.

LAIV is a nasal spray vaccine particularly developed for young people. In 2012, the UK Department of Health recommended annual vaccination with LAIV for those who aged between 2 and 16. However, safety data for its use in teenagers with egg allergy and/or asthma are limited. Some guidelines do not recommend using LAIV in children under 5 with a history of recurrent wheeze or asthma. A research was carried out to evaluate the safety of using LAIV in children with egg allergy and asthma.

779 young people aged between 2 and 18 with egg allergy were immunized with LAIV. 40% had experienced an allergic reaction to egg in the past 12 months, 35% had experienced previous anaphylaxis to egg and 57% had been diagnosed of asthma or recurrent wheeze.

Within 2 hours of vaccination, 9 participants (1.2%) experienced a local allergic reaction with symptoms like a skin rash, sneezing, and itchiness. 221 participants reported delayed events potentially due to the vaccine, but none of them were admitted to hospital. After 4 weeks of vaccination, there was no increase in respiratory tract symptoms, assessed with an asthma control test.

This study consolidates previous findings that in young people with egg allergy, the likelihood of LAIV triggering a systemic allergic reaction is low. When the wheezing symptoms are well controlled and without evidence of active wheezing in the 72 hours before immunization, use of LAIV in children at risk of wheeze is suggested to be appropriate. Meanwhile, alertness to the occurrence of anaphylaxis and facilities for its treatment are emphasized in all settings providing vaccination.

Source: www.bmj.com

Updates on Setting up and Operating a Community (Retail) Pharmacy in Hong Kong in Professional, Legal and Business Perspective

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ABSTRACT

The Legislative Council of Hong Kong passed the Pharmacy and Poisons Ordinance Bill 2014 on January 2015. According to the Pharmacy and Poison Ordinance, the retail sale of prescription drugs and other pharmaceutical products is only allowed by an authorized seller of poisons. And, the premises is required to be under the control of a registered pharmacist. In this Pharmacy and Poison (Amendment) Ordinance 2015, a new definition of “pharmaceutical products” and “medicine” is described. This new definition of “pharmaceutical products” and “medicine” definitely affects the operation of pharmacy, especially community/retail pharmacy. This report is to update the procedures in set-up a new community/retail pharmacy in professional, legal and business perspective, and to review the major laws related to the operation of community/retail pharmacy in Hong Kong.

Keywords: *Pharmacy and Poison Ordinance, Community Pharmacy, Retail Pharmacy, Professional, legal and business perspective, setting up a pharmacy, operating a pharmacy, Pharmacy Practice in Hong Kong*

INTRODUCTION

The Pharmacy and Poison (Amendment) Ordinance 2015 (Chapter 138 of the Laws of Hong Kong) was published in the Gazette on 30 January 2015 following the Legislative Council of Hong Kong passed the Pharmacy and Poison Ordinance Bill 2014 on 21 January 2015. All provisions of this ordinance, except section 21, and section 37, have taken into effect on 6 February 2015. Practicing in the related trade and industry, pharmacists have to understand clearly the new definition of “pharmaceutical Product” and “medicine” in this ordinance.⁽¹⁾

“Pharmaceutical product and medicine mean any substance or combination of substances –

- (a) presented as having properties for treating or preventing disease in human beings or animals; or
- (b) that may used , or administered to, human beings or animals, either with a view to –
 - (i) restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; or
 - (ii) making a medical diagnosis.

With changes of the ordinance, the management of the pharmacy must know well the newly passed Pharmacy

and Poison (Amendment) Ordinance when setting up a new retail pharmacy in Hong Kong. The existing pharmacies also definitely need to adjust their ways of operations in some degree to comply with the newly passed ordinance. This study is divided into 2 major sections: (I) Update on setting up a new retail pharmacy in Hong Kong; (II) Review the major laws related to operating a community pharmacy and the Code of Practice for Authorized Sellers of Poisons as effective on 1 June 2015.

I. UPDATE ON SETTING UP A NEW RETAIL PHARMACY

According to section 11, 12, 13, 13A, 21, 22, 23, 24 and 28 of the Pharmacy and Poisons Amendment Ordinance, only the Authorized seller of Poisons (ASP) is allowed to run a retail business possessing and selling Part I and Part II poisons in registered premises under the control of a registered pharmacist. The latest major steps to set up a new retail pharmacy are described in section I-a below.

I-A. Major Steps to Set Up a New Retail Pharmacy in Hong Kong

The major steps in setting up a retail pharmacy includes:

- 1) **Premises:** Look for a proper place for the registration of premises.
- 2) **Employees:** Employ the needed persons, such as a person-in-charge, a pharmacist, technicians, other shop helpers.
- 3) **Business Registration Certificate:** Get a Business Registration Certificate as required by the Business Registration Ordinance. Meanwhile, decoration of the premises can be started after consulting the pharmacist about the requirement of the layout of the dispensing area and the facilities required. Remember that display of logo in the prescribed form in subsection 1 of Pharmacy and Poisons Regulation is not permitted before the approval of registration according to the section 13A of the Pharmacy and Poisons Ordinance 2015.
- 4) **Application:** Prepare and submit an application for the registration of premises of ASP to the Drug Office of the Department of Health. The current address of Retailers Regulatory Unit under Traders Licensing and Compliance Division of Drug Office is Rm2550, 25/F, Wu Chung House, 213 Queen's Road East, Wanchai, Hong Kong (as of 25 August 2015). The office will provide a letter of receiving with a reference number for your record once the complete application received. Please see attachment 1 (page 1 and 2) for the checklist downloaded from the Drug Office's website (<http://drugoffice.gov.hk>).

- 5) **Interview:** After the application is accepted by the Pharmacy and Poisons Board, the office will arrange an interview for the ASP to-be or any person-in-charge nominated by ASP to-be, the nominated pharmacist and maybe a representative of the company (usually its owner or director). The purpose of the interview is to evaluate if the ASP to-be or any person-in-charge nominated by ASP to-be is a fit and proper person to conduct a retail sale of poisons in accordance with section 13 of the Pharmacy and Poisons Ordinance. In sector I-b of this study, preparation for the interview is suggested and discussed.
- 6) **Inspection:** Once the applicant passes the interview, a public office of the Drug Office will inspect the actual locations of premises in person to see if the premises are suitable for conducting the retail sale of poisons. The public office will collect a set of sample of prescription label(s) and warning label(s), a set of sample of store and pharmacist stamps, a sample of customer's receipt generated from the cash register, a copy of Handbook for Employees / Rules for Employees (員工守則) and any related document if necessary. The office will also reconfirm the proposed shop and dispensing hours at this time.
- 7) **Licensing fee:** After passing the inspection and approved by the Pharmacy and Poisons Board, a letter to inform your approval and a bill for licensing fee will send to the premises. The amount of fee is HK\$1000 as listed in section 9 of Pharmacy and Poisons Regulations. Pay the fee in specified place and then collect the license at the office as instructed.
- 8) **Display a logo:** The logo in the form prescribed in subsection 1 of the ordinance shall be displayed under section 13A of the Pharmacy and Poisons Ordinance. At the time, the authorized seller of poisons at the registered premises under the control of registered pharmacist is authorized to conduct retail sale of poisons in accordance with section 11, 12, 13, 13A of the Pharmacy and Poisons Amendment Ordinance.

Once the certificate of registration is collected, the process of registration of premises of Authorized Seller of Poisons is completed.

I-B Suggested Preparation of the Interview

To evaluate if the nominated authorized seller of poisons is fit and proper to conduct the retail sale of poisons, an interview by public officers (usually a senior pharmacist and a pharmacist

of the Retail Regulatory Unit) will be scheduled. Usually, the nominated person-in-charge of the premises, the pharmacist and maybe a representative of the company (usually its owner or director) are requested to attend the interview. Questions regarding the laws related to pharmacy and pharmaceutical products, and the operation of the premises will be asked. It is strongly suggested to review and understand the related laws before attending the interview. Please refer section II below for the laws related to the pharmacy and pharmaceutical products for more information. Questions commonly asked such as:

- a) Definition of Authorized Seller of Poisons
- b) Definition of pharmaceutical products and medicine
- c) Overview of major Laws of Hong Kong related
- d) Overview of categories of pharmaceutical products
- e) Classification of pharmaceutical products and examples of pharmaceutical products of each category;
- f) Requirements of sale of pharmaceutical products in different categories.
- g) Labeling requirements of pharmaceutical products.
- h) Knowledge about purchasing and receiving pharmaceutical products from suppliers for sale in the premises.
- i) Knowledge about possession and storage of pharmaceutical products in the premises.
- j) Code of Practice for Authorized Seller of Poisons.
- k) Knowledge about the record books (i.e. Prescription Record Book, Antibiotics Record Book, Dangerous Drug Register, Part I (S1) Sale Record Book and Psychotropic Substances Record Book).

II. REVIEWS THE MAJOR LAWS RELATED TO OPERATING A COMMUNITY (RETAIL) PHARMACY IN HONG KONG

In section II-a of this study, the major laws related to pharmacy and pharmaceutical products in daily operation in a pharmacy are described. The Code of Practice for ASP as effective 1 June 2015 will be discussed in section II-b. In addition, seven examples are provided at the end of this section for further elaboration.

II-A Relevant Statutes and Regulations

The relevant statutes and regulations regarding pharmacy, pharmaceutical products and other matters related daily operation of a pharmacy are listed and described in the following table.

Table 1. Major Laws of Hong Kong related to operating a community (retail) pharmacy in Hong Kong⁽¹⁾

Chapter	Title	Brief Description
138	Pharmacy and Poisons Ordinance	To make provisions relating pharmacy, pharmaceutical products and poisons. Under this ordinance, there are five Regulations: Cap 138A: Pharmacy and Poisons Regulation Cap 138B: Poisons List Regulations Cap 138C: Course of Training, Study and Examination for Applicants for Registration as Pharmacists Regulations Cap 138D: Pharmacy and Poison (Pharmacy and poisons Appeal Tribunal) Regulations Cap 138E: Pharmacists (Disciplinary Procedure) Regulations
137	Antibiotics Ordinance	To restrict the sale and supply of certain antibiotic substances. Under this ordinance: Cap 137A Antibiotics Regulations
134	Dangerous Drug Ordinance	To consolidate the law relating to dangerous drugs. To restrict the sale, supply, dispensing, manufacturing, import/export of dangerous drugs and other related matters. Under this ordinance: Cap134A Dangerous Drug Regulation

Chapter	Title	Brief Description												
132	Public Health and Municipal Service Ordinance	Within this ordinance, some provisions involve the regulation and control of the preparation, sales, labeling and advertisement of food or drugs. The purpose is to protect generally purchasers of food and drugs from unfitted food or drugs for human consumption. Under this ordinance, Regulations related to Food and Drugs: - Cap 132H Coloring Matter in Food Regulations - Cap 132R Dried Milk Regulation - Cap 132U Sweeteners in Food Regulation - Cap 132V Food Adulteration (Metallic contamination) Regulations - Cap 132W Food and Drugs (Composition and Labeling) Regulations - Cap 132X, Cap132Y, Cap132Z, Cap132AA Food Business related Regulations - Cap 132AP, Cap132AQ Milk related regulations - Cap 132AR Mineral Oil in Food Regulations - Cap 132BD Preservatives in Food Regulation												
549	Chinese Medicine Ordinance	To make provisions for the registration of proprietary Chinese Medicines, the licensing of traders of Chinese Medicines, and others related matters Under this ordinance: - Cap549B Chinese Medicine Practitioners (Fees) Regulation - Cap549C Chinese Medicine Practitioners (Registration) Regulation - Cap549E Chinese Medicine (Fees) Regulation - Cap549F Chinese Medicine Regulation - Cap549G Chinese Medicine Traders (Regulatory) Regulation												
60	Import and Export Ordinance	To regulate and control the import / export of articles into / from Hong Kong. To grant licenses for import / export of articles. Under this ordinance, Regulations related: - Cap60A Import and Export (General) Regulations - Cap60B Import and Export (Fees) Regulations (Please note that to import/export pharmaceutical product, the business body may require to register with the Pharmacy and Poison Board as a licensed wholesale dealers or licensed manufacturer in accordance with the Pharmacy and Poison Ordinance)												
231	Undesirable Medical Advertisements Ordinance	To control and restrict certain advertisement relating to medical and health matters												
362	Trade Description Ordinance	To prohibit false, misleading or incomplete trade descriptions / information in respect of goods or services in the course of trade. To prohibit certain unfair trade practices.												
352	Waste Disposal Ordinance	To control and regulate the production, storage, collection and disposal of waste including chemicals and pharmaceutical products. To grant license and register of places and persons connected with such activities. Under the ordinance, Regulations related: - Cap354C Waste Disposal (Chemical Waste) (General) Regulation - Cap354I Waste Disposal (Chemical Waste)(General) Regulation (Application of Section 4 and Parts III, IV, V and VI) Notice 1993 - Cap354J Waste Disposal (Charges for Disposal of Chemical Waste) Regulation (Please note that the sector code for Chemicals and Chemical Products is 351-2. The industry type is 3522 Drug and Medicines.) Suggest to look at the information provided on the website of Environmental Protection Department.												
303	Radiation Ordinance	To control the import, export, possession and use of radioactive substances. To grant, cancel, suspend or renew licenses issued under this ordinance. Under this ordinance, Regulations related: - Cap303A Radiation (Control of radioactive substances) Regulations - Cap303B Radiation (Radioactive Apparatus) Regulations												
310	Business Registration Ordinance	In accordance with this ordinance, to start a business in Hong Kong, any person, any sole proprietorship or partnership or a company registered under the Company Ordinance in Hong Kong shall apply a business registration within one month of the commencement. Under this ordinance, Regulation related: Cap310A Business Registration Regulations												
57	Employment Ordinance	To provides the required conditions of employment in Hong Kong. To require certain protection and benefits for the employees in Hong Kong including*: <table border="0"> <tr> <td>a) Wage protection</td> <td>e) Sickness allowance</td> <td>i) Long service payment</td> </tr> <tr> <td>b) Rest days</td> <td>f) Maternity Protection</td> <td>j) Employment protection</td> </tr> <tr> <td>c) Holidays with pay</td> <td>g) Statutory paternity leave</td> <td>k) Termination of employment contract</td> </tr> <tr> <td>d) Paid annual leave</td> <td>h) Severance payment</td> <td>l) Protection against anti-Union discrimination</td> </tr> </table> *Suggest to look at the information provided on the website of Labour Department.	a) Wage protection	e) Sickness allowance	i) Long service payment	b) Rest days	f) Maternity Protection	j) Employment protection	c) Holidays with pay	g) Statutory paternity leave	k) Termination of employment contract	d) Paid annual leave	h) Severance payment	l) Protection against anti-Union discrimination
a) Wage protection	e) Sickness allowance	i) Long service payment												
b) Rest days	f) Maternity Protection	j) Employment protection												
c) Holidays with pay	g) Statutory paternity leave	k) Termination of employment contract												
d) Paid annual leave	h) Severance payment	l) Protection against anti-Union discrimination												
509	Occupational safety and Health Ordinance	To require that safety and health protection shall be provided to employees in workplaces, both industrial and non-industrial. To set out the basic requirements for accident prevention, fire prevention, safe and healthy working environment, hygiene at workplace, first aid at workplace, as well as safe manual operations in workplaces. Under this ordinance, regulations related: - Cap509A Occupational Safety and Health Regulation - Cap509B Occupational Safety and Health (Display Screen Equipment) Regulation												
608	Minimum Wage Ordinance	To define the minimum wage. To require employers to keep records of the total number of hours worked by employees who earns HK\$13,300 or less per month.												
282	Employee's Compensation Ordinance	To regulate that employers must be in possession of a valid employee compensation insurance cover. To establish a no-fault, non-contributing employee compensation system for work injuries. Under this ordinance: - Cap282A Employees' Compensation Regulations - Cap282B Employees' Compensation (Rules of Court) Rules												
486	Personal Data (Privacy) Ordinance	To protect the privacy rights of a person in relation to personal data. To establish the Six Data Protection Principles for proper handling of personal data. Six Data Protection Principles (DPPs): - DPP1: Data Collection Principle - DPP2: Accuracy and Retention Principle - DPP3: Data Use Principle - DPP4: Data Security Principle - DPP5: Openness Principle - DPP6: Data Access and Correction Principle Any misuse / inappropriate use of personal data or unauthorized disclosure of personal date is considered a criminal offense under this ordinance.												

II-B Review the Code of Practice for Authorized Seller of Poisons as effective on 1 June 2015

The Code of Practice for Authorized Seller of Poisons (The Code) become effective on 1 June 2015. Three major sections are included: a). Section 1: Premises, b). Section 2: Management and Staff, c). Section 3: Services and System of operation.

In section 1, the general requirements and standards of the registered premises are clearly described, such as the display of the certificate of Registration of Premises and the certificate of Registration of Pharmacist, the security system for storage of controlled drugs, dispensing facilities required, the layouts and decoration of the premises meeting any health, safety and environmental requirements provided by the relevant government departments. The code also stated that ASP has the responsibility to ensure that the registered premises comply with the professional responsibilities of its pharmacist. The dispensing area must be clean and in good order. It is reserved for dispensing purpose only. Locked cabinets or other locked receptacles must be provided in compliance with the law requirements. Disposal of pharmaceutical wastes shall comply with the laws such as the Waste Disposal Ordinance. The disposal of dangerous drugs shall inform the Department of Health and the process of destruction must be witnessed by an inspector.

In Section 2, the general requirements and standard of managing a retail pharmacy described in accordance with the relevant legislations. The Code emphasis that an ASP must take all reasonable steps to ensure its pharmacy operated in compliance with the relevant statutes, regulations and the Code. All staffs involved in the sale, receipt and storage of pharmaceutical products must be trained adequately in a reasonable time period. ASP must ensure all advertising and promotional activities in compliance with relevant legislations, for instance Undesirable Medical Advertisement Ordinance, Public Health and Municipal Service Ordinance, and Trade Description Ordinance. ASP must be in full co-operation with any inspector in his carrying out of duties under legislation. It is the responsibility of ASP to submit to the Secretary of the Pharmacy and Poisons Board in the Mouth of January in each year a list showing the address of the registered premises and the name of the registered pharmacist who control in person of such premises.

In Section 3, the requirements on procurement, storage, sale, supply, record keeping and dispensing medicines are stated generally and clearly. It is now required to purchase controlled medicines from the manufacturers, wholesalers or other retailers in the form of written order (such as electronic order). All written purchase orders and corresponding invoices must be kept and retained for inspection on the premises for 2 years from the date of the transaction. An ASP may also supply the controlled medicines to a purchaser for the purpose of his trade, business or profession by means of wholesale dealings. And, a written order must be obtained from the purchaser before the completion of the sale. The written order must include:

- a) name and address of the purchaser
- b) trade, business or profession of the purchaser
- c) name and quantity of the product requested
- d) the purpose of which it is purchased
- e) the date of which it is written
- f) the signature of the purchaser

If the controlled medicines requested are Part I First Schedule Poisons, the sale may be recorded in the Part I (S1) Poisons Record Book instead of a written order in accordance with Section 22 Limitation on sale of Part I poisons of Cap 138.

II-C Examples

Example 1: *A registered pharmacist, a body or unincorporated body of persons plans to carry on a business of retail sale of prescription drugs and other pharmaceutical products in Hong Kong.*

To carry on a business of retail sale of prescription drugs and other pharmaceutical products, a registered pharmacist, a body or unincorporated body of persons shall be as an authorized seller of poisons, but not a listed seller of poisons. Laws related to register of premises of an authorized seller of poisons¹:

Cap 138 Pharmacy and Poison Ordinance

Section 11: Authorized sellers of poisons

Section 12: Premises are required to be under the control of a registered pharmacist

Section 13: Registration of premises

Section 13A: Display of Logo

Cap 310 Business Registration Ordinance

Example 2: *Sale of both Part I and Part II poisons by an Authorized Seller of Poisons.*

An authorized seller of poisons is allowed to sell both Part I and Part II poisons at the registered premises under the control of a registered pharmacist (See Example 1 for details of registration of premises). The sale of such poisons must comply with the conditions and requirement required by the relevant Laws of Hong Kong as below:¹

Cap 138 Part 2 Pharmacy and Poisons Board

Section 4B: Code of conduct and code of practice

(Code of Practice of Authorized Seller of Poisons)

Part 6 Sale and Possession of Poisons

Section 21: Conditions of sale of Part I poisons

Section 22: Limitations on sale of Part I poisons

Section 24: Possession of poisons by retailers

Section 26: Conditions of sale of Part II poisons

Section 27: Poisons to be labeled, etc.

Cap 138A Part I Preliminary

Regulation 3: Application of section 22 restricted to the First Schedule

Part II Additional Restrictions on the Sale of Poisons

Regulation 9: Additional restriction of sale of poisons in the Third Schedule

Part III Supplementary provisions with respect to labeling and containers of poisons

Regulation 12: Manner of labeling containers

Regulation 13: Labeling of name of poisons

Regulation 14: Labeling of particulars as to proportions of the poisons

- Regulation 15: "Poison" to be in English and Chinese (see also Fifth Schedule for more)
- Regulation 16: Special precautions in the case of certain articles
- Regulation 17: Name of seller and address of premises
- Regulation 18: Form of containers of poisons
- Regulation 38: Disclosure of composition of medicines
- Regulation 38A: Labeling of certain medicines (Medicine, which is not included in Part I of Poisons List or in the schedule to the Antibiotics Regulations, shall be labeled with the dosage and the route and frequency of administration clearly legible in English and Chinese.)

Example 3: Requirements for labeling Part II poisons.

Part II poisons shall be labeled with the information including:

- 1) Name of poison.
- 2) If more than one ingredient is a poison, the proportion of each poison contained to the total of the ingredients in the preparation.
- 3) Name and address of the seller of poison.
- 4) Label eligibly in English and Chinese the dosage and route and frequency of administration.
- 5) Medicines made up ready for internal treatment of human consumption except insulin and substances included in the First Schedule: "Caution. This substance is dangerous to exceed the stated dose." 「注意: 服食過量有危險。」
- 6) For external medicines, label with statement: "For external use only. 祇供外用。"
- 7) And others special labeling requirement if applicable in accordance with legislation. (See Regulation 16 and Schedule 5 of Pharmacy and Poisons Regulations)

Laws related to labeling of Part II poisons⁽¹⁾:

- Cap 138A Section 27: Poisons to be labeled, etc.
- Regulation 13: Labeling of name of poison
- Regulation 14: Labeling of particulars as to proportions of the poison
- Regulation 15: "Poison" to be in English and Chinese. (Part II poison do not label with the word "Poison" but see also Fifth Schedule for additional requirements)
- Regulation 16: Special precautions in the case of certain articles
- Regulation 17: Name of seller and address of premises
- Regulation 37: Labeling by Licensed manufacturers.
- Regulation 38: Disclosure of composition of medicines
- Regulation 38A: Labeling of certain medicines

Example 4: Requirements of dispensing labels.

All prescribed medicines dispensed with the prescriptions signed and dated by the registered medical practitioners,

registered dentists or registered veterinary surgeon, and all medicines dispensed (including Non-poison, Part II, Part I only or Schedule 1 Poisons) in the present of a registered pharmacist must affix with a dispensing label with the following information:

- 1) Name of patient
- 2) Date of dispensing
- 3) Name and address of the pharmacy
- 4) Name of medicine (trade name or pharmacological name)
- 5) Dosage per unit (in English and Chinese)
- 6) Method of use, dosage and frequency of administration (in English and Chinese)
- 7) Precautions where applicable

Laws related to the labeling requirements⁽¹⁾:

- Cap 138A Section 27: Poisons to be labeled, etc.
- Regulation 13: Labeling of name of poison
- Regulation 14: Labeling of particulars as to proportions of the poison
- Regulation 16: Special precautions in the case of certain articles
- Regulation 17: Name of seller and address of premises
- Regulation 37: Labeling by Licensed manufacturers.
- Regulation 38: Disclosure of composition of medicines
- Regulation 38A: Labeling of certain medicines
- Code of Practice for Authorized Seller of Poison (in accordance with Section 4B of Cap 138)
- Appendix A Mandatory requirements for labeling of dispensed medicines

(Please note that the requirements for labeling Part II poison shall be complied if the dispensed medicines are Part II poisons.)

Example 5: Requirements and restriction on sale of antibiotics (such as erythromycin) to a patient in a pharmacy.

Erythromycin is a substance included in the schedule I of the Antibiotics Regulations. According to section 4 of the Antibiotics Ordinance and section 3.1 of the Code of Practice for the Authorized Seller of Poisons, erythromycin shall be sold by a registered pharmacist or an ASP against a prescription signed and dated by a registered practitioner, registered dentist or registered veterinary. According to Section 7 of the Antibiotics Ordinance (Cap137), the prescription and the Prescription Book for recording are retained in the premises for a period of 2 years from the date of dispensing. At the time of dispensing, the date dispensed, the quantity dispensed, the name including manufacturer's name and HK registration number shall be marked on the prescription. In case of a prescription which may be dispensed on more than once, a copy of that prescription shall be maintained in the book, and which book is retained for a period of 2 years from the date of dispensing. All records shall be maintained and opened for inspection by an inspector appointed by Department of Health under section 9 of Cap 137.

A prescription must be in writing and include the following:

- a) Signature and date of the prescriber
- b) Address of the prescriber
- c) Name and address of patient
- d) The total amount of the medicine to be supplied and the dose to be taken or administered
- e) If the prescription is given by a registered dentist, the words "For Dental Treatment Only 僅限牙科醫療用" are written.

- f) If the prescription is given by a registered veterinary surgeon, the words "For Animal Treatment Only 僅限醫治禽畜用" are written.

Laws related:⁽¹⁾

Cap 137

Section 4 Antibiotics Ordinance

Section 7 Maintenance of records

Section 9 Inspections and enforcement of Ordinance

Cap138A

Regulation 9 Additional restriction of sale of poisons in the Third Schedule (about requirements of a prescription)

Code of Practice for ASP

Section3.1 Sale and Supply of Medicines

Section3.2 Dispensing Medicines under the Authority of a Prescription

Please see Example 4 above for the requirement of labeling of dispensed medicine.

Example 6: Requirements and restrictions on sale of dangerous drugs (such as diazepam) to a patient in a pharmacy.

Diazepam is listed in the Schedule 1, Schedule 3 and Part I of the Pharmacy and Poisons Regulations. It is also listed in Part I of the First schedule of the Dangerous Drug Ordinance. According to the Regulation 9 of Pharmacy and Poisons Regulation, Section 31 of Dangerous Drug Ordinance, Regulation 3 of Dangerous Drug Regulation, section 3.1 and 3.2 of the Code of Practice for Authorized Seller of Poisons, diazepam shall be dispensed against a prescription. In addition to the requirements of a prescription for Third schedule drugs under the Pharmacy and Poisons Regulations, the prescription of diazepam must

- a) be written in ink or otherwise be indelible;
- b) the address of the authorized prescriber;
- c) signed and dated by the authorized prescriber;
- d) the name, identity card or any proof of identity number, address of the patient;
- e) the total amount of the dangerous drug or the preparation to be supplied

When dispensing a prescription prescribing a dangerous drug (such as diazepam), a person (the pharmacist or a person under the supervision of the pharmacist) mark on the prescription the date, the quantity dispensed, the name of drug including the manufacturer's name and HK registration number on the prescription. The prescription should be kept and retain on the premises for 2 years from the date of dispensing.

Laws related:⁽¹⁾

Cap134 Dangerous Drug Ordinance

Section 31 Supply of Dangerous Drug on prescription

Cap138A

Regulation 9 Additional restriction of sale of poisons in the Third Schedule (about requirements of a prescription)

Code of Practice for ASP

Section 3.1 Sale and Supply of Medicines

Service 3.2 Dispensing Medicines under the Authority of a Prescription

Service 3.4 Record Keeping

Appendix C Form specified in the First Schedule to the Dangerous Drugs Regulations

Example 7: Labeling requirements and restrictions of a consumed product for diabetic patient for sale in the pharmacy.
No advertising for the treatment of any endocrine disease

including diabetes in accordance with the Undesirable Medical Advertisements Ordinance. However, according to the Schedule 4 of the Undesirable Medical Advertisements Ordinance (Cap 231), a consumed product may advertise with the claims (i), (ii), (iii), (iv) below only if the following disclaimer is included¹ – "This product is not registered under the Pharmacy and Poisons Ordinance or the Chinese Medicine Ordinance. Any claim made for it has not been subject to evaluation for such registration. This product is not intended to diagnose, treat or prevent any disease. 此產品沒有根據《藥劑業及毒藥條例》或《中醫藥條例》註冊。為此產品作出的任何聲稱亦沒有為進行該等註冊而接受評核。此產品並不供作診斷、治療或預防任何疾病之用。" The claims allowed are:

- i) "This product is suitable for people concerned about blood pressure. 此產品適合關注血糖的人士服用。";
- ii) "This Product may assist in stabilizing blood sugar. 此產品或有助於穩定血糖。";
- iii) "This product is intended for people concerned about blood sugar. 此產品以關注血糖的人士為對象。";
- iv) "This product is for the consumption by people concerned about blood sugar. 此產品供關注血糖的人士服用。"

In addition, all pre-packed food products are required to have Nutritional Labeling according to the Food and Drugs (Composition and Labeling) Regulations (Cap 132W).

SUMMARY

As almost all provisions of the Pharmacy and Poisons Amendment Ordinance comes into effect on 1 June 2015, all pharmacist, authorized seller of poisons, persons-in-charge of ASP and other staffs of pharmacies should familiarized with the newly passed ordinance to avoid any unintentional mal-practices at the registered premises. This study draws out some important points for quick reference of the amendment ordinance, and also provides some study tips for those who are planning to set up a retail business in sale of controlled substances and other pharmaceutical products in Hong Kong. For preparing the interview of registration of premises of ASP, it is strongly recommended to read through carefully the amendment ordinance (Cap138), Antibiotics Ordinance (Cap137), Dangerous Drug Ordinance (Cap134), Undesirable Medical Advertisements (Cap231), Chinese Medicine Ordinance (Cap 549) and their subsidiary regulations. It is also necessary to skim through and aware of other related legislations, such as those listed in Table 1. Remembered that a successful business depends on the gradual build-up of reputation and business revenues through practicing in profession and legal manner.

Ms KWONG, Suk Fan Phyllis is a Registered Pharmacist. She obtained her Bachelor of Science in Pharmacy from the University of Wisconsin, Madison in USA in 1993 and Master of Science in Clinical Pharmacy in 2007 from the University of Sunderland in England. Her email address: kwongps@foxmail.com

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**DEPARTMENT OF HEALTH
PHARMACEUTICAL SERVICE
INSPECTION AND LICENSING SECTION**

Room 2550, 25/F, Wu Chung House, 213 Queen's Road East, Wan Chai, Hong Kong,
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4A

CHECKLIST

Application for Registration of Premises of an Authorized Seller of Poisons

Please submit this checklist with the following documents. If you answer "No" to any questions below, please provide a written explanation.

Have you submitted

	<u>Yes</u>	<u>No</u>
(1) A completed application form?	☐	☐
(2) Copy of Business Registration Certificate?	☐	☐
(3) (a) For limited companies : (i) Copy of Certificate of Incorporation and (ii) Copy of Directors' List (e.g. "Form AR1" from Companies Registry or for, newly formed limited companies, full set of "Form NC1" or "Form NC1G")? OR (b) For companies run by sole proprietorship : Copy of "Form 1(a)" from the Business Registration Office? OR (c) For companies run by partnership : Copy of "Form 1(c)" from the Business Registration Office?	}	☐
(4) A list including name(s) in English and Chinese, Hong Kong Identity Card number(s) and posts of the sole proprietor/ partners/ directors and staff?	☐	☐
(5) A signed declaration of each owner (i.e. sole proprietor or partner) or director, and each staff member indicating whether he/she has been an owner, a director or an employee of other trader(s) of western medicines (i.e. importer/exporter, retailer, wholesaler or manufacturer, regardless of whether the trader is still in business)? [If so, please list out the relevant information, including the English name(s) of the trader(s) and the period involved.]?	☐	☐
(6) Statement of qualifications and relevant experience of the sole proprietor/ partners/ directors and all staff members?	☐	☐
(7) Testimonials from previous employer(s) certifying the above relevant experience?	☐	☐
(8) Copy of the Certificate of Registration and Practicing Certificate of the registered pharmacist?	☐	☐
(9) Floor plan of the Dispensary including the total area, name and address of the Dispensary stamped with the company chop?	☐	☐
(10) Floor plan of the Dispensing Room including the total area, name and address of the Dispensary stamped with company chop?	☐	☐
(11) Statement of each owner (i.e. the sole proprietor or partner) or director, and each staff member indicating whether he/she is being prosecuted or has any previous conviction both of drug-related offences [If so, please list out the details of the case]?	☐	☐
(12) Signed statement of appointment of all staff members by the owner (i.e. the sole-proprietor or partner) or director indicating their position in the applicant company?	☐	☐

(DO12/2013)

Makes Everything He Does As His Interest – An Interview with Mr. Michael Ling

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ABSTRACT

Michael Ling may be a familiar name to many hospital pharmacists and other members of pharmacy profession. Despite his retirement in 2012, Mr. Ling is still serving the Kwong Wah Hospital as an honorary pharmacy advisor. Right before he started this interview with The Hong Kong Pharmaceutical Journal today, he was still very busy with lots of work. Since his pharmacist registration in 1980, he has devoted most of his time as a hospital pharmacist and, now, is still making contribution to our healthcare system to enhance medication safety and to educate pharmacy students. In this interview, we are glad to have Mr. Ling to share with us his experience, how he helps shape our profession and his secret in keeping up his passion with his work.

Keywords: Michael Ling, hospital pharmacist, The Journal of Practising Pharmacists, Pharmaceutical Society of Hong Kong, Pharmacy and Poisons Board, Pharmacy services

INTRODUCTION TO MR. MICHAEL LING

Mr. Ling obtained his degree of Bachelor of Pharmacy in the Chelsea College, University of London (now King's College) in the United Kingdom in 1975. With a keen interest in clinical pharmacy, he pursued the Master of Clinical and Hospital Pharmacy in the University of Iowa, as he believed that clinical pharmacy is more advanced in the United States. Afterwards, he became a registered pharmacist in Hong Kong in 1980. Soon after his registration, he secured a place as the first pharmacist in Grantham Hospital, where he worked for 11 years. Later he moved on to Kwong Wah Hospital and had served the hospital for 21 years as the Senior Pharmacist, and later the Department Manager until his retirement. Soon after he returned to Hong Kong, he joined the Practising Pharmacist Association of Hong Kong (PPAHK), and became a committee member and later the vice-president of the PPA. During his career, Mr Ling once sat as the vice-president of the Pharmaceutical Society of Hong Kong (PSHK) and had been one of the founding member of the Society of Hospital Pharmacist of Hong Kong (SHPHK) in 1983. He had also been in the presidential post of the SHPHK for 3 years.

After his retirement, he was invited to stay at the KWH, as a recognition to his contribution, as an honorary pharmacy advisor to raise awareness of medication safety there as well as helping the development of the hospital as well. Moreover, he is also a surveyor of The Australian Council on Healthcare Standards. Michael has dedicated over 30 years to medication quality and safety since he joined the profession in 1980. Meanwhile, he is a guest lecturer in the CUHK, HKU, IVE, Caritas Institute of Higher Education and HKU SPACE to share his experience in risk management and drug safety.

THE INTERVIEW

PJ: Thank you Mr. Ling to accept the invitation from HKPJ to talk to us. To begin the interview, we learned that you were the first pharmacist in Grantham Hospital? What were your duties at that time? We guess they are quite different from what we do now?

Mr. Ling: At that time, most of the hospital pharmacies were managed by dispensers or senior dispensers, except in government owned hospitals, such as the Princess Margaret Hospital (PMH), Queen Elizabeth Hospital (QEH) and Queen Mary Hospital (QMH). So I was the first and the only pharmacist employed by Grantham Hospital, which was a subvented hospital before the establishment of Hospital Authority. I was responsible for drug procurement and drug budget management. Besides, I also improved the dispensing service, published drug bulletins and drug formulary for the hospital.

PJ: What else did you do at that time? We heard that you were quite active in certain local pharmacist organizations.

Mr. Ling: I was a member and later the vice-president of the PPAHK. I helped PPAHK to publish the first local pharmacist journal, Practising Pharmacist, which was the predecessor of Hong Kong Pharmaceutical Journal. In the mid-80s, we had more and more hospital pharmacists in Hong Kong coming back from countries like the UK, US, Australia and Taiwan. We thought our pharmacy services could be developed to meet similar standards as in those countries. At that time the

hospital sector was more progressive than other sectors, so we founded the SHPHK with a few comrades. Back in the 1980s, it was not compulsory to label drugs if they were dispensed by doctors. I was in the Pharmacy and Poisons Board in the early 1990's and one of the improvements I did was to advocate for mandatory drug labelling.



Photo 1. The first few issues of *Journal of Practising Pharmacists*. Mr. Ling had been the Chief Editor since 1983.

PJ: It seemed that our profession had been developing quite quickly between the 80s and 90s. Did the profession have any tough times?

Mr. Ling: There were some hard times for us but opportunities were there too. We were quite frustrated by the unsatisfactory progress on separation of dispensing from prescribing proposed during the early 1980s. At that time, hospital dispensers struck for higher salary. Together with a rocketing drug cost, more pharmacists were employed in hospitals in an attempt to tackle those crises. This formed an opportunity for us. In the 90s, a medication incident in the Prince of Wales Hospital (PWH) increased the public's awareness of medication safety. On the other hand, new technology was deployed in pharmacy. All these were only possible if more pharmacists joined us. The first few batches of local graduates met such need. During and after the financial crisis in 1997-1998, expansion of hospital pharmacy stopped, and many graduates could only work as dispensers or salespersons in pharmaceutical companies temporarily. And then everything got better after 2003 when HA acquired all government-run General Outpatient Clinics (GOPCs) and some hospital pharmacies under the HA started to extend service to 24 hours. I understand that some of the young pharmacists may worry about their future. There may be some hard times ahead but one can always overcome challenges if one has a will. All one need is to always get oneself well prepared.

PJ: What do you think the young pharmacists or pharmacy students should do to prepare themselves well and contribute to our profession?

Mr. Ling: Be open-minded and try to learn everything. For me, I did not stop thinking of new ways to improve our service even though I was doing something very repetitive. I always try to figure out why I have to do this, how to do it in a better way, and if there may be any hidden problems. We could think like a student, in a way so as to keep ourselves open-minded and take an interest in everything around us.

PJ: We now understand your key to make achievements in your career. Then, what have you done in the past that you are really satisfied with?

Mr. Ling: It is about medication safety too. In the past, some of the products might not have generic names on the packages or they shared very similar appearances. To avoid such undesirable incidents, some local manufacturers were invited to discuss how together we could improve the safety features on the packages. They adopted some of our recommendations and together we avoided some potential look-alike-sound-alike issues. However, I always emphasize that manufacturers should not be blamed for every medication incident. Every colleague has the responsibility to pick the correct item. Communication is also important. We are not just putting up warnings or posters in the pharmacy. We have to listen to our colleagues' opinions, understand their difficulties and then reach a consensus. People will only practise accordingly if we have their buy-in.



Photo 2. Making a speech in the Medication Safety for International Pharmaceutical Federation in Jerusalem in 1996.

PJ: Do you have any regrets for something that you could not make it work?

Mr. Ling: I have to say it is the Pharmacy Private-Public Partnership Programme. We proposed it and made some progress a few years ago. Our original plan was to release some patients to community pharmacy for dispensing. Then for various reasons, the project was aborted. Another thing

is, due to my passion in clinical pharmacy, I hope there could be more clinical pharmacists in more specialties in the future. I also hope that there will be more leaders, with passion and leadership, to lead our profession. There is not enough communication between pharmacists in different sectors too. If we could learn to be more considerate and more willing to have communication among ourselves, there could be more collaborations between different sectors of pharmacy and together we can go further.

PJ: You worked in this sector for such a long time. Did you encounter anyone that you really admire or appreciate?

Mr. Ling: If you are talking about pharmacists, I would say they are Mr. Ng Kim Wah, Mr. Daniel Ho and Ms. Chiang Sau Chu. I am impressed by their enormous passions that support them to develop our profession. There are still some people who are not pharmacists but I appreciate a lot too. Dr. Ko Wing Man is one of them. He is a good leader and a sincere, nice person who do things in a reliable and practical way.

PJ: After 30 years as a hospital pharmacist, if you are given a chance to start again, would you still opt for hospitals?

Mr. Ling: Sure. I have an enormous interest in clinical pharmacy, but I have no regrets even though in most of the days I have been doing things related to quality and safety. I love talking to patients, but I learnt so much from the management work and was involved in various projects to improve pharmacy services for the public. After all, I still have many chances to talk to patients. I have joined the outreach programmes arranged by the CUHK School of Pharmacy, and the SHPHK, which have given me the opportunities to educate patients in drug education talks. I would like to add that we should not limit ourselves to therapeutics only. As I mentioned, we should always keep ourselves open-minded. There are still lots of things apart from therapeutics for us to learn. I like clinical pharmacy but I also have vast interests in people management, pharmacy automation and IT systems. I love doing what I am interested in. And I am interested in everything I encounter. That's how I get ready for every opportunity.



Photo 3. Mr. Ling gave a patient educational talk in an elderly centre.



Photo 4. Mr. Michael Ling and two of his best partners in his career, Mr. Ng Kim Wah (Left) and Ms. Chiang Sau Chu (Middle).

PJ: Our last question. Is there any particular person you would like to thank for helping you or supporting you in your life?

Mr. Ling: Oh, there are many. I thank all people I met in my life who had established everything with me. Each Chief Pharmacist (from both the Department of Health and the Chief Pharmacist Office of Hospital Authority) had given me lots of opportunities to develop this sector, my career and myself. I was inspired by them. I am also grateful for having Prof. Kenneth Lee and Ms. Chiang Sau Chu as my partners in my career.

Last but not least, we have to thank Mr. Ling to spare a nice afternoon with us to share his story and his key to success. We all wish he could enjoy his retired life.

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Biosimilar Pharmaceutical Products of Recombinant Human Growth Hormone (rhGH) Currently Available on Market

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ABSTRACT

For a long time the juvenile disorder of growth had been treated with purified human growth hormone extraction until the first generation of synthetic growth hormone was introduced based on the recombinant DNA technology in the early 1980s. Since the patents of the biotechnology-derived growth hormones have gradually expired, manufacturers have developed a variety of off-patent biopharmaceuticals by adopting the same technological approach but different manufacturing processes. After going through a centralized procedure based on the biosimilar concepts, currently there are two biosimilar recombinant human growth hormone (rhGH) products which have been granted marketing approval by the European Medicines Agency (EMA). The procedure includes comparability studies with a reference product in terms of quality, safety and efficacy as well as long-term pharmacovigilance. This review intends to give an overview of how these biosimilar products have been developed and regulated.

Keywords: human growth hormone, somatropin, protropin, biosimilar drugs, biotechnological process, genotropin, humatrope

INTRODUCTION

Natural Human Growth Hormone

Human growth hormone (hGH), also known as somatotropin, is a natural hormone synthesized, stored and secreted by somatotrophs in the anterior pituitary gland in a pulsatile fashion. It is a single chain peptide of 191 amino acid residues that corresponds to a molecular weight of 22 kDa. Its structure is stabilized by 2 disulphide bridges forming a large (Cys⁵³ - Cys¹⁶⁵) and a small (Cys¹⁸² - Cys¹⁸⁹) loop.⁽¹⁾

During childhood and adolescence, hGH promotes protein synthesis for general tissue growth as a result of the stimulation of insulin-like growth factor 1 (IGF-1) produced in

the liver. It also promotes linear bone growth by stimulating the formation of cartilage in growth areas of bones. Moreover, hGH can trigger lipolysis in adipose tissues and decrease glucose utilization to regulate the body composition.⁽²⁾

hGH is primarily used as a replacement therapy in patients with growth deficiency (GHD) who suffer from growth retardation, poor bone density, reduced muscle strength, insulin resistance and impaired cardiac function due to the inability of their pituitary glands to produce sufficient hGH. It can also be used to treat patients with growth failure but normal endogenous GH secretion, such as Prader-Willi syndrome, Turner syndrome, chronic renal insufficiency and Short Stature Homeobox-containing Gene (SHOX) deficiency.⁽³⁾ Usually hGH is administered through subcutaneous injection.

Prior to 1985, growth hormone (pit-hGH) extracted from pituitary glands of human cadavers was used. However, the availability of the pit-hGH was limited because GH is species specific and only small amounts could be obtained from the cadavers.⁽⁴⁾ There was also evidence indicating that some preparations were contaminated with infectious agents, such as patients having Creutzfeldt-Jakob disease with incubation periods up to 40 years.⁽⁵⁾ Therefore, use of pit-hGH for therapy was prohibited in most countries and it was replaced by recombinant human growth hormone (rhGH) that could be rapidly and abundantly produced. Furthermore, it eliminates the risk of pathogen transmission from pit-hGH donors.⁽⁶⁾

Recombinant Human Growth Hormone

Protropin: the First-generation rhGH

The first generation of the biosynthetic hGH using recombinant DNA technology was protropin (Genentech Inc, San Francisco). It was first engineered in 1979 and made commercialized on 17 October 1985 upon the approval from the U.S. Food and Drug Administration (FDA).⁽⁷⁾ *Escherichia coli* was chosen as the host of choice because hGH is a biologically active, nonglycosylated protein that does not require post-translational modifications to function properly. As all of the *E. coli* proteins start their peptide elongation with an S-adenosyl methionine

during the translation, protropin contains the same primary sequence of 191 amino acids but with an additional methionine present at the N-terminal end. This polypeptide is called somatrem.⁽⁸⁾

To produce the rhGH, the DNA coding for hGH is first constructed by combining a chemically reporter DNA fragment with the complementary DNA (cDNA) derived from pituitary mRNA. Then the hybrid gene is inserted into a suitable bacterial expression vector and introduced into *E.coli*. Transcription and translation of the inserted DNA to synthesize rhGH will subsequently take place in the host cells when they are cultured and multiplied in a selective medium.⁽⁹⁾ A batch of manufactured host cells is taken from the master clone to create a working cell stock. And the working cell stock is cultivated in a bioreactor where cells proliferate and produce a high yield of rhGH, which is extracted and purified.⁽¹⁰⁾

Table 1 shows a list of major patented rhGH products currently available on market.⁽¹¹⁾ Due to the high rate of antibody formation caused by methionine at the N-terminal end of the polypeptide,⁽¹²⁾ a variety of methionyl-free rhGH has been developed, i.e. using somatropin as the active substance, which prompted a series of patent-related lawsuits.⁽¹³⁻¹⁶⁾

Biopharmaceuticals using *E. coli* as the Expression System

rhGH products can be synthesized in a specific *E.coli* strain that has been modified by the insertion of a plasmid carrying the gene for human growth hormone. The product would then be secreted into the cytoplasm.⁽¹⁷⁾ rhGH products can also be synthesized by a specific *E.coli* strain as a precursor that consists of the rhGH molecule preceded by the secretion signal of a protein in *E.coli*. This precursor is directed to the plasma membrane of the cell. The signal sequence is removed and the native protein is secreted into the periplasm so that the protein is folded appropriately. Periplasmic production can eliminate the need for refolding as proteins can form their correct configuration of disulfide bonds in the oxidizing environment of the bacterial periplasm.⁽¹⁷⁾ Examples include **Genotropin**, **Humatrope** and **Nutropin**.⁽¹⁸⁻²¹⁾

Although *E.coli* is an ideal tool for the rapid production of rhGH, one of the major problems is the requirement of extra steps before purification, such as protein refolding and

cell disruption due to the deposition of the target product into insoluble aggregates. As a result, the prolonged production process decreases yields and increases the production cost.⁽²²⁾

Biopharmaceuticals using Eukaryotic Cells as the Expression System

In view of the problems associated with the recombinant protein production in *E.coli*, some manufacturers utilize eukaryotic cell lines to produce rhGH, which can secrete the recombinant products directly to the culture medium.⁽²³⁾ This can simplify the manufacturing processing as the recombinant proteins are recovered directly in the culture broth without extra steps for cell disruption. For example, **Saizen** is produced in a mammalian cell line (mouse C127) modified by the insertion of the human growth hormone gene, and are secreted through the cell membrane into the cell culture medium for collection and purification. High secretion efficiency without being spatially constrained by bacterial periplasm provides great yields of high-quality recombinant products.⁽²⁴⁾

BIOSIMILAR DRUGS OF HUMAN GROWTH HORMONE

Since the patents on the formulation of the reference rhGH products have gradually expired, pharmaceutical manufacturers have developed a variety of similar off-patent biopharmaceuticals called 'biosimilars' or 'similar biological medicinal products' as shown in **Table 2**. They are complex proteins harvested from various manufacturing processes employing different expression systems with different extraction and purification processes.⁽²⁵⁾

Before being launched on the market, the biosimilar rhGH products are assessed by a strict regulatory framework proposed by the European Medicines Agency (EMA). Unlike generic products, they should show similar active ingredients and demonstrate bioequivalence in quality, safety and efficacy as compared to the reference rhGH products.⁽²⁶⁾ **Figure 1** shows the comparison of the respective requirements for regulatory approval between the reference and the biosimilar products. Different from the reference products, safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required in the non-clinical studies for the approval of the biosimilar products.⁽²⁷⁾

Table 1. Major patent drugs of rhGH available on market

Product Name	Active Substance	Innovator (Country)	Authorization Date by FDA	Expression System	Indications
Genotropin	Somatropin	Pfizer (USA)	24/08/1995	<i>E.coli</i> K12	Growth hormone deficiency, Prader-Willi syndrome, Small for Gestational Age, Turner syndrome, and Idiopathic Short Stature
Humatrope	Somatropin	Eli Lilly (USA)	08/03/1987	<i>E.coli</i>	Growth hormone deficiency, Turner syndrome, idiopathic short stature, SHOX deficiency
Norditropin	Somatropin	Novo Nordisk (USA)	08/05/1995	<i>E.coli</i> MC1061	Growth hormone deficiency, short stature associated with Noonan syndrome, short stature associated with Turner syndrome
NutropinAq	Somatropin	Genentech Inc. (USA)	29/12/1995	<i>E.coli</i>	Growth hormone deficiency, idiopathic short stature, Turner syndrome and chronic kidney disease
Saizen	Somatropin	Merck Serono (USA)	08/10/1996	Mouse C127 cell line	GH deficiency
Zomacton	Somatropin	Ferring (Australia)	25/05/1995	<i>E.coli</i>	GH deficiency

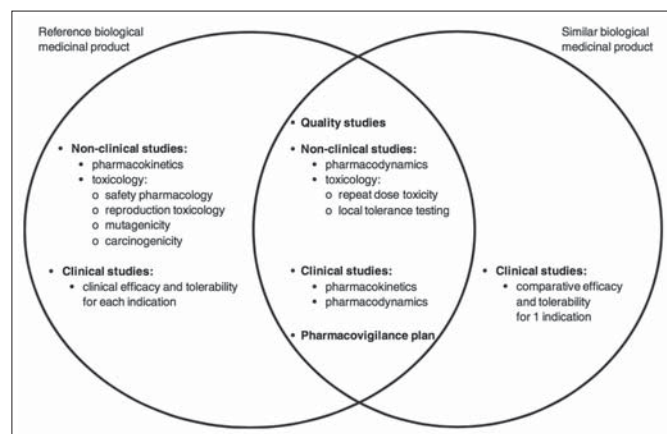


Figure 1: Different requirements for regulatory approval by the European Medicines Agency between reference biopharmaceuticals and similar biopharmaceuticals with a similar active substance⁽²⁷⁾

Table 2 shows a list of biosimilar rhGH products available in various countries. In the beginning Omnitrope, Valtropin and Somatropin biopartners were approved by the EMA.⁽²⁸⁻³⁰⁾ However, Valtropin was later withdrawn in 2012. Jintropin, Hypertropin and Scitropin A are lower-cost alternatives for biosimilar rhGH products, but they have not been given marketing approval by the EMA because of their lacking supporting literature documents regarding the comparability studies with a reference product specified.⁽³¹⁾ Omnitrope is chosen for demonstration because it is the first biosimilar product granted marketing approval.

Omnitrope: the First Biosimilar Product of rhGH Approved by the EMA

Omnitrope is a rhGH variant composed of 191 amino acid residues with a molecular weight of 22.125 kDa, taking Genotropin as the reference product. It is produced in an *E. coli* strain modified by the addition of the gene for hGH, giving an amino acid sequence identical to the natural hGH produced by the pituitary gland. The pharmaceutical form of Omnitrope is a powder and solvent for solution for subcutaneous injection.⁽²⁸⁾

Regulatory Approval of Omnitrope

Quality data

The quality of Omnitrope is compared with that of the reference product Genotropin. The manufacturing process and

process controls are described, while analytical comparability studies are conducted for physiochemical and structural characterization as well as purity and impurity determination. In addition, stability studies are conducted to assess the effect of storage conditions on the quality. Any difference in their quality attributes should be justified in relation to its potential impact on safety and efficacy.^(27,32)

Non-clinical comparative studies

Non-clinical comparative studies involve in vitro studies via receptor-binding studies and cell proliferation assays as well as in vivo pharmacodynamic studies through weight-gain assay and tibia growth assay using rat model. Moreover, considering the immunogenic potential of rhGH, at least one repeat dose toxicity study would be conducted for toxicokinetic measurements. By determining the antibody titres, cross-reactivity and neutralising capacity, the presence of host cell proteins (HCPs) and impurities in the biosimilar product would be detected.⁽²⁷⁾

Clinical comparative studies

The clinical comparability studies include pharmacokinetic/pharmacodynamics studies in healthy volunteers, and subsequently comparative clinical efficacy and safety trials in most sensitive and relevant patient population to demonstrate the therapeutic equivalence between the biosimilar product and the reference product.⁽²⁶⁾

Pharmacokinetic/pharmacodynamics studies

Pharmacokinetics studies were conducted through single-dose subcutaneous administration in healthy volunteers. Omnitrope shows a similar pharmacokinetic profile as its reference product Genotropin.⁽³³⁾

Clinical efficacy studies

The final comparability exercises include the clinical phase III, which aims to compare Omnitrope with the reference product Genotropin in terms of long-term clinical efficacy and immunogenic safety. Usually the clinical phase III is performed to show if the biosimilar is therapeutically equivalent to the originator in the most sensitive and relevant patient population. As in the assessment of Omnitrope, a randomized clinical trial was performed in GHD children (2-14 years) that were the

Product Name	Active Substance	Expression System	Reference Product	Authorization Date (Country)*	Producer
Omnitrope	Somatropin	<i>E.coli</i>	Genotropin	12/04/2006 (EU) 20/04/2009 (Can) 29/09/2010 (Aus) 01/11/2013 (NZ)	Sandoz
Valtropin	Somatropin	<i>Saccharomyces cerevisiae</i>	Humatrope	24/04/2006 (EU) (Withdrawn in 2012)	Biopartners
Somatropin Biopartners	Somatropin	<i>Saccharomyces cerevisiae</i>	Humatrope	05/08/2013 (EU)	Biopartners
Jintropin	Somatropin	<i>E.coli</i>	NI	1997 (CN)	GeneScience
Hypertropin	Somatropin	<i>E.coli</i>	NI	2007 (CN)	NeoGenica BioScience
Scitropin A	Somatropin	<i>E.coli</i>	NI	2005 (SN)	SciGen

* EU=European Union; Can=Canada; Aus=Australia; NZ=New Zealand; CN=China; SN=Singapore

most sensitive to growth hormone. Among 89 GHD children, 44 patients received Omnitrope and 45 patients received Genotropin for 9 months. The four primary efficacy endpoints were body height, height standard deviation score (HSDS), height velocity (HV) and height velocity standard deviation scores (HVSDS). **Figure 2** shows the data recorded as mean height velocity standard deviation scores before the treatment and after 3, 6 and 9 months of treatment. After 9 months, patients with Genotropin treatment were switched to Omnitrope treatment. The result showed that there were no statistical differences between both treatment groups. The treatment response was not affected by switching from Genotropin to Omnitrope.^(33,34)

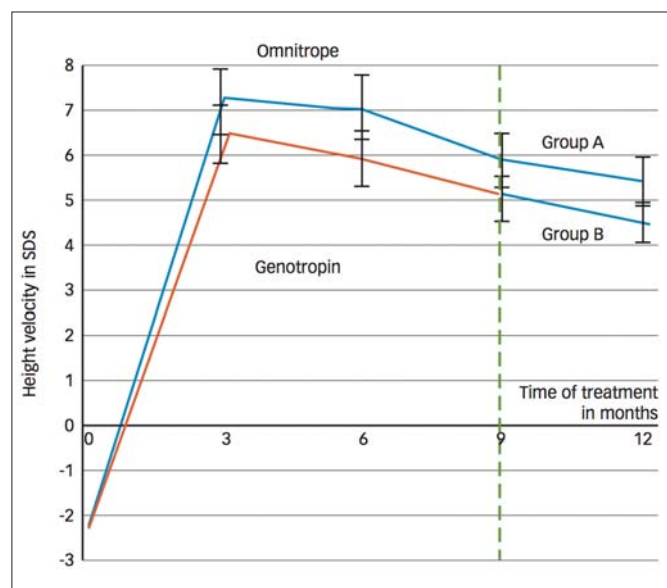


Figure 2: Mean height velocity standard deviation scores: Omnitrope versus Genotropin⁽³³⁾

The secondary endpoints, IGF-1 and IGFBP-3 serum levels, were also measured. Since the same GH receptors were involved in all approved indications of rhGHs, the EMA would permit, given similar safety and efficacy, the extrapolation of data from Omnitrope-treated GHD children to other indications of Genotropin, letting the use of Omnitrope in indications for which no study has formally been performed.⁽²⁶⁾

Clinical Tolerability Studies

Even if the biosimilar product is therapeutically equivalent to its reference product, their immunogenic safety may be different. Since low quantities of variants or impurities may not be found in the non-clinical testing, the immunogenic safety can only be determined in clinical trials.⁽³⁵⁾ The immunogenic potential may vary among different rhGH preparations and is influenced by a number of factors like the nature of active substances, impurities, manufacturing process and target of patients.⁽³⁶⁾ These factors may contribute to undesired host immune response to the recombinant protein, as the result of which may reduce drug efficacy or even lead to fatal adverse reactions. Therefore, before approval, 12-month comparative immunogenicity data are collected. The occurrence of anti-GH and anti-HCP antibodies against *E. coli* proteins is closely followed.

During the primary 9-month trial, it was found that about 60% of Omnitrope-treated patients developed anti-GH antibodies but all patients developed anti-HCP antibodies without any effect on growth rate. Comparatively, only 2% and 0% of Genotropin-treated patients respectively developed anti-GH and anti-HCP antibodies.⁽²⁷⁾ Further clinical investigation showed that the development of anti-GH antibodies was induced by high concentrations of host-cell proteins from the early stage of drug development. Therefore, the manufacturing process for Omnitrope was modified with additional purification steps to remove the contaminants during the drug development so that the concentration of host-cell proteins in Omnitrope was within the range of other authorized rhGH products. Consequently, after 12 months, no patients developed anti-GH antibodies while only one patient developed anti-HCP antibodies among 51 treatment-naïve children.⁽²⁷⁾

Pharmacovigilance Plan

After marketing approval, long-term post-marketing surveillance studies are required to assess the long-term safety and to detect any rare events of immunogenicity in the same group of patients treated with Omnitrope.⁽²⁶⁾ The result has shown that Omnitrope is therapeutically consistent with Genotropin and biosimilar rhGH products in terms of safety and efficacy.

CONCLUSION

The manufacturing process of biosimilar rhGH products varies among different manufacturers. The biosimilar rhGH products may be made from different expression systems, extraction and purification processes. All these factors may affect the characteristics, safety and efficacy of a biosimilar product. Therefore, the biosimilar rhGH products undergo the centralized procedures by the EMA before receiving marketing approval. Comparability assessments are carried out to assess if a biosimilar product is similar to a reference product in terms of quality, safety and efficacy. The comparability assessments include pharmacokinetic and pharmacodynamics studies on both in vivo and in vitro bioassays, clinical efficacy, quality, safety and immunogenicity studies. Long-term post-marketing surveillance studies are needed to assess the rare immunogenicity in specific indications.

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) to fill in their answers there.)

1. A lack of growth hormone in childhood will result in what sort of health problem?

- I. Slow mental development.
- II. dwarfism.
- III. slim.

- A. I. only
- B. II. only
- C. I. & II only
- D. All of above.

2. Which outward sign below is not the symptoms of growth hormone deficiency?

- A. hyperglycaemic
- B. poor bone density
- C. reduced muscle strength
- D. Impaired cardiac function.

3. hGH can be used to treat all the following health problem except

- A. homeobox-containing gene deficiency.
- B. Prader-Willi syndrome.
- C. Turner syndrome.
- D. Down syndrome.

4. The following brand product is rhGH except

- A. Saizen.
- B. Nutrotropin.
- C. Atropin.
- D. Zomacton.

5. Which one below is not applied to the physical-chemical properties of the natural human growth hormone?

- A. It's molecular weight is 122 KDa.
- B. It consists of 2 disulphide bridges.
- C. It has two loop structure.
- D. It is a single chain polypeptide.



2 CE Units

Biosimilar Pharmaceutical Products of Recombinant Human Growth Hormone (rhGH) Currently Available on Market

6. Which company uses a mammalian cell line for production of a recombinant human growth hormone?

- A. Pfizer
- B. Novo Nordisk
- C. Merck Serono
- D. Genetech Inc.

7. To file a biosimilar biopharmaceutical in Europe, which thing below is not required?

- A. Comparative efficacy study.
- B. Repeat dose toxicity.
- C. Data of Pharmacodynamics study.
- D. Mutagenicity study.

8. Comparability assessments are carried out to assess in terms of all characteristics to a reference product except

- A. Safety
- B. Clinical efficacy
- C. Cost
- D. Quality.

9. Periplasmic production of a recombinant product has the advantage of

- A. Bypassing refolding problem of the recombinant product.
- B. Easier Purification
- C. Easier concentration
- D. Giving a higher yield.

10. hGH should not be given to a kid continuously for

- A. longer than one year
- B. less than a year
- C. until an acceptable adult height
- D. until the adult age

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 223(D&T)

From Aerodynamics to Inhalation Technique - More about Inhaled Medications

1. B 2. C 3. D 4. C 5. A 6. C 7. D 8. A 9. B 10. D

First-line treatment for chronic hepatitis B (CHB) in adults¹⁻³

Viread
tenofovir disoproxil fumarate 300 mg

Maximizing
outcomes
in CHB out
to 8 years

One liver. One life.  One VIREAD.

- ▶ Potent and sustained viral suppression⁵
- ▶ 0% resistance detected through 8 years^{4,5}
- ▶ Regression of fibrosis or cirrhosis⁶

Abbreviated Prescribing Information (HK-SEP11-US-OCT10)

Presentation: Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). **Indications:** 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults and pediatric patients 12 years of age and older. **Dosage:** **Adults:** One tablet once daily taken orally, without regard to food. **Pediatric patients:** CHB: Not recommended; HIV-1: One tablet once daily taken orally, without regard to food for patients ≥ 12 years of age and ≥ 35 kg. **Elderly:** Insufficient data to make dose recommendations for patients >65 years. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min. **Contraindications:** None. **Warnings and Precautions:** Lactic acidosis/severe hepatomegaly with steatosis; severe exacerbation of hepatitis after discontinuation of anti-HBV treatment; new onset or worsening renal impairment; coadministration with products containing TDF or adefovir dipivoxil; patients coinfecting with HIV-1 and HBV; decreases in bone mineral density; fat redistribution; immune reconstitution syndrome; early virologic failure. **Interactions & Side effects:** refer to Package Insert.

Before prescribing, please consult full prescribing information which is available upon request.

VIREAD is a registered trademark of Gilead Sciences, Inc., or its related companies.

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Utilities and Limitations of Polymerase Chain Reaction in Pharmaceutical and Food Analysis

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ABSTRACT

As one of the most powerful technique in biological sciences, PCR-based method has been widely used for amplifying and analyzing both DNAs and RNAs in various biological samples from human, animal and plants. It is a fast and user-friendly qualitative method comparing to the traditional cloning methodology, which is tedious and time consuming. However, this technique has its inherent shortcomings, which should not be neglected whenever used for quantitative analysis. In this present article, the types, utilities and limitations of PCR in pharmaceutical and food analysis are reviewed and described. Some influencing factors affecting the efficiency and applicability of PCR are addressed with particular attention on the effect of sample processing on the reliability of quantitative applications.

Keywords: Polymerase chain reaction (PCR), pharmaceutical and food analysis, application, limitation, processing methods, reliability

INTRODUCTION

A Brief History of Polymerase Chain Reaction (PCR)

Polymerase chain reaction (PCR) has revolutionized the biological sciences since its' first description by Kleppe *et al* in 1971.^[1] Kleppe, K, E Ohtsuka [1],⁽²⁾ As one of the most powerful molecular techniques, it allows people to analysis nucleotides in various fields such as clinical diagnosis, forensic medicine, food authentication and microbial identification.⁽³⁾ Its first laboratory application was first described by Saiki and collaborators in 1985.⁽⁴⁻⁷⁾ The impact of its use in many fields earned the Nobel Prize in Chemistry for Kary Mullis in 1993. Since then, applications of PCR spread like mushrooming and so far have been documented in more than 350,000 publications according to a figure shown in pubmed.com.

Why PCR is so popular in biological science? Researchers believe that it is due to its versatility, specificity and sensitivity that the technique possesses.⁽²⁾ This technique allows people to rapidly and specifically amplify either DNA or RNA materials from very tiny amount to a visible and analytical quantity otherwise would not be determined by other methods for both qualitative and quantitative purposes. By staining the amplified

products with either a chemical dye (ethidium bromide) or labelling them with a fluorescent dyes on primers prior to amplification, the products could be visualized on agarose gel followed by extraction and analysis with other methods.

The PCR Process and Its Reaction Components

The PCR process is basically accomplished via repeat amplification of a target DNA fragment under a programmed reaction condition. At the beginning of each cycle, dsDNA has to be denatured by heat to form ssDNA and then duplicated with the help of a primer and an enzyme called DNA polymerase. The former is a short polynucleotides complementary to one region of the target ssDNA. Hence, a typical PCR cycle is comprised of three steps in different temperature patterns: (1) denaturation causing the two complementary strands to separate at 94°C; (2) hybridization allowing the specific primers to bind to the DNA at 45-50°C and (3) extension during which further nucleotides will be added to the developing DNA strand at 72°C, the ideal working temperature for the thermostable DNA polymerase enzyme to play its best physiological role (**Figure 1A**). Such cycles are repeated to double the DNA molecules, and finally a million molecules will be cloned for detection in around two hours.⁽⁸⁾

The number or quantity of nucleotide derived could be estimated based on the following formula:⁽²⁾

$$C = C_0(1+E)^n$$

$$E = 10^{-1/s} - 1; \text{ if } E = 1 \text{ then } s = -3.3219$$

where,

C: final amount of DNA

C₀: initial amount of DNA

E: efficiency

n: number of cycles

s: slope of the exponential phase.

In order to complete a PCR reaction, some strict requirements have to be met. Firstly, an optimal pH has to be maintained for the PCR reaction to take place. This requirement means a proper buffer is required. Secondly, a proper concentration of magnesium chloride (MgCl₂) as a cofactor for the polymerase enzyme is needed. Thirdly, deoxynucleotide triphosphates (dNTPs) consisting of the four bases adenine (A), thymine (T), cytosine (C) and guanine (G) serve as "bricks" for the DNA strands and supply energy for the reaction. Fourthly, a target DNA should be present. Fifthly, PCR primers including forward primer and reverse primer to anneal

to a unique address in the target DNA is required. They are required because DNA polymerase can only kick off replication from a small stretch of dsDNA to synthesize more identical product. Sixthly, a thermostable DNA polymerase enzyme selected depending on the application for the automation of the process, normally Taq DNA polymerase is used. (Figure 1B)

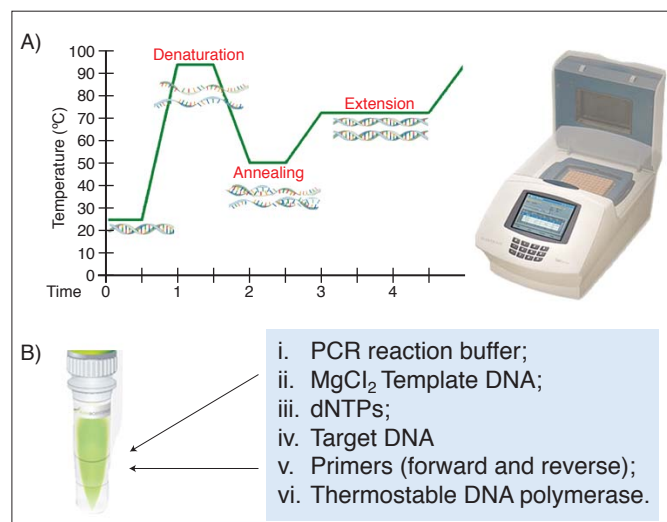


Figure 1. The amplification cycle and requirements in a Polymerase chain reaction (PCR). (A).The process of one amplification cycle in PCR is composed of three steps including denaturation, annealing and extension, which will be repeated for many times; (B). The strict requirements of the reaction including: i) PCR Reaction; ii) magnesium chloride ($MgCl_2$); iii) deoxynucleotide triphosphates (dNTPs); iv) Target DNA; v) PCR primers including forward primer and reverse; vi) thermostable DNA polymerase enzyme.

Efficiency of each PCR experiment depends on the quality and purity of the source DNA. The target DNA should be as pure as possible and only contain the target of interest. The fragment length and the intactness determinate the quality of target DNA, whereas the contaminants in sample matrices affect the purity of DNA.⁽⁹⁾ Besides, the isolation of the target DNA from the complicated sample matrix may bring out coexistence of PCR inhibitors such as plant-derived polysaccharides, polyphenolics, feed additives, or extraction reagents like EDTA, isopropanol and so on, eventually these contaminants could inhibit the enzymatic activity of polymerase and indirectly affect the PCR products.^(10, 11)

TYPES, UTILITIES AND LIMITATIONS OF PCR FOR PHARMACEUTICAL AND FOOD ANALYSIS

Different Types of PCR

During the past three decades, PCR analysis is highlighted as the most widely used molecular technique for the characterization of particular DNA fragments with various functions from human, animal and plant samples. In recent years, improvements for the performance and specificity of PCR analysis have been achieved, and some modifications have been developed such as Multiplex PCR, Nested PCR, reverse transcriptase PCR (RT-PCR) as well as real-time PCR.⁽¹²⁻¹⁵⁾

Multiplex PCR is widely used in the diagnosis of disease due to its advantage of simultaneous amplification of multiple sequences, e.g., different pathogens in a single sample or different sequences in specific genes.^(12, 16) In pharmaceutical

field, the multiplex allele-specific PCR has been successfully employed by a herbal medicine Rhubarb (official Da-huang) who has many adulterants in the market for the authentication based on the polymorphisms of a short maturase K gene.⁽¹⁴⁾

Besides, the Nested PCR involves a double process of amplification by using two sets of primers thereby increasing the sensitivity of the analysis, however, its performance is limited by the probability of contamination during the transfer from the first product to the second one.⁽¹³⁾

RT-PCR has been employed particularly for amplification of RNA molecules so that the expression of a target gene or the sequence of an RNA transcript could be examined.⁽¹⁷⁾ Beyond the detection of the presence of specific DNA, quantitative real-time PCR (qPCR) provides information of the exact expression levels of the target nucleic acids (DNA, RNA and cDNA) in even small amount of sample matrix. It is a more powerful approach in pharmaceuticals for the analysis of gene expression when combined with reverse transcription.⁽¹⁵⁾ One successful example is the genome sequencing of herb Tulsi (*Ocimum tenuiflorum*) unravels key genes by RT-qPCR in different tissues of five species.⁽¹⁸⁾

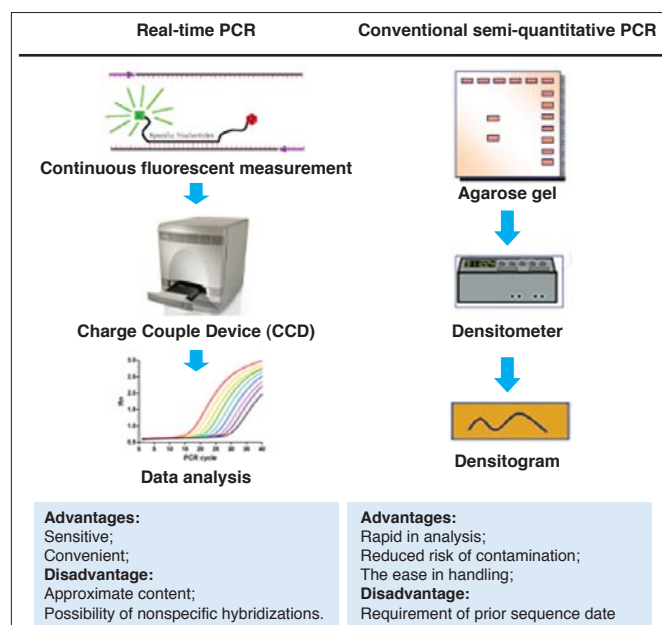


Figure 2. Comparison of end-point PCR and real-time PCR. Compared with conventional semi-quantitative PCR, which is employed for the approximation of the relative amounts of nucleic acids, real-time (qPCR) is utilized to do quantification analysis for target DNA, mRNA or cDNA present within different samples by using fluorescence detection systems.

Both conventional semi-quantitative PCR and real-time PCR are helpful and reliable nucleic acid amplification methods (Figure 2). Comparatively, real-time PCR has its superior advantages such as less labor-intensive, higher throughput, more accurate, and most importantly, detectable in real time, which allows the detection by fluorescence emitted from a reporter molecule during the whole process of amplification.⁽²⁰⁻²³⁾ An increasing number of studies have employed this technique in their experimental design, for example, the quality control of the traditional Chinese medicine (TCM) *Anoectochilus roxburghii*,⁽²⁴⁾ *Lycium barbarum*,⁽²⁵⁾ and TCM Formula Si-Wu-Tang.⁽²⁶⁾ Furthermore, the application of real-time RT-PCR extends the advantages of real-time PCR by measuring

mRNA levels in extremely low amounts of sample matrix with good reproducibility, rapidity and accuracy.^(19, 27) Besides, the occurrence of Multiplex Real-time RT-PCR enables multiple genes to be characterized simultaneously by recognizing fluorochromes and analyzing melting curves, causing more and more attention in the basic research field.⁽²⁸⁾ In addition to the above mentioned major utilities of PCR, there are many other types like Long-range PCR, Single-cell PCR, Fast-cycling PCR, Methylation-specific PCR (MSP), Hot start PCR, High-fidelity PCR, In situ PCR, Variable Number of Tandem Repeats (VNTR) PCR, Asymmetric PCR, Repetitive sequence-based PCR, Overlap extension PCR, Assemble PCR, Intersequence-specific PCR (ISSR), Ligation-mediated PCR, Miniprimer PCR, Solid phase PCR and Touch down PCR, etc.⁽²⁹⁾ With the development of technology and analyzing methods, PCR as a key molecular methodology must gain further improvement to fulfill the more and more need in identifying and determining target gene expression levels in humans, plants and animals.

Pitfalls of Quantitative Real-time Reverse-transcription Polymerase Chain Reaction (RT-PCR)

Although the RT-PCR is quite useful for the quantification of steady-state mRNA levels in basic research of pharmaceuticals and food science, there are lots of pitfalls and disadvantages that require attention. Individual RT and PCR efficiencies should be corrected for experimental variations to achieve a good quantitative result.⁽³⁰⁾ Besides, the reference genes are critical for the reliable performance of RT-qPCR.⁽³¹⁾ Bustin *et al.* addressed several points to be discussed through a deep insight into this field, briefly listed in **Box 1**.⁽³²⁾ As suggested by Bustin, the transcriptome is context-dependent, making its information flexible and variable, together with the inherent limitations existed in RT-PCR, the result is not so biologically relevant. Chaillou also claimed that quantifying target mRNA using real-time RT-qPCR requires an accurate normalization method and should be confirmed without generating misleading results by determining the normalization factors (NFs).⁽³³⁾ Collectively, the experimental design is of utmost importance for researchers to get a good result of RT-qPCR analysis.

Box 1: Several points highlighted in the application of RT-PCR.

SEVERAL POINTS HIGHLIGHTED FOR RT-PCR

1. The quality and quantity of RNA templates;
2. Standardization of methodology;
3. Standard internal controls;
4. Amplicon-specific standard curve by using a strictly controlled reference mRNA, cDNA preparation or mixture;
5. Consensus of intra-sample variability;
6. Normalization of both *in vitro* and *in vivo* samples;
7. Be careful of the heterogeneity of material and the use of additional techniques.

EFFECT OF PROCESSING ON DNA EXTRACTION AND PCR ANALYSIS

With a broad consensus, the processing condition may affect the quality and quantity of the DNA, rendering the results unreliable.⁽¹⁰⁾ As shown in **Figure 3**, processing methods involving heating, autoclaving, pH variations, sonication and mechanical treatments may affect the DNA quality by causing hydrolysis, oxidation and deamination of the source DNA. The CTAB method was equally effective for DNA extraction from both raw and processed materials (concentration 71–229 µg/ml, A260/A280: 1.7–2.00, **Tables 1**). Besides, Even trace

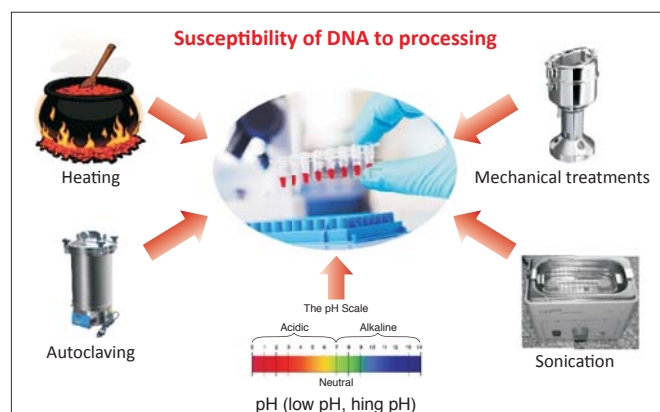


Figure 3. The susceptibility of DNA to processing prior to PCR analysis. Target DNA is susceptible to the processing methods including heating, autoclaving, pH variations, sonication and mechanical treatments, which may cause DNA degradation and thus affecting the results of PCR analysis.

Table 1. Quality of extracted pea DNA and MON 810 (genetically modified maize) DNA after autoclaving and sterilization using cetyl trimethyl ammonium bromide (CTAB) method.(adopted from Bergerova et al)⁽³⁴⁾

Sample treatment				Sample treatment			
pH	time (min)	[c] DNA (µg/ml)	A260/A280	time (min)	[c] DNA (µg/ml)	A260/A280	
Pea at 120°C				Pea at 100°C			
2.25	2	71.61	1.93	10	90.63		
	5	73.89	1.93	20	150.83		1.87
	10	72.76	1.97	30	90.38		1.92
4.25	2	165.43	1.75	10	225.45		1.83
	5	158.34	1.86	20	221.17		1.86
	10	170.2	1.88	30	97.96		1.77
7.6	2	177.94	1.87	10	208.97		1.74
	5	98.72	1.88	20	164.83		1.98
	10	211.8	2.08	30	182.57		1.84
MoN 810 at 120°C				MoN 810 at 100°C			
2.25	2	87.83	1.89	10	103.87		1.91
	5	110.21	1.94	20	79.37		1.7
	10	74.07	1.97	30	92.02		1.99
4.25	2	99.71	1.76	10	85.82		1.86
	5	70.23	1.87	20	79.48		2
	10	59.46	2.1	30	137.03		1.81
7.6	2	192.41	1.97	10	147.34		1.78
	5	10072	1.87	20	94.64		1.79
	10	229.8	2.01	30	164.82		1.82

amount of DNA contamination can mislead PCR analysis by false positive results.⁽³⁵⁾ On the other hand, although some processing methods may cause DNA degradation, the ability of PCR amplification may still be acceptable to provide information for the qualitative determination. Herein, we summarized several processing methods and their influence on PCR analysis with experimental evidence.

Heating

DNA degradation (denaturation) caused by the high temperature commonly occurs during the heating process. At above 100°C, the secondary structure are irreversibly lost.⁽³⁶⁾ Proven by *Mori K*, the bioactive component anthocyanin in red-wine grape was decreased to less than half due to the degradation as well as the inhibition of mRNA transcription of anthocyanin biosynthetic genes under high temperature (maximum 35°C, compared to the control berries at maximum 25°C).⁽³⁷⁾

Autoclaving

Although the autoclaving at 121°C may destroy DNA partially and thereby reducing the sensitivity of PCR, the samples may also still available for the amplification and subsequent analysis, e.g., the determination of genetically modified organisms (GMOs) in soy beans and maize.⁽³⁸⁾ The DNA damage may also be aggravated by the higher pressure during the sterilization process, e.g., transgenic components in soymilk⁽³⁸⁾ and genetically modified soybeans.⁽³⁹⁾

pH Variations

Accelerated by heat process, acid-catalyzed reactions depurinate DNA in many kinds of plants and food.⁽⁴⁰⁾ In contrast, DNA is more stable at high pH like 8.5-9.5.⁽¹⁰⁾ The combined effect of pH and temperature has drawn more attention in food science in the analysis of tomato, soybean flour, tofu and so on.^(41, 42) Moreover, during the isolation and concentration of soybean, the combined effect of low and high pH occurred and the DNA fragments of the protein at different length may lead to positive amplification.⁽⁴³⁾

Sonication

The sonication also causes the DNA degradation even after a short period of 5 min or a long time of 8 h, and the influence decreased with time extension; nevertheless, the amplification remains achievable for PCR analysis, demonstrated by *Debode F et al.* in soybean flours.⁽⁴⁴⁾

Mechanical Treatments

Interestingly, researchers elaborated that the mechanical treatments of raw materials like shearing,⁽⁴⁵⁾ grinding,^(41,46) stirring, blending⁽⁴⁷⁾ as well as homogenization^(34, 46) may also induce DNA degradation. All of these processing procedures may affect the quality and quantity of DNAs in sample matrix. In order to succeed the PCR amplification, the amplicon needs to be selected with caution. PCR primers for different sizes of DNA degradation were listed in **Table 2**. Particularly, amplicons above 400 bp are inapplicable after autoclaving

and sterilized samples, as reported by *Bergerova*⁽³⁴⁾. The sterilization at 100°C allows amplicons to amplify at pH 7.6 and pH 4.25 for a short time; while the autoclaving procedure at 120°C. 0.1 MPa resulted in the degradation of DNA in the time-dependent manner especially under acidic condition. Concluded from the table, the size, processing methods and duration may negatively affect the PCR efficacy, especially for the quantitative determination of specific DNA fragments.

Table 2. Limitations of analysis based on DNA amplification after processing food matrices.

Conditions	pH	Time (min)	Amplicons (bp)						
			<100	<200	<300	>300	>400	>700	>1300
Sterilisation at 100 °C	2.25	10	+	+	+	-	-	-	-
		20	+	+	+	-	-	-	-
		30	+	+	+	-	-	-	-
	4.25	10	+	+	+	+	-	-	-
		20	+	+	+	-	-	-	-
		30	+	+	+	-	-	-	-
	7.6	10	+	+	+	+	-	-	-
		20	+	+	+	+	-	-	-
		30	+	+	+	+	-	-	-
Autoclaving at 120 °C (0.1 Mpa)	2.25	2	+	+	+	-	-	-	-
		5	+	+	+	-	-	-	-
		10	+	+	+	-	-	-	-
	4.25	2	+	+	+	-	-	-	-
		5	+	+	+	-	-	-	-
		10	+	+	+	-	-	-	-
	7.6	2	+	+	+	-	-	-	-
		5	+	+	+	-	-	-	-
		10	+	+	+	-	-	-	-

+ = DNA amplification yes; " - " = DNA amplification no

CONCLUSION

The rapidity, convenience, sensitivity and specificity enable PCR a powerful technique with great spectrum of applications in pharmaceuticals and food science. Different types of PCR methods could be applied for different purposes with respective advantages and disadvantages, among which real-time PCR is the most favorable one due to its superior advantages. However, the PCR analysis has its inherent shortcomings, and the processing method is one of the most important determinants for a success PCR analysis, which should be paid more attention to. Beyond the aspects discussed in this review, the DNA extraction process, complexity of the sample matrix and the DNA quantification system also influence the PCR results. Undoubtedly, the safety and quality of medicines and foods requires further development and refinement of the PCR analysis.

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MOMENTS LIKE THIS...

SOVALDI® transforms HCV therapy, allowing many more patients the opportunity of cure†

- The nucleotide polymerase inhibitor with pan-genotypic activity¹ and a high barrier to resistance²
 - ≥90% cure across genotype 1-6 with 12 weeks of SOVALDI + Peg-IFN + RBV in previously untreated HCV mono-infection adults^{1*}
 - An all-oral 24-week option available for those patients unsuitable for Peg-IFN^{1*}
 - No adverse drug reactions specific to SOVALDI¹
- In the context that SOVALDI has mainly been studied in combination with RBV, with or without Peg-IFN

SOVALDI is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

†The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy.^{3,4}

*12-week all-oral SOVALDI + RBV regimen for GT 2.

 **SOVALDI®**
SOFOSBUVIR
400 mg TABLETS
HCV treatment transformed

SOVALDI Abbreviated Prescribing Information

Presentation: Film-coated tablet containing 400 mg of sofosbuvir. **Indications:** In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. **Dosage:** Adults: One 400 mg tablet, taken orally, once daily with food. Elderly: No dose adjustment is warranted for elderly patients. Renal impairment: No dose adjustment is required for patients with mild or moderate renal impairment. The safety and appropriate dose have not been established in patients with severe renal impairment or end stage renal disease requiring haemodialysis. Hepatic impairment: No dose adjustment is required for patients with mild, moderate or severe hepatic impairment. The safety and efficacy have not been established in patients with decompensated cirrhosis. Patients awaiting liver transplantation: The duration of administration should be guided by an assessment of the potential benefits and risks for the individual patient. Paediatric population: The safety and efficacy in children and adolescents aged <18 years have not yet been established. No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Sovaldi is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection. Treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection; Treatment of patients with genotype 5 or 6 HCV infection; Interferon-free therapy for genotype 1, 4, 5 and 6 HCV infection; Co-administration with other direct-acting antivirals against HCV; co-administration with telaprevir and boceprevir is not recommended. Pregnancy and concomitant use with ribavirin; Use with potent P-gp inducers; Renal impairment; HCV/HBV (hepatitis B virus) co-infection; Paediatric population below age of 18; Women of childbearing potential; Pregnancy and lactation; Moderate influence on ability to drive and use machines. **Undesirable effects:** Sovaldi has mainly been studied in combination with ribavirin, with or without peginterferon alfa. In this context, no adverse drug reactions specific to sofosbuvir have been identified. The most common adverse drug reactions occurring in subjects receiving sofosbuvir and ribavirin or sofosbuvir, ribavirin and peginterferon alfa were fatigue, headache, nausea and insomnia.

Before prescribing, please consult full prescribing information which is available upon request.

SOVALDI is a registered trademark of Gilead Sciences, Inc., or its related companies.

Reference: 1. Sovaldi Hong Kong Prescribing Information (EUJAN14HKFEB14). 2. Kris V Kowdley et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicenter phase 2 trial. Lancet 2013 Mar. 3. AASLD & IDSA. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014 Dec. 4. European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2015. Journal of Hepatology. 2015 Mar.



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Discussion Forums for consultation of the establishment of Pharmacy Council – with the students of the two Pharmacy schools in Hong Kong

The Pharmaceutical Society of Hong Kong (PSHK), as one of the many driving forces behind the establishment of the Pharmacy Council in Hong Kong, values and proactively seeks opinions from stakeholders. Members of the Taskforce and PSHK General Council took the opportunity in November 2015 to meet, introduce and collect opinions from our current pharmacy students on separate occasions from the Chinese University of Hong Kong (CUHK) and the University of Hong Kong (HKU).

The executive committee members of the Taskforce, Mr. Benjamin Kwong and Mr. Philip Chiu (also President of PSHK), talked about the background and rationale behind the proposal of establishing a Pharmacy Council in Hong Kong. The mission, vision and function of the proposed Pharmacy Council were shared, preceding an open forum for students to express their views.



Photo at The Chinese University of Hong Kong: Mr Benjamin Kwong, Dr. Keary Zhou, Mr Philip Chiu (left to right)

Thoughts from students included concern on the lack of development of the profession and whether there would be sufficient career opportunities once they graduate. We explained that having a governing body led by a Pharmacist majority rather than the current Pharmacy and Poisons Board (PPB) would have a lot of advantages in the development of



Students participated in the discussion (at the Chinese University of Hong Kong)

the profession. The PPB is not responsible for developing the pharmacy professions, whereas the Pharmacy Council, which consists mainly of pharmacists who would be in the best position to drive development opportunities of the profession.

The question of how the proposed Pharmacy Council can help control commonly seen 'malpractice' in community pharmacies, which are relatively loosely-controlled at the moment was raised. Dr. Keary Zhou, a Taskforce executive committee member, pointed out that currently many private pharmacies rely heavily on non-functional activities to drive revenue, which may not be reliable for a healthy pharmacy business. The Pharmacy Council can advocate opportunities in how the public and private pharmacy market can collaborate to bring in more functional roles to community pharmacies and thereby reducing unintended malpractices.

Another student expressed concern on whether we would counter resistance in the transitioning of responsibilities from the current regulatory body, the PPB, to the proposed Pharmacy Council. As with every reform proposals of a profession there ought to be different opinions. That is the reason the PSHK will continue to listen to stakeholders using various platforms, in particular the community pharmacists, to address concerns and to openly communicate the importance of unity as we work together towards self-governance of our pharmacy profession. It is only when the profession is polarized that we give up the governing rights which are rightly ours, to the mercy of other parties.



Students concentrated in listening to Mr Philip Chiu's explanation (at The University of Hong Kong)



Mr Philip Chiu at the forum at The University of Hong Kong

General Council of the Pharmaceutical Society of Hong Kong 2016

President	Mr. CHIU, Philip	General Committee members	Mr. Benjamin Kwong	Mr. Edward Yau
Vice Presidents	Mrs. Mary Cheng		Mr. Chris Lee	Dr. Connie Woo
	Ms. Chiang Sau Chu		Mr. Peter Leung	Ms. Ritchie Kwok
Hon. Secretary	Ms. Cadence Yan		Dr. Keary Zhou	Mr. Matthew Wong
Hon. Treasurer	Ms. Tony Li		Mr. Andy Wong	Mr. Dick Sung
Pharmacy & Poisons Board members		Ms. Chiang Sau Chu	Mr. Benjamin Kwong	Mr. Andy Wong

Aubagio (Sanofi-Aventis)

Prepared by Andy Lam and edited by Lucilla Leung

Active Ingredient:

Teriflunomide

Presentation:

Each AUBAGIO film-coated tablet contains 14 MG OF TERIFLUNOMIDE; Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side ('14') and engraved with a corporate logo on the other side.

Pharmacological Properties:

Pharmacotherapeutic group: Selective immunosuppressants, ATC Code: L04AA31.

Mechanism of action

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

Pharmacodynamic effects

- **Immune system:** Teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of less than $0.3 \times 10^9/L$, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.
- **Potential to prolong the QT interval:** In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo.
- **Effect on renal tubular functions:** In the placebo-controlled studies, mean decreases in serum uric acid at a range of 20 to 30% were observed in patients treated with teriflunomide compared to placebo. Mean decrease in serum phosphorus was around 10% in the teriflunomide group compared to placebo. These effects are considered to be related to increase in renal tubular excretion and not related to changes in glomerular functions.

Indications:

AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).

Posology and method of administration:

Posology: The recommended dose of AUBAGIO is 14 mg once daily.

Special populations

- **Elderly population:** Used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.
- **Renal impairment:** No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis.
- **Hepatic impairment:** No dosage adjustment is necessary for patients with mild and moderate hepatic impairment.
- **Paediatric population:** The safety and efficacy of AUBAGIO in children aged from 10 to less than 18 years has not yet

been established. There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis. No data are available.

Method of administration

The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. AUBAGIO can be taken with or without food.

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with severe hepatic impairment (Child-Pugh class C).
- Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/L. Pregnancy must be excluded before start of treatment.
- Breast-feeding women.
- Patients with severe immunodeficiency states, e.g. AIDS.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia.
- Patients with severe active infection until resolution
- Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome

Special warnings and precautions for use:

• Monitoring

Before treatment: Blood pressure, Alanine aminotransferase (ALT/SGPT), Complete blood cell count including differential white blood cell and platelet count.

During treatment: Blood pressure, Alanine aminotransferase (ALT/SGPT), complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during treatment.

• Accelerated elimination procedure

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/L, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide.

• Hepatic effects

Elevations of liver enzymes have been observed in patients receiving teriflunomide. These elevations occurred mostly within the first 6 months of treatment.

• Blood pressure

Elevation of blood pressure may occur during treatment with teriflunomide. Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter.

• Infections

Initiation of treatment with teriflunomide should be delayed in patients with severe active infection until resolution.

• Respiratory reactions

No cases of interstitial lung diseases (ILD) have been reported with teriflunomide in the clinical trials.

However, ILD, which is a potentially fatal disorder, has been reported during treatment with leflunomide, the parent compound.

• Haematological effects

A mean decrease less than 15% from baseline affecting white blood cell count has been observed.

- **Skin reactions**

No cases of severe skin reactions have been reported with teriflunomide in the clinical trials. In patients treated with leflunomide, very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported.

- **Peripheral neuropathy**

Cases of peripheral neuropathy have been reported in patients receiving AUBAGIO. Most patients improved after discontinuation of AUBAGIO. However, in some patients the neuropathy resolved and some patients had persistent symptoms.

- **Vaccination**

No clinical data are available on the efficacy and safety of vaccinations regarding primary immune response to neopathogens. The use of live attenuated vaccines may carry a risk of infections and should, therefore, be avoided.

Immunosuppressive or immunomodulating therapies

Co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated.

- **Switching to or from AUBAGIO**

In MS patients, the median $t_{1/2}$ was approximately 19 days after repeated doses of 14 mg. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO.

- **Lactose**

Since AUBAGIO tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

Drug Interactions:

Pharmacokinetic interactions of other substances on teriflunomide

- **Potent cytochrome P450 (CYP) and transporter inducers:** Co-administration of repeated doses of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide resulted in an approximately 40% decrease in teriflunomide exposure.
- **Cholestyramine or activated charcoal:** It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to

a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired.

Pharmacokinetic interactions of teriflunomide on other substances

- **Effect on CYP2C8 substrate:** There was an increase in mean repaglinide C_{max} and AUC, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*.
- **Effect on oral contraceptive:** There was an increase in mean ethinylestradiol C_{max} and AUC₀₋₂₄ and levonorgestrel C_{max} and AUC₀₋₂₄ following repeated doses of teriflunomide.
- **Effect on CYP1A2 substrate:** Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine, suggesting that teriflunomide may be a weak inducer of CYP1A2 *in vivo*.
- **Effect on warfarin:** A 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone.
- **Effect on organic anion transporter 3 (OAT3) substrates:** There was an increase in mean cefaclor C_{max} and AUC following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 *in vivo*.
- **Effect on BCRP and/or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:** There was an increase in mean rosuvastatin C_{max} and AUC following repeated doses of teriflunomide.

Side Effects:

Adverse reactions reported with AUBAGIO in placebo-controlled studies are shown below. Frequencies were defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Uncommon: Anaemia, Mild thrombocytopenia (platelets $< 100 \text{ G/L}$)

Very rare: Interstitial lung disease (Based on leflunomide data only), Pancreatitis

Forensic Classification:

P1S1S3

Note: This summary does not include all parts of the prescribing information due to limited space. Please refer to the full prescribing information for further details.

System organ class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)
Infections and infestations	Influenza, Upper respiratory tract infection, Urinary tract infection	Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Oral herpes, Tooth infection, Laryngitis, Tinea pedis
Blood and lymphatic system disorders		Neutropenia
Immune system disorders		Mild allergic reactions
Psychiatric disorders		Anxiety
Nervous system disorders	Paraesthesia	Sciatica, Carpal tunnel syndrome, Hyperaesthesia, Neuralgia, Peripheral neuropathy
Vascular disorders		Hypertension
Gastrointestinal disorders	Diarrhoea, Nausea	Vomiting, Toothache
Skin and subcutaneous tissue disorders	Alopecia	Rash, Acne
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Myalgia
Renal and urinary disorders		Pollakiuria
Reproductive system and breast disorders		Menorrhagia
General disorders and administration site conditions		Pain
Investigations	Alanine aminotransferase (ALT) increase	Gamma-glutamyltransferase (GGT) increase, Aspartate aminotransferase increase, Weight decrease, Neutrophil count decrease, White blood cell count decrease
Injury, poisoning and procedural complications		Post-traumatic pain

STRIVERDI® RESPIMAT®

(Boehringer Ingelheim)

Prepared by Fiona Yuen and edited by Ivy Chan

Active Ingredient:

Olodaterol (as hydrochloride)

Presentation:

Clear, colourless, solution for inhalation

1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

The delivered dose is 2.5 microgram Olodaterol (as olodaterol hydrochloride) per puff.

The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Pharmacological Properties:

Olodaterol has a high affinity and high selectivity to the human β_2 -adrenoceptor.

In vitro studies have shown that olodaterol has 241-fold greater agonist activity at β_2 -adrenoceptors compared to β_1 -adrenoceptors and 2299-fold greater agonist activity compared to β_3 -adrenoceptors.

The compound exerts its pharmacological effects by binding and activation of β_2 -adrenoceptors after topical administration by inhalation.

Activation of these receptors in the airways results in a stimulation of intracellular adenylyl cyclase, an enzyme that mediates the synthesis of cyclic-3', 5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.

Olodaterol has the pre-clinical profile of a long-acting selective β_2 -adrenoceptor agonist (LABA) with a fast onset of action and a duration of action of at least 24 hours.

Indications:

STRIVERDI® RESPIMAT® is indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).

Dosage & Administration:

Posology

The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler. Two puffs from the Respimat inhaler comprise one medicinal dose.

Adults

The recommended dose is 5 microgram olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day.

The recommended dose should not be exceeded.

Elderly population

Elderly patients can use STRIVERDI® RESPIMAT® at the recommended dose.

Hepatic impairment

Patients with mild to moderate hepatic impairment can use Striverdi Respimat at the recommended dose.

There are no data available for the use of STRIVERDI® RESPIMAT® in patients with severe hepatic impairment.

Renal impairment

Renally impaired patients can use STRIVERDI® RESPIMAT®

at the recommended dose. There is limited experience with the use of STRIVERDI® RESPIMAT® in patients with severe renal impairment.

Paediatric population

There is no relevant use of STRIVERDI® RESPIMAT® in the paediatric population (under 18 years).

Method of administration

To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health professional.

Contraindications:

STRIVERDI® RESPIMAT® is contraindicated in patients with hypersensitivity to olodaterol or to any of the excipients.

Precautions:

Asthma

STRIVERDI® RESPIMAT® should not be used in asthma. The long-term efficacy and safety of olodaterol in asthma have not been studied.

Acute bronchospasm

STRIVERDI® RESPIMAT®, as a once daily maintenance bronchodilator should not be used for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy.

Hypersensitivity

As with all medications, immediate hypersensitivity reactions may occur after administration of STRIVERDI® RESPIMAT®.

Paradoxical bronchospasm

As with other inhaled medicines STRIVERDI® RESPIMAT® may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs STRIVERDI® RESPIMAT® should be discontinued immediately and alternative therapy substituted.

Systemic effects

Long acting β_2 -adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT>0.44s), and in patients who are unusually responsive to sympathomimetic amines.

Patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalized for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) were excluded from the clinical trials. Therefore the experience in these patient groups is limited. STRIVERDI® RESPIMAT® should be used with caution in these patient groups.

Cardiovascular effects

Like other β_2 -adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, β -adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown.

Hypokalaemia

β_2 -adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum

potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia

Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose.

Anaesthesia

Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics due to an increased susceptibility to the adverse cardiac effects of beta-agonist bronchodilators.

STRIVERDI® RESPIMAT® should not be used in conjunction with any other medication containing long-acting beta₂-adrenergic agonists.

Patients who have been taking inhaled, short acting beta₂-adrenergic agonists on a regular basis (e.g. four times a day) should be instructed to use them only for symptomatic relief of acute respiratory symptoms.

The use of STRIVERDI® RESPIMAT® may lead to positive results in doping controls.

Drug Interactions:

Adrenergic agents

Concomitant administration of other adrenergic agents (alone or as part of combination therapy) may potentiate the undesirable effects of STRIVERDI® RESPIMAT®.

Xanthine derivatives, steroids or diuretics

Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalemic effect of adrenergic agonists.

Beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of STRIVERDI® RESPIMAT®. Therefore STRIVERDI® RESPIMAT® should only be given together with beta-adrenergic blockers (including eye-drops) if there are compelling reasons for their use. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

MAO Inhibitors and tricyclic antidepressants, QTc prolonging drugs

Monamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of STRIVERDI® RESPIMAT® on the cardiovascular system.

Pharmacokinetic drug-drug interactions

No relevant effect on systemic exposure to olodaterol has been observed in drug-drug interaction studies with co-administration of fluconazole, used as model inhibitor of CYP2C9.

Co-administration of ketoconazole as potent P-gp and CYP inhibitor increased systemic exposure to olodaterol by approximately 70%. No dose adjustment is necessary.

Co-administration of olodaterol and tiotropium had no relevant effect on the systemic exposure to either of the two drugs.

In vitro investigations have shown that olodaterol does not inhibit CYP enzymes or drug transporters at the plasma concentrations achieved in clinical practice.

Side Effects:

Summary of the safety profile

The most common adverse reactions at the recommended dose were nasopharyngitis, dizziness, hypertension, rash and arthralgia. These were usually mild or moderate in intensity.

Tabulated summary of adverse reactions

The frequencies assigned to the undesirable effects listed below are based on the crude incidence rates of adverse drug reactions (i.e. events attributed to olodaterol) observed in the olodaterol 5 microgram dose group (1035 patients), pooled from 6 placebo-controlled, parallel group clinical trials in COPD patients with treatment periods ranging between 4 and 48 weeks.

Frequency is defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class / MedDRA Preferred Term	Frequency
<u>Infections and infestations</u> Nasopharyngitis	Uncommon
<u>Nervous system disorders</u> Dizziness	Uncommon
<u>Vascular disorders</u> Hypertension	Rare
<u>Skin and subcutaneous tissue disorders</u> Rash	Uncommon
<u>Musculoskeletal and connective tissue disorders</u> Arthralgia	Rare

Description of selected adverse reactions

Occurrence of rash may be considered a hypersensitivity reaction with STRIVERDI® RESPIMAT®; as with all topical absorbed medication, other hypersensitivity reactions may develop.

Beta₂-agonist adverse reaction profile

STRIVERDI® RESPIMAT® is a member of the therapeutic class of long-acting beta₂-adrenergic agonists. Therefore, the occurrence of undesirable effects related to the beta-adrenergic agonist class should be taken into consideration, such as tachycardia, arrhythmia, palpitations, myocardial ischaemia, angina pectoris, hypertension or hypotension, tremor, headache, nervousness, insomnia, dizziness, dry mouth, nausea, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis.

Forensic Classification:

P1S1S3

SUCRATE[®] gel

(Sucralfate 1g/5ml)

Actively treat GERD & Gastritis with lesser early relapse
Heal damaged G.I. lesions & promote complete recovery

Indication

Gastro-esophageal reflux disease (GERD), gastritis and peptic ulcers of various origin

Composition

Per 5ml sachet containing 1 gram of sucralfate gel

Product mechanism and features

Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

Active ulcer healing is achieved through better reconstruction of mucosal architecture and thus prevents early relapse.

- Patented gel form with double surface area of bio-adhesion to ulcerated G.I. tissues
- Does not affect acid secretion - no influence on digestion and micro-organism killing in the stomach (especially relevant for the weak elderly)
- Easily swallowed with good tolerance

Dosage

One sachet 2-4 times a day, according to physician's judgement.

Manufacturer & origin

Product of Lisapharma S.p.A., Italy.

Made in Italy.



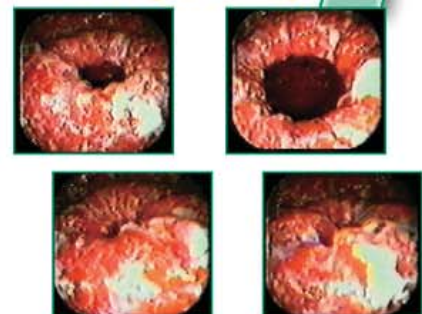
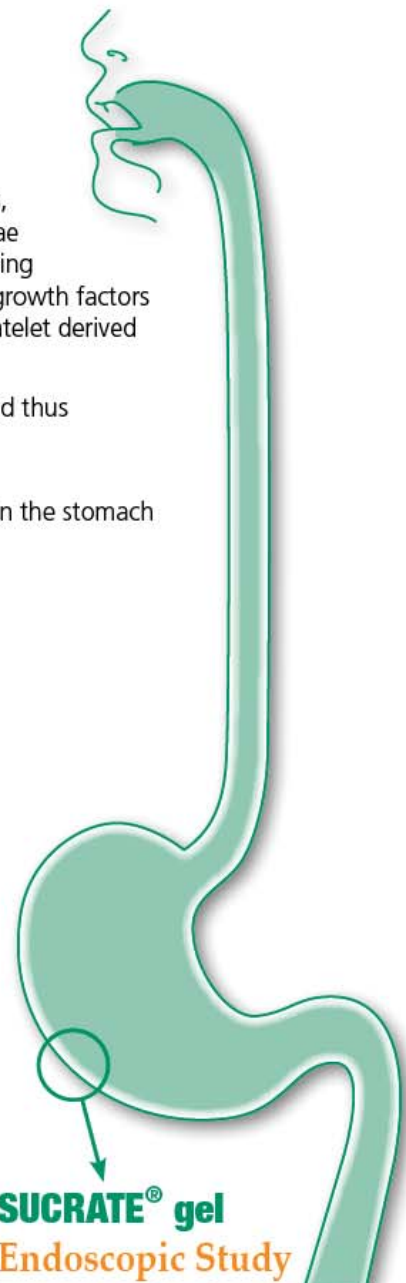
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Distributor:

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Product Enquiry: 2774 8385



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