# HONG KONG PHARMACEUTICAL JOURNAL

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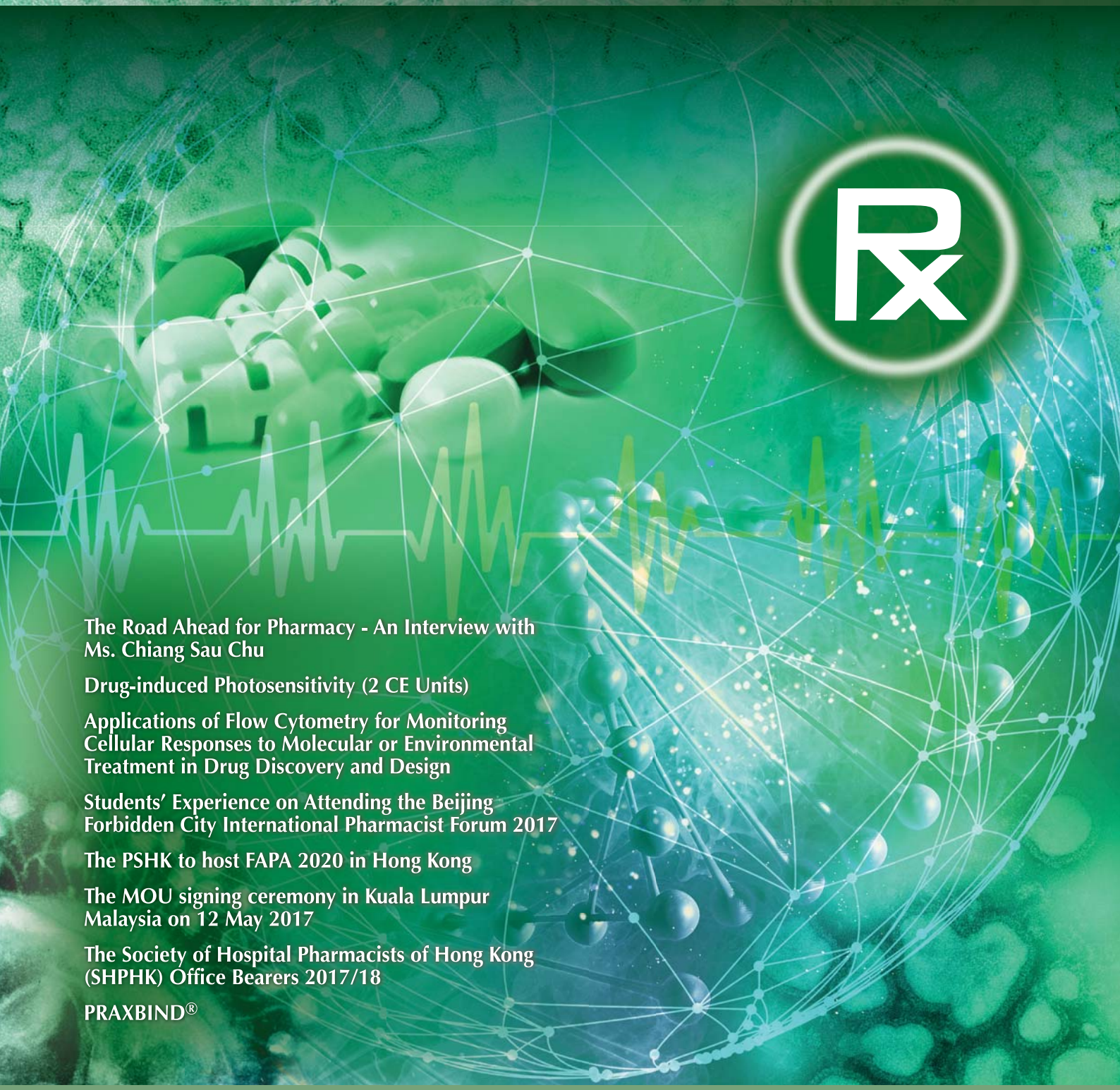

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# The Importance of Having a Strong Pharmaceutical Professional Alliance

*"The highest and best form of efficiency is the spontaneous cooperation of a free people"* (Bernard Baruch,1921)

I am so glad to present to you the latest issue of Hong Kong Pharmaceutical Journal. Although it is a little big late, it is finally released. To me, it is also a release as I can have a break for a while.

In this issue, we specifically report an interview with Ms. CHIANG Sau Chu, who is a veteran pharmacist amongst our profession. She shared with us her successful story since she returned to Hong Kong to kick off her professional career. She reminded us how to be professional. I can only summarize her achievements after reading the report in one statement; *i.e.* with vision with success. Therefore, I encourage all our junior pharmacists to go through this report and meditate what she said.

A profession, according to the definition of Webster's Dictionary, is a calling requiring specialized knowledge and often long and intensive academic preparation. Pharmacy practice is a kind of profession because the mission of the pharmacy profession is to improve public health through ensuring safe, effective, and appropriate use of medications.

In order to be empowered the right for executing these missions, lengthy and systematic trainings are required.

Medicines today have great power to heal and to improve the quality of life for millions of people. But medicines also may do serious harm if not taken correctly. Pharmacists are essential for optimizing medication use and improving patient health; i.e. to serve society as the profession responsible for the appropriate use of medications, devices, and services to achieve optimal therapeutic outcomes. The pharmacist is a key health care professional in helping people achieve the best results from their medications. This is where the role of the pharmacist is most important.

The practice of pharmacy could be quite diverse in today's environment. It could be the interpretation, evaluation, and implementation of medical orders; the dispensing of prescription drug orders; participation in drug and device selection; drug administration; drug regimen review; the practice of tele-pharmacy wherever it is; drug or drug-related research; the provision of patient counseling; the provision of those acts or services necessary to provide pharmacist care in all areas of patient care; and the responsibility of drugs and devices, proper and safe storage of drugs and devices, and maintenance of required records. The practice of pharmacy also includes continually optimizing patient safety and quality of services through effective use of emerging technologies and competency-based training.

Hence, pharmacy practice nowadays, could mean in a wide range of settings: community pharmacies, hospitals, long term care facilities, the pharmaceutical manufacturing or research, mail service, managed care, and government. **It is a diverse and rewarding career, with opportunities for patient care, scientific research and innovation.**

Whatever pharmacy practice it is, if a pharmacist wants to expand his/her career or maybe simply in need of a few more friends, professional networking or alliance is a great option for a professional whether he/she is interested in strengthening his/her network. Forming a professional alliance can be useful to group of individuals, agency, or organization facing a task that overextends its present human, financial or organizational resources and abilities.

During the process of alliance building, there are some factors which can affect its attractiveness, influence and sustainability in the long run. Although people enter into formal alliances for various reasons; in most cases, it is in response to a treat, in cases of similar or shared beliefs, economic inter-dependence and/or groups share the same members. Because alliance formation not only involves organizations that have similar interests; some also enlist members based on personalities and personal interests, long lasting alliance could only be established if one or more parties take it upon themselves to further their own interests beyond what they could accomplish individually, which means that they have to give in sometimes for the sake of collaborating with one another to achieve a goal.

Not only that professional people have to be brought together to accomplish a specific goal or purpose which will benefit all members of the group in some way, a task in today's complicated atmosphere also requires the application of combined efforts. Two articles in this issue, namely the drug-induced photosensitivity, and the application of flow cytometry for new drug discovery and design, are good examples to exemplify how complicate problem or task could be solved by cross- or multi-disciplinary approach.

All and all, the main message we want to convey to you is that together we stand and in order to achieve something we cannot be separated from each other.

Cheung Hon-Yeung
*Editor-in-Chief*
*August 25, 2017*

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

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- Pharmaceutical Techniques & Technology
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Comments on any aspects of the profession are also welcome as Letter to the Editor.

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

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

*Prepared by Annie Tsoi, Hercules Tse*

## Subsidizing Drugs for Patient with Rare Disease

**Date: April 30, 2017**

Rare diseases pose huge financial burdens for the patients and their family. Orphan medication and new medication come top of the expense list of these patients. Patient groups and lawmakers from all parties have urged the government to subsidize medicine for patients suffering from four rare genetic diseases. The stir formed following the death of a young mother with the rare disease, tuberous sclerosis, weeks after her emotional appeal to the lawmakers for drug subsidies. The mother left behind a daughter, 13, born with the same genetic condition as her mother. Tuberous sclerosis complex (TSC) is a condition that causes tumors to grow in vital organs such as the brain and the kidneys. The medication for treating TSC is not listed in the hospital formulary and costs around $20,000 per month. The medication is expected to be subsidized for patient with certain cancers from low income families in July under the Samaritan Fund. Dozens representing Alliance for Rare Diseases and Tuberous Sclerosis Complex Association protested outside the government office at Tamar and representatives claimed that the government is not willing to set clear definition to rare disease and attempt to formulate policies around it. They also submitted a letter for the government officials for their consideration.

The government proposed a new Community Care Fund assistant program to enable early use of expensive medication for patients in need and it will start accepting applications from the early August 2017.

Source: www.scmp.com

## PCSK9 Inhibitor Shown to Prevent Cardiovascular Events

**Date: May 4, 2017**

PCSK9 inhibitors, a novel class of antihyperlipidaemic agents, have been approved for some time. They have shown promising lipid lowering effects even on patients not responding to traditional lipid-lowering therapy. However, previously no large scale clinical trial had been conducted to demonstrate its safety and efficacy in preventing cardiovascular events.

The FOURIER trial randomized 27,564 patients with atherosclerotic cardiovascular disease and taking at least 20mg of atorvastatin (or equivalent) to receive evolocumab (140mg every two weeks or 420mg every month) or placebo. The median follow-up duration was 26 months.

After 48 weeks of treatment in the evolocumab group, LDL was reduced to less than 70mg/dl in 87% of patients, and less than 40mg/dl in 67% of patients. Compared to the placebo, evolocumab significantly reduced the risk of primary composite endpoint (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization). The primary composite endpoint occurred in 9.8% of patients in the evolocumab group as compared to 11.3% in the placebo group ($P<0.001$). In terms of safety, evolocumab caused more injection site reaction than the placebo (2.1% vs. 1.6%, $P<0.001$). There were no significant differences in occurrence for other side effects.

Source: www.nejm.org

## Exercise in Weight Control of Elderly

**Date: May 18, 2017**

A significant proportion of older adults are obese. In the United States, more than 33% of older adults are obese. Obesity is linked to many chronic diseases, leading to a decline in physical function. Weight lost in these patients might be associated with frailty, and a decrease in muscle and bone mass.

A study was conducted to investigate whether exercising will affect elderly adults. The lifestyle intervention trial, LITOE trial, enrolled sedentary (defined as less than 1 hour of exercise per week) older American adults with a mean age of 70 years older and a mean BMI of 35, who showed signs of frailty in the physical performance test. A total of 160 participants were randomized into 4 groups: control group, aerobic exercise, resistance exercise, aerobic and resistance exercise group each for 26 weeks. Each exercise group (excluding control) had three training sessions per week, depending on the study group, each session lasted 60 minutes for aerobic and resistance groups or 75-90 minutes for aerobic and resistance groups. All groups followed a calorie restricted diet and had visits to the dietitian. The primary outcome was the score on the physical performance test, which included tasks such as standing up from a chair, walking 50 feet, and climbing up a flight of stairs.

After 6 months, performance test results were similar in all groups, respectively 14% in aerobic exercise group, 14% in resistance exercise group, and 21% in the combination aerobic and resistance exercise group. Weight decreased in all group excluding the control group. The authors concluded that in terms of physical status improvement in obese adults, weight management with combined aerobic and resistance exercise was more effective than aerobic or resistance exercise alone.

Source: www.nejm.org

## EMA: Changes Recommended for Vancomycin Prescribing Information

**Date: May 19, 2017**

Vancomycin is a glycopeptide antibiotic used for treating serious infections caused by gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) that are resistant to many other antibiotics. At the request of the Spanish medicines agency, a review has been carried out by the European Medicines Agency (EMA) for vancomycin-containing medicines.

Vancomycin is known to have a low oral bioavailability, so it is usually administered intravenously. The indications for oral vancomycin are *Clostridium difficile* infections and staphylococcal enterocolitis. In the recent recommendation made by EMA, oral vancomycin can still be used in *Clostridium difficile* infections, yet the later indication is no longer recommended. This conclusion was made after reviewing current data and finding that there was inadequate evidence in supporting its use.

EMA also reviewed the recommended dosage for vancomycin by infusion. It was found that their previously recommended dosage had often led to suboptimal vancomycin level in blood, therefore concluding that the starting dose should be calculated according to the patient's weight and age. The subsequent dose adjustments should be made based on the serum concentrations.

These recommendations will be submitted to the European Commission for approval before applying to all European Member states.

Source: www.ema.europa.eu

## New Biologic for Rheumatoid Arthritis: Sarilumab

**Date: May 22, 2017**

A new monoclonal antibody targeting interleukin-6 receptors, sarilumab, was recently approved by FDA. It is indicated for treating moderate to severe rheumatoid arthritis patient with intolerance or inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs).

The efficacy of sarilumab was demonstrated in several clinical trials. In the MOBILITY trial, 1197 patients with rheumatoid arthritis and inadequate response to methotrexate were randomized to receive sarilumab 150mg, sarilumab 200mg, or placebo every 2 weeks together with weekly methotrexate. The achievement rate of ACR20 at week 24 was 58.0% and 66.4% for the 150mg group and 200mg group respectively, compared to 33.4% for placebo (P<0.0001). In the MONARCH study, sarilumab was compared with adalimumab, another biologic DMARD. 369 patients were randomized to receive sarilumab 200mg or adalimumab 40mg every two weeks. The mean change in DAS28-ESR were -3.28 in sarilumab group and -2.20 in adalimumab group (P<0.0001), showing that sarilumab was superior to adalimumab when used at these doses.

Side effects observed for sarilumab include neutropenia, increased ALT and upper respiratory infections.

Source: www.bmj.com

## Metformin Alters Gut Microbiome of Individuals with Treatment Naive Type 2 Diabetes

**Date: May 22, 2017**

Metformin is the first line therapy for many diabetic patient, however the mechanism of the drug is not exactly known. Recent research indicated the possibility of the gut microbiota as metformin's site of action.

A double blinded trial randomized treatment naive patients into two groups: placebo and metformin for 4 months. After 4 months, the results showed that metformin has a strong effect on gut microbiome. This result was later confirmed by switching the placebo group to taking metformin after 6 months after the trial started. Fecal samples were transferred from both placebo and metformin treated group to germ free mouse, result showed that there was significant improvement in the glucose tolerance in the mice that received the metformin altered microbiota.

The investigation of metformin microbiota interaction in a gut simulator showed that metformin can affect common biological functions in species of two phyla, and many of the metformin-regulated genes. This study provided evidence for the connection between gut microbiota and some of metformin's anti-diabetic effects.

Source: www.nature.com

## Oral Glucocorticoid Sparing Effect of Benralizumba in Severe Asthma

**Date: May 22, 2017**

Researchers have been looking in the effect of benralizumab, a monoclonal antibody that helps prevent asthma exacerbations. This drug can potentially reduce the amount of oral glucocorticoid severe asthmatics have to take in order to manage their conditions.

A total of 220 patients were randomized either to take 30 mg of benralizumab or a placebo, either every 4 weeks or 8 weeks, for the total period of 28 weeks. The primary outcome of the study was the change in oral glucocorticoid dose from the start of the 28 weeks. The results from the study showed that benralizumab is superior to the placebo, on both dosing arrangements.

The dose declined by 75% in patients assigned to the intervention group and there was a drop of 25% in the control group. Benralizumab also lowered the occurrence of asthma exacerbations compared to the placebo without more adverse reactions.

Source: www.nejm.org

# Singapore: Risk of HBV Reactivation Associated with HCV Treatment

**Date: May 26, 2017**

The Singapore Health Sciences Agency issued a product safety alert, warning that hepatitis B virus (HBV) can be reactivated in patients treated with direct-acting antivirals (DAAs) regiments that are interferon-free for hepatitis C virus (HCV) infection. In some cases, the reactivation caused liver failure and even death. Since HCV can suppress HBV replication, the adverse effect is believed to be caused by rapid decline of HCV in the body, and DAA's lack of activity against HBV.

Different medical agencies oversea have received reports of such adverse effect. The European Medicines Agency (EMA) reviewed reports of HBV reactivation in patients treated by DAA for HCV co-infection, and identified 30 such cases. It recommended that patients should be screened for HBV before initiating DAA for HCV treatment.

The US Food and Drug Administration (FDA) also reviewed its adverse event reporting system and found 24 cases, in which two patients had died and one had required liver transplant. There had been different HCV genotypes and baseline HBV infection status among these cases. The HBV reactivation was observed after four to eight weeks after the initiation of HCV treatment. In addition to screening for HBV infection for patients starting DAA treatment for HCV infection, FDA also recommended that the package inserts should update relevant warnings.

Source: www.hsa.gov.sg

# The Road Ahead for Pharmacy - An Interview with Ms. Chiang Sau Chu

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***Figure 1**. A photo of Ms. S.C. Chiang*

## BACKGROUND

Ms. Chiang Sau Chu is the pioneer of pharmacy informatics in Hong Kong. After her graduation in the United Kingdom, she returned to Hong Kong and spent 32 years in the Hospital Authority (HA) with numerous achievements revolutionizing the hospital pharmacy system, which includes the Corporate Drug Dispensing History, Express Dispensing System, Pharmacy Dispensing Automation System, Computerised Automatic Refill System (CARS), In-Patient Medication Order Entry System (IPMOE), Medication Decision Support, eHealth Record - Medication Terminology Table, some of which were imitated by overseas pharmacies. Ms. Chiang has also received numerous international awards. She also facilitates the Supply Chain Modernization after the medical incidence of fungal contamination of Allopurinol in 2009.

She retired in May 2015 from her role as the Senior Pharmacist of the Chief Pharmacist's Office (CPO). At that time, we saw a profound improvement in public hospitals' pharmacy services and we also caught up with the 30-years lag in service quality and facilities within 5 years compared to the United States, which we feel very proud of and confident about. This is admired by many visitors coming from different countries who would like to learn more about the designs of our systems, which positioned us at the very forefront of public hospital pharmacy service. Ms. Chiang hopes that her team of healthcare and IT professionals picks up the momentum that has been established previously and further improves our pharmacy services. She feels deeply grateful and honored that the technology she developed based on pharmacy informatics would be fully utilized by all kinds of pharmacies in Hong Kong.

In this interview, Ms Chiang shared with us her important work in the community setting in Hong Kong, her valuable experience from overseas pharmacies and her views on how local pharmacists, young or experienced, can work together to move the profession forward.


***Figure 2**. At the Forbidden City Conference with the PSHK delegation in Beijing 2016*

**PJ: Thank you for granting us this interview. How is your life after retirement?**

**Ms. Chiang:** After I retired from my position as the senior pharmacist at the CPO, my life is still very much engaged with the pharmacy profession as there are still a lot to do in the community setting in Hong Kong. I am currently the Director of the Pharmaceutical Care Foundation Hong Kong where the foundation provides visiting pharmacist service to old age homes, rehabilitation centers and individual elderlies in the community. Our visiting pharmacists provide a variety of services, including the proper keeping of residents' medication records; making suggestions on how to improve the drug storage conditions; training the care givers to adhere to and realize the importance of the Social Welfare Department operational guideline on 3 checks and 5 rights proper drug documentations; appropriate drug disposal, and encourage staff to report "near misses" and medication incidents. Most importantly, the care givers have a better understanding in medication safety and pay more

attention in their daily operations such as drug dispensing, checking and administration processes.

The foundation is expanding since its establishment in 2007 and is now serving more than 50 old age homes where around 20 of them are under the government. We have secured government funding for the 6th consecutive year as the government recognizes the significance of the results achieved by our foundation, to improve medication safety and overall quality of healthcare. There is still more work to be done to increase the awareness of, not only young pharmacists, but more importantly, the general public on the suboptimal healthcare standards, especially on medication safety, in elderly centers.

***Figure 3***. *Family photo in Chinese New Year 2016*

**PJ: You have been on the frontline of revolutionizing our profession and have travelled to different countries to understand the overseas practice. What are your thoughts on the new generation of local pharmacists, and what are the differences when comparing with overseas pharmacists?**

**Ms. Chiang:** I have travelled to the United States, Singapore, Mainland China, Taiwan, Korea, Malaysia, Japan, Australia and other countries, and I have had the chance to learn about their practice by visiting hospitals and community pharmacies, to understand the role of pharmacists and their work responsibilities. One of the major differences between hospital pharmacists in Hong Kong and overseas is their eagerness to participate in clinical research. Some overseas institutions even have specific requirements for promotions, such as publishing a certain number of research articles. Clinical research conducted by pharmacist is crucial to show the efficacy and importance of pharmacist interventions in order to have greater bargaining power for more resources to be allocated to our profession as well as to move our profession forward.

In earlier years, pharmacists graduated from overseas brought their experiences abroad back to Hong Kong, and they have great incentives to help transform and advance the pharmacy profession. Honestly, sometimes I could not help but wonder if the career structure of local pharmacists is a bit too stable, where a decent and stable income does not provide enough incentive to take on new challenges and push the profession further. This is especially true after marriage and starting a family, along with busy dispensing work.

***Figure 4***. *Leading the Hong Kong Pharmaceutical Care Foundation in serving the elderly*

**PJ: With busy workload and personal considerations, how can pharmacists help contribute to the advance in the profession?**

**Ms Chiang:** It is understandable to seek a more stable job after having your family. Let me share my personal story with you: earlier on in my career, after establishing the Dispensing Labeling System and Pharmaceutical Supplies System in 1986 and delivering my son and daughter, I had thought of becoming a hospital pharmacist to be involved in less challenging work and have more time to raise my family.

Despite having been appointed as the Department Manager of Queen Elizabeth Hospital in 1991, I was called back by the then-Chief Pharmacist Mrs. Sen to stay in the pharmaceutical headquarter as a senior pharmacist. I led the pharmacy informatics team to establish the Computerised Automatic Refill Systems (CARS) within 6 months which has then been used by the hospital authority since 1993. These achievements kept me devoted to the profession even after my retirement. With increasing automations, dispensing becomes more efficient and pharmacists should have more time for clinical patient care activities.

I hope young pharmacists treat their career as more than just a job and avoid being a dispensing machine and should rather, focus more on counselling and empowering patients and giving advice to physicians on patients regimen. A simple case would be, which often happens in public hospitals, is that the doctor prescribes a medication for 16-20 weeks, which I still have yet to find a reason why such practice is acceptable and this is surely far from any good patient care. Pharmacists should give feedback to physicians and work together to avoid medication wastage and offer better management of medication treatments. I also challenge them to proactively participate in conferences, subscribe to journals and take initiative to conduct clinical research whenever there are opportunities. Pharmacists in the US and the UK also mentor their pharmacy interns and inspire passion in their work that we may need to do more.

**PJ: The pharmacy practice in other countries has been part of the whole package of healthcare reform. Say in the UK, National Health System (NHS) have introduced advanced service and local service in the community pharmacy to reduce the hospital burden. Can Hong Kong learn from their system?**

**Ms. Chiang:** Frankly speaking, from my 34-year experience, it is never easy to implement substantial changes in the system. It is too complicated and involves many stakeholders. It requires extensive experience in executive, professional and financial aspects. One must also have strong management skills including changing management and communications skills. Different pharmacy associations have different projects to work on. Generally, it takes a long time for the change to be experimented even if things go smoothly.

The current Hong Kong public healthcare system is heavily funded by taxpayers. The highly subsidized public hospital system provides its citizens with equitable access to healthcare services with well recognized quality. Under this system, each citizen obtains the same type of health service and no one should be denied adequate healthcare through lack of means. Anyone who wants to reform this tax-based system would be regarded as deprivation of citizens' welfare. Any policies attempting to change this system would not be successful and would not be understood by its citizens, especially the government still enjoys a huge surplus.

However, Hong Kong population ages too rapidly. After 20 years, one out of four citizens would be over 60 and their healthcare needs are 6 to10 times more than that of adolescence. Aging population is usually accompanied by an increase in prevalence of chronic diseases which requires long term medication treatments. Expenditure on drug is around 4 billion which increases by 10% each year and accounts for 10% of Hospital Authority's total healthcare expenditure. The drug expenditure is greatly influenced by the fluctuation of economic performance. In my opinion, only when there is an organization that coordinates with hospitals and the Social Welfare Department to handle the chronic diseases of the elderly, the wastage of hospital resources can be reduced. In order to cater to as many patients as possible, the duration of follow-up consultation increases from three months to four months or even 6 months. The hospital pharmacy just follows the prescription and dispenses all medications for four or six months. The medications dispensed might be wasted if the physicians amend the prescription for patients who are admitted before follow up.

***Figure 5***. *On her retirement party with by her husband, Edward and the Secretary of Food and Health, Dr Ko Wing Man*

**PJ: What can be done to nourish and motivate the next generation pharmacists?**

**Ms. Chiang:** Previously I travelled to Taiwan and realized that pharmacy students there really cared about the pharmacy development. They established pharmacists groups and acted as ambassadors. By adopting the experience from Taiwan, the Pharmaceutical Society of Hong Kong establishes its Young Pharmacist and Student Chapter to harness and translate the zest and interests among young pharmacists into an influential voice that aims to improve the professional profile of pharmacists. It is believed that enthusiasm can only be fostered through this kind of organization but not through their work.

In Hong Kong, many medication-related voluntary activities are one-off. For example, many pharmacy students volunteered for the drug exhibition held by the Hong Kong Jockey Club. However, after the activities, many of them lost contact. Therefore, an organization like the Young Pharmacist and Student Chapter is important to gather these students together, allowing the sustainability of manpower for future activities. A special mentorship program aiming at promoting enthusiasm among younger pharmacists would be launched this year. One mentor would coach four pharmacists based on their strengths and spark their interest in the most-updated development in the pharmacy profession.

**PJ: Some pharmacy students worry that the market is saturated and there are less jobs available in the profession than a few years ago. What advice would you offer to these students?**

**Ms. Chiang:** I heard that some students were waiting for the second intake by HA. It is understandable why students want to get into HA as it has the benefit of being coached by senior pharmacists where there is a systematic approach to analyze mistakes and the setting allows one to improve oneself quite quickly. Other positions outside of HA may require more independent planning, work and responsibilities while having less welfare. For example, working in the industry might not be as attractive when compared to HA, but once you get past the beginning, it is a very rewarding prospective career that the society needs. The skills and knowledge that you will learn, such as GMP and PICS, will be extremely valuable. However, keep in mind that, whichever path you choose, each path has its own set of unique challenges - and if one way doesn't work, there are always alternatives. How do they know which path will suit them the most? They need to explore and reach out for more opportunities even before graduation, like visiting pharmacist services to old age homes. With more exploration, they will learn about themselves as well as which career path aligns best with their abilities and interests, as "all roads lead to Rome".

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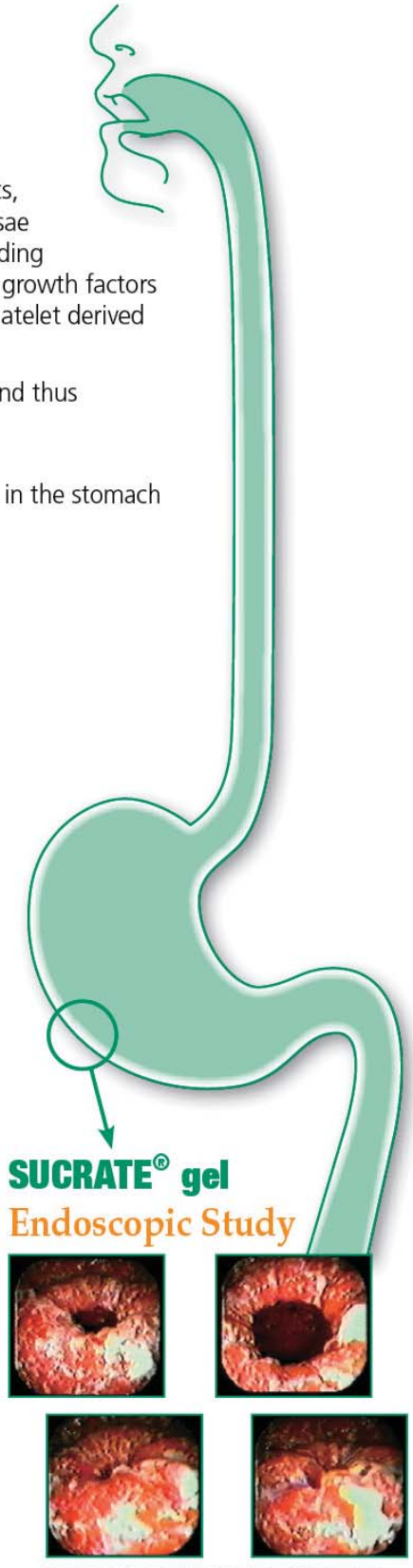


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# Drug-induced Photosensitivity

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## ABSTRACT

**Drug-induced photosensitivity is a common adverse drug reaction that occurs when a photosensitiser reacts to normally harmless doses of ultraviolet radiation, or occasionally visible light. Photosensitivity is either phototoxic or photoallergic in nature, which differ in onset, mechanism and presentation. Symptoms of drug-induced photosensitivity reactions, such as pain, erythema, pruritus, oedema and papules, may resemble those of sunburn. Antihistamines, corticosteroids, ice packs and soothing creams are commonly used in the management of photosensitivity reactions. Pharmacists should advise patients how these photosensitisers react to electro-magnetic waves to help prevent drug-induced photosensitivity.**

***Keywords:*** *photosensitivity, phototoxicity, photoallergy, sunscreen*

## INTRODUCTION

Cutaneous drug eruption is one of the most common adverse drug reactions, with an overall incidence of 2 to 3% in hospitalised patients.[1] Some manifestations, such as angioedema, erythroderma, Stevens-Johnson syndrome and toxic epidermal necrolysis, are severe and potentially life-threatening; whereas other conditions like acne and psoriasis rarely cause morbidity or mortality.

Photosensitivity occurs when a drug (photosensitiser), systemically in or topically on the skin, reacts to normally harmless doses of ultraviolet radiation, or occasionally visible light.[1] For healthcare professionals, estimating the incidence of drug-induced photosensitivity reactions is difficult because of the resemblance between sunburn and a mild photosensitivity reaction.[2] Patients on photosensitisers should be well informed of the potential for these reactions and the approaches to help prevent them.

## CLASSIFICATION AND MECHANISM

A drug-induced photosensitivity reaction is either phototoxic or photoallergic **(Table 1)**.[3] Differentiation between phototoxicity and photoallergy is often challenging as many drugs are implicated in both reactions.

A phototoxic reaction is more common and non-immunologic in nature. An excited phototoxin leads to the production of reactive oxygen species that damage cell components **(Figure 1)**. The reaction is immediate and resembles exaggerated sunburn.[2] Eruptions usually occur on exposed skin, with clear demarcation between exposed and unexposed areas. This reaction is dependent on the dose of the photosensitiser and the intensity of sunlight.

**Table 1. General characteristics of phototoxicity and photoallergy[4]**

| | Phototoxicity | Photoallergy |
|---|---|---|
| Relative incidence | High | Low |
| Mechanism | Non-immune-mediated | Immune-mediated |
| Characteristics | Exaggerated sunburn | Dermatitis |
| Onset | Immediate (minutes to hours) | Delayed (as long as 24 to 72 hours) |
| Distribution | Usually sun-exposed skin only | Mainly sun-exposed skin, may spread to unexposed areas |
| Amount of agent required for photosensitivity | Large | Small |
| Potential for cross reactivity | No | Yes |

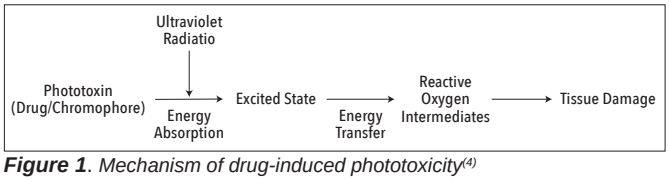


***Figure 1****. Mechanism of drug-induced phototoxicity[4]*

In contrast, a photoallergic reaction is less common and immunologic in nature. A photoallergen undergoes a structural change upon radiation and forms a complete antigen with proteins in the skin **(Figure 2)**. As an immunologic response, there is usually a delay between exposure and onset of the first eruption. Afterwards, a photoallergic reaction can be caused by minimal level of exposure.[2] In severe cases, the reaction may also affect areas that are protected from sunlight.

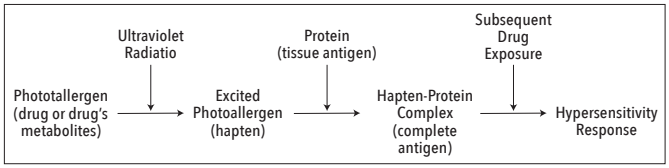


***Figure 2****. Mechanism of drug-induced photoallergy[4]*

## CAUSATIVE AGENTS

A wide range of medications have been reported to cause photosensitivity, including amiodarone, chlorpromazine, antimicrobials (e.g. doxycycline, ofloxacin and voriconazole) and dermatologic agents (e.g. acitretin, isotretinoin and tretinoin).[2-6] They can absorb ultraviolet and/or visible light – an essential characteristic for the agent to be regarded as a

photosensitiser.[2] However, evidence is mostly observational because rigorous proof is only possible by photochemical testing on healthy individuals.

The British National Formulary (BNF) recommends the cautionary label "Protect your skin from sunlight – even on a bright but cloudy day. Do not use sunbeds" on a list of preparations that may cause phototoxic or photoallergic reactions **(Table 2)**.[6] It also indicates that many drugs other than those listed, such as phenothiazines and sulphonamides, may cause reactions in susceptible patients on rare occasions.

The U.S. Food and Drug Administration (FDA) has also made available to the public a list of medications that can cause sensitivity to the sun **(Table 2)**.[7] However, discrepancies in information between authorities may lead to challenges for healthcare professionals in providing drug-specific advice and identifying causative agents of drug-induced photosensitivity.

**Table 2. Comparison of preparations recommended by the BNF to use the label "Protect your skin from sunlight" and Medicines that can cause sensitivity to the sun listed by the FDA[6,7]**

| *Preparations recommended by the BNF to use the label "Protect your skin from sunlight"* | *Medicines that can cause sensitivity to the sun listed by the FDA* |
|---|---|
| demeclocycline<br>doxycycline [capsules, modified-release capsules, dispersibletablets and tablets]<br>nalidixic acid<br>ofloxacin | antibiotics, e.g. ciprofloxacin, doxycycline, levofloxacin, ofloxacin, tetracycline, trimethoprim |
| voriconazole | antifungals, e.g. flucytosine, griseofulvin, voriconazole |
| chlorpromazine [solution, suppositories and tablets] | phenothiazines, e.g. chlorpromazine, fluphenazine, promethazine, thioridazine, prochloroperazine |
| adapalene<br>alitretinoin<br>isotretinoin<br>isotretinoin [gel]<br>tretinoin [external preparations] | retinoids, e.g. acitretin, isotretinoin |
| amiodarone | |
| pimecrolimus<br>tacrolimus [topical] | |
| simeprevir | |
| sodium aurothiomalate | |
| | antihistamines, e.g. cetirizine, diphenhydramine, loratadine, promethazine, cyproheptadine |
| | cholesterol lowering drugs, e.g. simvastatin, atorvastatin, lovastatin, pravastatin |
| | diuretics, e.g. hydrochlorothiazide, chlorthalidone, chlorothiazide, furosemide, triamterene |
| | non-steroidal anti-inflammatory drugs, e.g. ibuprofen, naproxen, celecoxib, piroxicam, ketoprofen |
| | oral contraceptives and estrogens |
| | psoralens, e.g. methoxsalen, trioxsalen |
| | sulphonamides, e.g. acetazolamide, sulphadiazine, sulphamethizole, sulphamethoxazole, sulphapyridine, sulphasalazine, sulphasoxazole |
| | sulfonylureas for type 2 diabetes, e.g. glipizide, glyburide |
| | alpha-hydroxy acids in cosmetics |

Some immunosuppressants, such as everolimus, sirolimus and tacrolimus, appear to increase the risk of developing skin cancer by impairing the capacity of the immune system to repair or destroy damaged cells.[8,9] Patients are advised to limit their sunlight exposure but it is not a drug-induced photosensitivity reaction.

## CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Symptoms of drug-induced photosensitivity reactions are very similar to those of sunburn.[4] A photosensitivity reaction typically results in pain, erythema, pruritus, oedema and papules **(Figure 3)**. In severe cases, formation of plaque-like urticarial lesions and vesicles is also possible **(Figure 4)**.

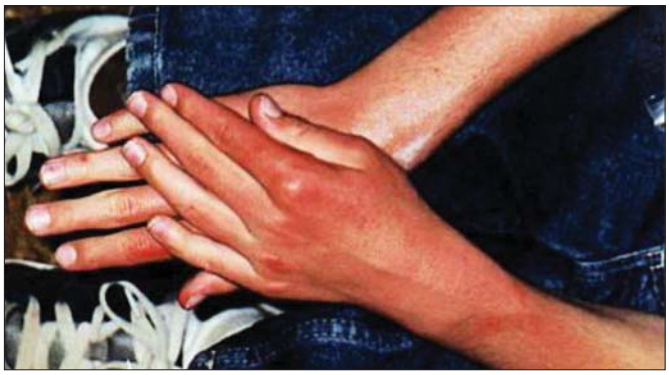

***Figure 3**. Painful, confluent, erythematous eruption in exposed areas after ingestion of doxycycline followed by sun exposure[15]*

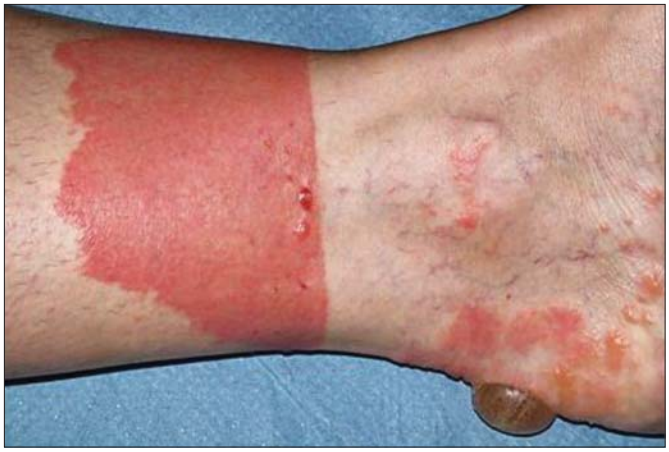

***Figure 4**. Acute, well-demarcated, erythematous plaque with vesicles after topical application of ketoprofen gel followed by sun exposure[15]*

These reactions are frequently diagnosed without specific tests, especially if they occur after the initiation of a known photosensitiser.[2] Photosensitisers are released into the circulation in several disease conditions and systemic metabolic disorders, for example polymorphic light eruption, porphyrias and xeroderma pigmentosum.

## MANAGEMENT

The appropriate treatment for a drug-induced photosensitivity reaction depends on the type of the reaction.[4] Treatment for phototoxic reactions is similar to that of sunburn. Discontinuing the suspected drug often accelerates resolution but sometimes reducing the dose may suffice. For photoallergic reactions, discontinuing the suspected drug is always necessary. Antihistamines and corticosteroids may be required to reduce the inflammation.

For both reactions, the use of ice packs and soothing creams may provide symptomatic relief. Antibacterial creams may be considered to prevent secondary infections if blisters are broken.[2]

## PREVENTION

The best means of prevention is a combination of avoidance of sunlight, use of broad-spectrum sunscreens that block both ultraviolet A (UVA) radiation (315-400 nm) and ultraviolet B (UVB) radiation (280-315 nm) and wearing protective clothing (e.g. wide-brimmed hats, sunglasses and shirts with high collars and long sleeves) **(Table 3)**.[2,4]

**Table 3. Tips to help prevent drug-induced photosensitivity**[2,4,11,12,13]

| |
|---|
| ☑ Avoid direct ultraviolet radiation exposure from natural sunlight and tanning beds. Avoid the sun between 10 a.m. and 3 p.m. in particular, when the atmosphere absorbs less ultraviolet radiation from sunlight |
| ☑ Use sunscreens |
| ☑ Choose a broad-spectrum sunscreen that blocks both UVA and UVB with an SPF of at least 15 |
| ☑ Apply sunscreen generously 15 minutes before sunlight exposure |
| ☑ Rub the sunscreen thoroughly into all bare skin, including scalp, face, ears, neck, back of knees and top of feet |
| ☑ Consider applying a lip balm with an SPF of at least 15 |
| ☑ Reapply at least every 2 hours, immediately after swimming or excessive sweating |
| ☑ Use protective clothing, e.g. broad-brimmed hats, sunglasses and shirts with high collars and long sleeves |

Sunburn Protection Factor (SPF) measures a sunscreen's ability to protect the skin from UVB. Sunscreens with an SPF of 15, 30 and 50 block approximately 93%, 97% and 98% of UVB respectively.[10] The Institute for Safe Medication Practices recommends choosing a sunscreen with an SPF of at least 15. Currently, there is no international standard for protection in UVA but the Protection Grade of UVA (PA) system is commonly used in Asian brands. Para-aminobenzoic acid (PABA) has a potential to cause or aggravate photodermatitis so sunscreens containing PABA should be avoided.[4]

A sunscreen is not as effective unless it is applied correctly. It should be applied 15 minutes before exposure and reapplied at least every two hours. Sunscreens with labels "water resistant" and "very water resistant" are effective for up to 40 minutes and 80 minutes in the water respectively. Even when using a water-resistant sunscreen, reapplication after getting out of the water or sweating is essential.

Different forms of sunscreens are available locally and internationally to cater for different needs.[14] Creams are suitable for dry skin and the face. Gels are good for hairy areas like the scalp. Sticks are for areas around the eyes. Sprays are sometimes preferred because they are more convenient to apply. Pharmacists should give clear instructions to patients on adequate and thorough application to all exposed skin. If the patient spends a significant amount of time outdoors, alternative therapy should be considered.[9] Short-term courses of photosensitisers may require temporary limitations on activities, while chronic therapy may necessitate alterations in daily activities. Pharmacists should look into the patient's normal activities and make appropriate recommendations.

Another strategy is to administer the medication concerned in the evening rather than during daytime, which allows maximum drug absorption and distribution during the night and minimises sun exposure.[11,15] However, this recommendation must be assessed on a drug-by-drug basis, taking into account its pharmacokinetic properties.

**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.)*

**2** CE Units

**Drug-induced Photosensitivity**

1. ***Which of the following is TRUE about the mechanism of photosensitivity?***
   (A) Only a small amount of agent is required for photosensitivity.
   (B) Photosensitivity is not immune-mediated.
   (C) Photosensitivity can be induced by ultraviolet radiation or visible light.
   (D Possible photosensitising agents are minimally identified.

2. ***Which of the following is the LEAST likely causative agent in a photosensitivity reaction?***
   (A) Amiodarone
   (B) Chlorpheniramine
   (C) Ciprofloxacin
   (D) Isotretinoin

3. ***Which of the following is/are possible in the prevention of photosensitivity?***
   (i) Avoidance of sunlight
   (ii) Use of broad-spectrum sunscreen
   (iii) Switch from photosensitising agents to alternative therapies
   (iv) Administer photosensitising agents in the evening

   (A) (i) only
   (B) (i) & (iii) only
   (C) (ii), (iii) & (iv) only
   (D) All of the above

4. ***Which of the following is FALSE about the use of sunscreens?***
   (A) The Protection Grade of UVA (PA) system is recommended by the Food and Drug Administration (FDA) in grading protection of UVA.
   (B) Reapply at least every 2 hours.
   (C) Sunscreen sprays are more convenient to apply.
   (D) Sunscreens with “very water resistant” label are effective for up to 80 minutes in water.

5. ***Which of the following may offer 99% protection against UVB?***
   (A) SPF 15
   (B) SPF 30
   (C) SPF 50
   (D) SPF 100

6. ***Which of the following is NOT a common manifestation of photosensitivity?***
   (A) Angioedema
   (B) Pain
   (C) Pruritus
   (D) Erythema

7. ***Which of the following is NOT common in the management of photosensitivity?***
   (A) Antihistamine
   (B) Warm packs
   (C) Corticosteroid
   (D) Antibacterial cream

8. ***Which of the following is an ingredient to be avoided in sunscreens for photosensitivity?***
   (A) Ecamsule
   (B) Para-aminobenzoic acid
   (C) Zinc oxide
   (D) Titanium dioxide

9. ***Which of the following is/are considered possible of causing photosensitivity by both the BNF and the FDA?***
   (i) Doxycycline
   (ii) Chlorpromazine
   (iii) Simvastatin
   (iv) Frusemide

   (A) (i) only
   (B) (i) & (ii) only
   (C) (ii) & (iii) only
   (D) (ii), (iii) & (iv) only

10. ***Which of the following may confirm the causative agent for a photosensitivity reaction?***
    (A) Genetic testing
    (B) Skin prick test
    (C) Photochemical testing
    (D) Complement fixation testing

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

***CE Questions Answer for 241(D&T)***

**A Drug Use Evaluation of Amoxicillin/Clavulanate in Hospital Setting: a Focus on Prescribing Patterns**

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

# Applications of Flow Cytometry for Monitoring Cellular Responses to Molecular or Environmental Treatment in Drug Discovery and Design

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**ABSTRACT**

**Flow cytometry is a good measurement system for monitoring cellular events after biochemical treatment or environmental exposure. This system is applicable for various types of cellular analysis; including collection and analyzes of data and real-time monitoring of cellular response to various treatment. The high speed quantitative high content analysis of cells makes it an attractive technology for drug discovery and development. Using the laser beam and fluorescence detectors in combination with appropriate biochemical dyes, flow cytometers can bring versatility and convenience to the benchtop and illustrate the rich data that are generated using a flow cytometer for drug screening and study.**

***Keywords:*** *Flow cytometry; drug discovery; drug design; cell sorting, cellular analysis; fluorescence emission and signal; biochemical dyes; laser*

## INTRODUCTION

In the last few decades, there has been the major challenge in the drive of discovery and development of new drugs.[1] This phenomenon is attributed to two vital factors; namely, requirements for tough empirical and sensible approach to drug discovery, and high standards of safety and therapeutic efficacy together with enormous increased costs of research and development and the clinical trials.[2]

Drug discovery or design aims at searching and developing a drug with high degree of chemotherapeutic index and specific action.[3,4] It requires logical approach to explore the exact action of a substance on biological systems on as much a rational basis as possible thus reducing to the minimum the trial and error approach.[5] It essentially involves the study of biodynamics of a bioactive compound besides the interaction between the molecules and molecules composing the biological objects, drug design also searches for the following explanations:[3]

(1) Effects of a compound on the basis of molecular interaction in terms of molecular structures or precisely the physico-chemical properties of the molecules involved;
(2) Various processes by which the drugs usually produce their pharmacological effects;
(3) How the drugs specifically react with protoplasm to elicit a particular pharmacological response;
(4) How the drug is modified or detoxicated, metabolized or eliminated by the organism;
(5) Probable relationship between biological activities with chemical structure.

In order to answer the above questions after treating some cells with a compound or exposure to an environmental parameter, it is necessary to apply a device that can in-situ monitor cellular responses to drug. It should not be merely speedy but also quantitatively high content analysis of the treated cells. Flow cytometry is a powerful tool for the rapid measurement and analysis of multiple parameters of individual cells within heterogeneous populations. It is helping transform every stage of preclinical and clinical development of drug, guiding new drug screening, evaluation, and monitoring.[6,7]

## FLOW CYTOMETRY

Flow cytometry is a microscopical technique dating back to 1930s and instruments have been commercially available since the 1970s. It was developed to allow high-speed quantitative analysis of cells and other particles.[8] Cell suspended in a steam of liquid are passed through a focused laser beam to generate optical signals, such as light scattering and fluorescence.[9] These signals are typically processed in real time.

It can measure cells for parameters that reflect a great multitude of biological conditions, from how individual cells react to a drug, to how the drug affects physiological systems such as immunity.[10,11] It allows simultaneous multi-parametric analysis of the physical and chemical characteristics of up to thousands of particles per second. Flow cytometry is routinely used in the diagnosis of health disorders, especially blood cancers, but has many other applications in basic research, clinical practice and clinical trials. A common variation involves linking the analytical capability of the flow cytometer to a sorting device, to physically separate and thereby purify particles of interest based on their optical properties. Such a process is called cell sorting, and the instrument is commonly termed a “cell sorter”.[12]

Multi-parametric analysis enables an extensive investigation of the complex interrelated mechanisms of drug action in cell-based systems. The ability to make high-content measurements has made flow cytometry an important tool used for drug discovery. It is used at every stage of the drug discovery cycle both in Pharma and Biotech companies, including target identification and validation, hit identification, lead and candidate selection and safety studies. In vitro and ex vivo flow cytometry methods are routinely employed in toxicology studies assisting in identifying and characterizing off-target effects at the single cell level.[5] Flow cytometry is used during clinical testing in order to assess both safety (e.g. anti-drug antibody testing) and pharmacokinetic assessments to monitor the plasma levels of protein and peptide based therapeutics.[6]

The technology has multiple applications in various fields, including molecular biology, pathology, immunology, plant biology and marine biology.[13,14] Additionally, it has broad application in medicine, especially in transplantation, hematology, tumor immunology and chemotherapy, prenatal diagnosis, genetics and sperm sorting for sex preselection. It is extensively used in research for the detection of DNA damage, caspase cleavage and apoptosis.[15,16] In neuroscience, co-expression of cell surface and intracellular antigens can also be analyzed. In marine biology, the auto-fluorescent properties of photosynthetic plankton can be exploited by flow cytometry in order to characterize abundance and community structure. In protein engineering, flow cytometry is used in conjunction with yeast display and bacterial display to identify cell surface-displayed protein variants with desired properties.[17,18]

### Related Applications

Cellular processes and events are probabilistic and take place in a context of complex varying environments, which they influence and which influence them.[19] For this reason, flow cytometry is an ideal methodology for cell and cancer biology research since it supports the multi-parametric analysis of individual cells and subpopulations in heterogeneous samples.[10,20]

Nowadays personal flow cytometer in the lab provides many advantages for cell and cancer biology studies. When cells are ready for analysis or rare tumor samples arrive, it's crucial to have a flow cytometer at hand, ready to go. Such as cell proliferation and apoptosis is important for both development and normal tissue homeostasis.[21,22] Cell proliferation, regulated by the cell cycle, can lead to an increase in the number of cells. Apoptosis, or programmed cell death, results in controlled self-destruction.[21] Many factors including stress, radiation, environmental exposure and treatment with small molecules can lead to changes in cell cycle, apoptosis, DNA damage, and cell proliferation, making these parameters important to study in various disciplines of cell biology. BD Biosciences offers a complete portfolio of reagents and tools to allow exploration of the cellular features of these processes.

## BIOCHEMICAL REAGENTS FOR SPECIFIC CELLULAR MONITORING

### Tool for Monitoring Cell Apoptosis

Apoptosis can be detected by the presences of phosphatidylserine (PS), which is normally located on the cytoplasmic face of the plasma membrane and translocations to the outer leaflet during apoptosis. PS bound to fluorochrome-labeled Annexin V in the presence of $Ca^{2+}$ can be detected by flow cytometry and cell imaging **(Figure 1)**.

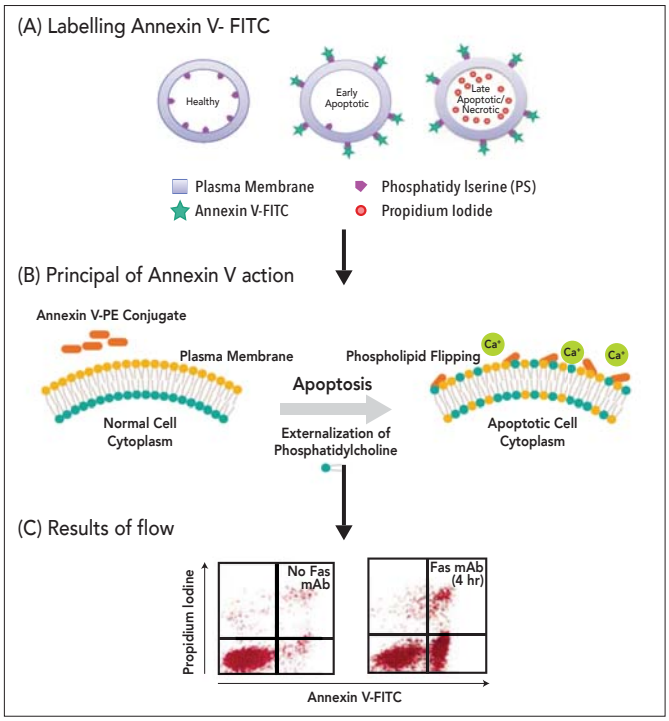


***Figure 1. Exposure of phosphatidylserine (PS) phospholipid on the extracellular face of the plasma membrane.*** *Exposure can be detected by dye-labeled PS-binding proteins, such as annexin V in a non-perturbing manner **(1A)**. The PS exposure is a rather early phenomenon in the apoptotic process **(1B)**. The data obtained by both flow cytometry and immunofluorescence with PS-specific antibodies demonstrate that the PS translocation can be observed. At the time when the barrier functions of the membrane are still not lost and the characteristic morphological changes undetected **(1C)**.*

The exposed PS was labeled with Annexin V-FITC and then these cells were stained with propidium iodide (PI) for distinguishing from three types of cells. First type, apoptotic cells can be stained green by Annexin V-FITC, but PI can't be stained. Apoptosis or apoptosis of the late stage cells dues to cell membrane damaged will be stained with both Annexin V-FITC and PI. Normal cells can't be stained with Annexin V-FITC or PI.

### Tools for Monitoring Mitochondrial Membrane Potential Change

Once apoptosis starts in the mitochondrial membrane potential change can be measured by cytometry using the BDTM mitoscreen (JC-1) flow cytometry kit JC-1 exists in monomer or aggregate form. As shown in **Figure 2**, healthy mitochondrial take up JC-1 leading to JC-1 aggregates which show high red fluorescence. Cells were left untreated **(Figure 2A)** or treated with staurosporine (1 µm, 4 h) to induce apoptosis **(Figure 2B)**. Cells were stained with JC-1 according to the protocol and analyzed on a BD FACSCalibur. Under normal physiological conditions **(Figure 2A)**, the mitochondrial contained higher electronegativity, resulting in JC-1 was present as aggregates when entering the mitochondrial, and the FL2 channel most observes red fluorescence; When cells toward to apoptosis **(Figure 2B)**, the depolarization of the mitochondria resulted

in the decrease of the electronegativity. JC-1 was present as monomer in the cytosol, and the green fluorescence was observed in the FL-1 channel.*R1-accumulation of JC-1 in healthy, normal mitochondria as JC-1 aggregates (high red fluorescence signal), R2-decrease in red fluorescence resulted by leakage of JC-1 from mitochondria, indicating depolarization of mitochondria membrane.

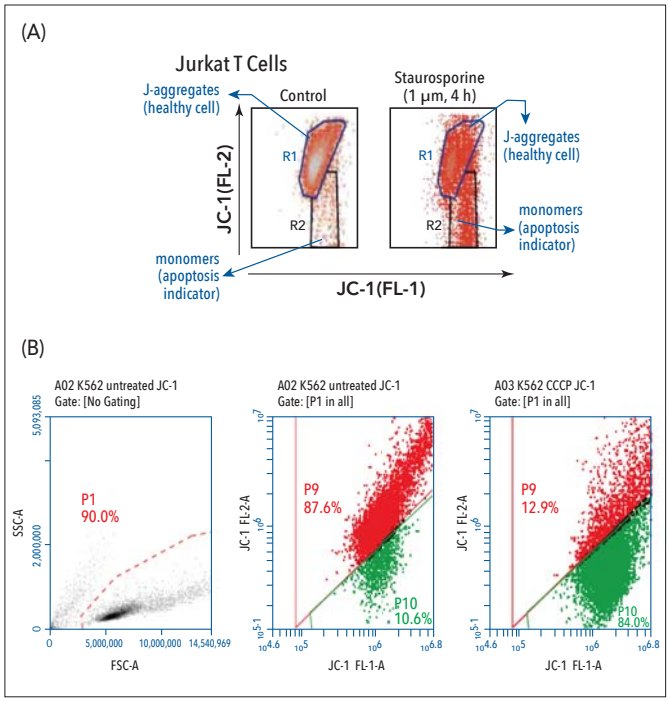


***Figure 2. Detection of mitochondrial membrane potential change by flow cytometry**. The loss of mitochondrial membrane potential is a hallmark for apoptosis. The BD Biosciences JC-1 Assay Kit measures the mitochondrial membrane potential in cells **(2A)**. In non-apoptotic cells, JC-1 exists as a monomer in the cytosol (green) and also accumulates as aggregates in the mitochondria which stain red. Whereas, in apoptotic and necrotic cells, JC-1 exists in monomeric form and stains the cytosol green by flow cytometry **(2B)**.*

## Tools for Caspase Activity Assay

Caspase activity assays are based on the use of synthetic tetrapeptide substrates which are designed such that proteolytic cleavage by active human or mouse caspases results in release of a fluorophore or chromophore which can be detected by spectrofluorometry. BD Biosciences offers a range of tools for caspase activity assays from individual fluorogenic peptide substrates and inhibitors, to kits, to ready-to-use assay plates. Activated caspase-3 is a proteolytic enzyme capable of specifically cleaving the AC-DEVD-AMC, which is cleaved between D (Aspartate) and AMC, allowing the AMC to be released before it emits fluorescence and then with caspase -3 inhibitor AC-DEVD-CHO, by specifically inhibiting the expression of Caspase-3, and then detect the fluorescence content, we can see the activation of caspase-3 expression **(Figure 3)**.

## Tools for Measuring DNA Content and Cell Proliferation

During the cell cycle phases, DNA levels change, facilitating the use of DNA to generate characteristic cellular DNA content profiles. BD Biosciences offers a wide variety of reagents to study the cell cycle. Reagents include DNA dyes such as

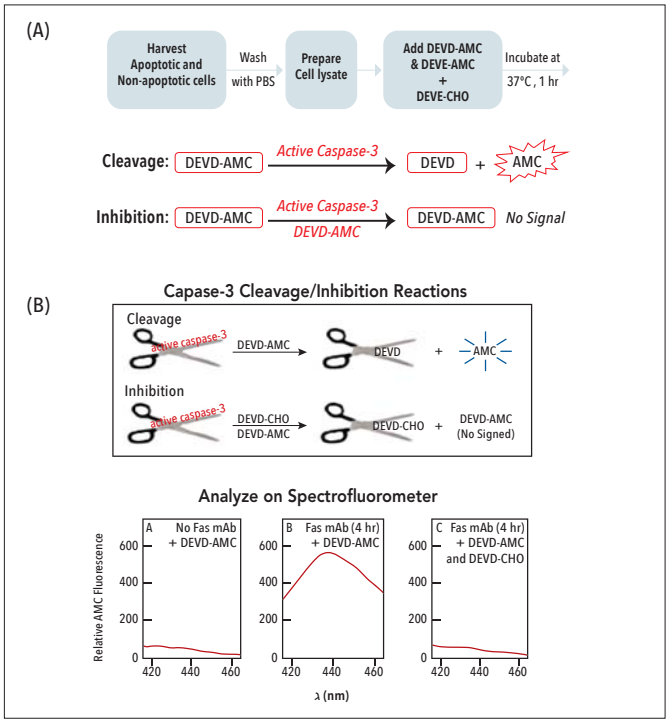


***Figure 3. Detection of caspase activation**. Release of mitochondrial factors, activation of cascade of cytoplasmic caspase enzymes and changes in cell membranes are followed by the loss of mitochondrial membrane potential. Caspase-3 is an important indicator for early apoptosis, since the earliest events of apoptosis stimulates activity of caspases, in which caspase-3 is major functional protein and other downstream apoptotic effectors. Members of the ICE/CED-3 cysteine protease family have key roles in apoptosis. The ICE family member Caspase-3 is activated early in apoptosis and appears to be involved in the proteolysis of several important molecules, including poly (ADP ribose) polymerase (PARP). Activated Caspase-3 cleaves PARP from its 116 kDa to an 85 kDa residual fragment. The cleavage site in PARP is C-terminal to Asp-216. The upstream sequence of the cleavage site, DEVD (Asp-Glu-Val-Asp), is utilized as a basis for the highly specific Caspase-3 substrate, Ac (N-acetyl)-DEVD-AMC (7-amino-4-methylcoumarin). Ac-DEVD-AMC is a synthetic tetrapeptide fluorogenic substrate for Caspase-3 (CPP32) and contains the amino acid sequence of the PARP cleavage site at Asp-216. The tetrapeptide substrate can be used to identify and quantify the Caspase-3 activity in apoptotic cells. Caspase-3 cleaves the tetrapeptide between D and AMC, thus releasing the fluorogenic AMC, which can be quantified in a spectrofluorometer **(3A)**. The substrate can also be used to study the inhibition of Caspase-3 by the tetrapeptide aldehyde, Ac-DEVD-CHO or any other inhibitor of Caspase-3. AMC has an excitation maximum 340nm-360nm and an emission maximum of 440-460nm **(3B)**.*

PI and 7-amino actinomycin D (7-ADD). In addition, the BD cycletest plus reagent kit includes PI and other reagents to degrade proteins and RNA to allow more precise DNA measurement **(Figure 4)**. In **Figure 4A**, apoptosis, the late stage of apoptosis will occur within the nucleus DNA fragmentation and fragmented phenomenon. When DNA is degraded by an endogenous endonuclease, a cut with a 3 'end or a DNA fragment is broken and a specific nucleotides labeled with fluorescent pigments such as FITC-dUTP are ligated to the DNA fragment under TdT The fluorescence intensity was proportional to the DNA fraction. The apoptotic cells were quantitatively analyzed according to the fluorescence intensity. The method could also be used for double-parameter analysis with PI staining. In addition to the percentage of apoptotic cells, also understand the apoptotic cells where the cell cycle (G0 / G1, S, G2 / M). **Figure 4B** shows DNA staining was used to determine the DNA cycle in the APO-Direct reagent group. DNA region was the same as the cell width. The cell width was

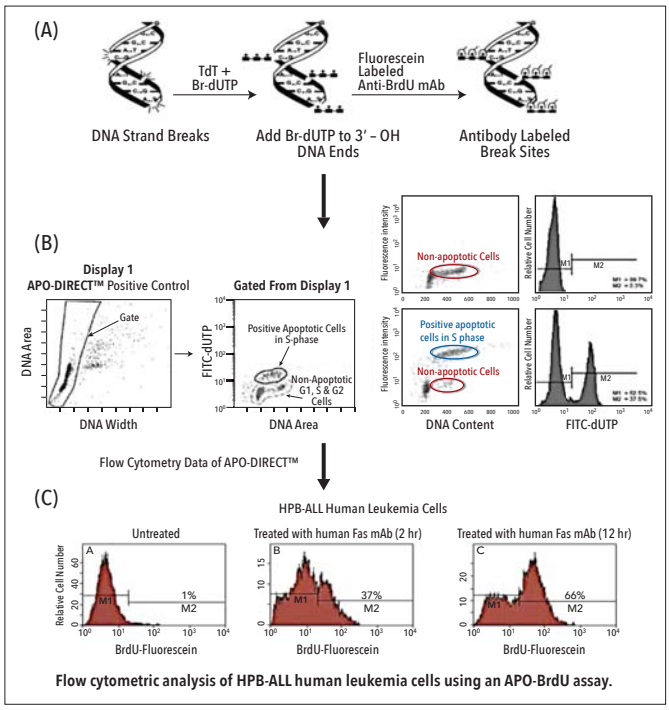


***Figure 4. Detection of DNA degradation during apoptosis****. DNA fragmentation is one of the last phases in apoptosis resulting from the activation of endonucleases during the apoptotic process. The BD™ APO-BrdU kit uses end labeling or the terminal deoxynucleotidyl transferase (TdT) nick end labeling (TUNEL method) to support the study of DNA fragmentation* ***(4A)****. In this assay, TdT catalyzes a template-independent addition of bromolated deoxyuridine triphosphates (Br-dUTP) to the 3'-hydroxyl (OH) termini of double- and single-stranded DNA* ***(4B)****. After the Br-dUTP is incorporated, these terminal sites of double- and single-stranded DNA are identified using flow cytometry by staining cells with labeled anti-BrdU. In contrast, the BrdU proliferation assay incorporates BrdU into newly synthesized DNA, into sites of DNA strand breaks, this also indicates the increase in cell death* ***(4C)****.*

twice as large as that of the cells. Double cell, the cell cycle should be excluded from the interference of the double body, from the DNA Width and DNA Area point map to select the first circle of cells without double, and then further analysis of these cells in the case of apoptosis. As shown above, apoptotic cells are predominantly in S phase. In **Figure 4C**, HPB-ALL human leukemia cells were treated with Fas mAb and DX2 Protein G2 hours (Panel 3B) 12 hours (Panel 3C) after the cells were fixed with Br-dUTP and TdT enzyme together, the use of fluorescen labeled anti-BrdU detection BrdU expression, The results showed that the expression of Br-dUTP in apoptotic cells was significantly increased

## DATA ANALYSIS

### Gating

The data generated by flow-cytometers can be plotted in a single dimension, to produce a histogram, or in two-dimensional dot plots or even in three dimensions. The regions on these plots can be sequentially separated, based on fluorescence intensity, by creating a series of subset extractions, termed "gates." Specific gating protocols exist for diagnostic and clinical purposes especially in relation to hematology. Individual single cells are often distinguished from cell doublets or higher aggregates by their "time-of-flight" (denoted also as a "pulse-width") through the narrowly focused laser beam.

The plots are often made on logarithmic scales. Because different fluorescent dyes' emission spectra overlap, signals at the detectors have to be compensated electronically as well as computationally. Data accumulated using the flow cytometer can be analyzed using software, e.g., JMP (statistical software), WinMDI, Flowing Software, and web-based Cytobank (all freeware), Cellcion, FCS Express, FlowJo, FACSDiva, CytoPaint (aka Paint-A-Gate), VenturiOne, CellQuest Pro, Infinicyt or Cytospec. Once the data is collected, there is no need to stay connected to the flow cytometer and analysis is most often performed on a separate computer. This is especially necessary in core facilities where usage of these machines is in high demand.

### Computational Analysis

Recent progress on automated population identification using computational methods has offered an alternative to traditional gating strategies. Automated identification systems could potentially help findings of rare and hidden populations. Representative automated methods include FLOCK[23] in Immunology Database and Analysis Portal (ImmPort), SamSPECTRAL[24] and flowClust[25] in Bioconductor, and FLAME in GenePattern. T-Distributed Stochastic Neighbor Embedding (tSNE) is an algorithm designed to perform dimensionality reduction, to allow visualization of complex multi-dimensional data in a two-dimensional "map" Collaborative efforts have resulted in an open project called FlowCAP (Flow Cytometry: Critical Assessment of Population Identification Methods,) to provide an objective way to compare and evaluate the flow cytometry data clustering methods, and also to establish guidance about appropriate use and application of these methods.[26]

## CONCLUSIONS

Flow cytometry is an attractive technology for drug discovery applications and it is used at many stages of this process. The ability to examine individual cells at the rate of thousands per second has made flow cytometry an attractive technology for investigating new drug candidates, evaluating the effectiveness of cancer treatments, and understanding mechanisms of cell health. Flow cytometry is becoming an ideal tool, particularly in an environment where primary cell-based assays are increasing being deployed to monitor drug responses. Therefore, it has been successfully applied to both cell and microsphere based bioassays in 96- and 384-well formats, to screen tens-of-thousands of compounds and identify novel bioactive structures.[27,28]

High-content multiparametric analysis capabilities have been exploited for assay multiplexing, allowing the assessment of biologic selectivity and specificity to be an integral component of primary screens. These and other advances in the last decade have contributed to the application of flow cytometry as a uniquely powerful tool for probing biologic and chemical diversity and complex systems biology.[11,29,30]

In this application, a duplex screening assay was developed to detect antibodies that bind specifically to $CD4^+$ on the surface of target cells but not to control cells that were CD4 negative. The assay was developed to screen a hybridoma library generated by immunizing mice with a cell line expressing CD4. The assay achieves two important cell-

based screening goals: (i) since the target binding protein was assayed in the context of living cell membranes, it maintains its natural conformation, and (ii) both target cells and control cells were present and analyzed in every well of the plates, combining a specificity and cross reactivity screen into one run.[31]

The use of cell-based screening technologies has become an integral component of drug discovery. The advancement of cell-based assays has enabled a better understanding of the interconnectedness of cellular pathways, a chance to focus on developing models for specific disease states, and the ability to explore relevant cellular biomarkers for therapeutics. With the advancement of high-throughput flow cytometry a new tool can be added to the arsenal of cell-based screening technologies. Incorporating flow cytometry into cell-based screening campaigns enables the use of multiplexed assays, thus effectively running multiple assays in each well. Because high-throughput flow cytometry is the preferred technology for analyzing particles in suspension, it is an ideal technology for screening assays that utilize non-adherent cells such as cells representing the immune system, microorganisms, or multiplexed bead arrays. Finally, this could revolutionize the drug discovery process in the near future that multiplexed screening assays can increase productivity, while providing a more thorough understanding of the complex effects of potential therapeutics.

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**Author's background**

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***Dr. CHEUNG Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong, is a Manufacturing Pharmacist and Biotechnologist. He has more than 400 publications and received many awards for both of his research and academic works.*

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# Students' Experience on Attending the Beijing Forbidden City International Pharmacist Forum 2017

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As Pharmacy students from Hong Kong, there is no doubt that we are familiar with the pharmaceutical practice and sectors in Hong Kong. However, information and knowledge in this world is enormous that we should always look for opportunities to explore pharmaceutical services and industries outside Hong Kong. We are so grateful that an opportunity was granted by the Pharmaceutical Society of Hong Kong (PSHK) for CUHK pharmacy students to participate in the Beijing Forbidden City International Pharmacist Forum 2017, in which we have experienced a lot that we would never acquire from textbooks. The PSHK delegation was led by Mrs. Mary Cheng, together with Mr. Benjamin Kwong, Mr. Tony Li, Prof. Joyce You, Mr. Vincent Tsui, Ms. Florence Kwan, Miss Mak Choi Ping, Mr. Tang Ka Ming, Mr. Yang Kwok To and Miss Yam Hoi Lai **(Picture 1)**.

***Picture 1.*** *Left to right (Back row: Florence Kwan, Benjamin Kwong, Mary Cheng, Joyce You, Vincent Tsui, Tony Li; Front row Mak Choi Ping, Yam Hoi Lai, Tang Ka Ming, Yang Kwok To)*

## PEKING UNIVERSITY THIRD HOSPITAL AND PEKING UNION MEDICAL COLLEGE HOSPITAL

We visited the Pharmacy Departments of two Class A tertiary comprehensive hospital named Peking University Third Hospital and Peking Union Medical College Hospital. Both hospitals introduced Rowa Vmax Box Picking Machine **(Picture 2)** in outpatient pharmacy to facilitate the drug distribution process. After the physicians prescribe medication, the prescription is sent to the pharmacy. The patients swipe their medical cards and the system would automatically locate the prescribed drugs. The robotic hands of Rowa Vmax Box Picking Machine push the boxed drugs to the conveyor belt and gather into a smart basket. Each smart basket is equipped with an RFID chip to record the patient's prescription information. The shelf is equipped with RFID reader which reads the RFID chip in the basket. **(Picture 3)** When the pharmacists swipe patients' ID, the specific compartment of the shelf placed with the corresponding basket would light up to remind the pharmacist to quickly and accurately find the patient's medications. The entire process remains at 16-20 seconds per prescription. Pharmacy Technicians are responsible for drug refill. After confirming the identity of the drugs, they place the drugs on the tracks for refill. **(Picture 4)** The greatest advantages of the automatic dispensing system include improving efficiency and accuracy of dispensing, and reducing the work intensity. Storage of drugs inside the machines allows better control of temperature and humidity of the drugs to ensure their quality. Nevertheless, this system is limited to the tablets that came in as original boxes or repacked as boxes. Those ampoules, vials, and refrigerated items still have to be manually picked by pharmacists. As shared by the pharmacists in Peking Union Medical College Hospital, pharmacists are not replaced by the machines in this automation. Instead, more time is allowed for them to optimize the pharmacy services by opening more service counters, conducting medication review and providing patient counseling. Consequently, patients' waiting time is greatly shortened and patients' satisfaction is improved. To further improve the situation of waiting, patients can know the status of dispensing by swiping their medical cards.**(Picture 5)**

***Picture 2.*** *Rowa Vmax Box Picking Machine*

***Picture 3.*** *The smart basket with RFID chip and shelf with RFID reader*

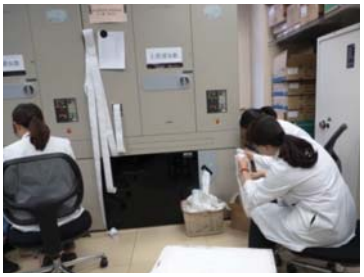
***Picture 4.*** *Refilling the Rowa Vmax Box Picking Machine*


***Picture 5.*** *Checking status of dispensing by swiping patients' medical cards.*

For inpatient pharmacy of both hospitals, Unit Dose Automatic Tablet Dispensing System is installed. Before the medications are filled into the Unit Dose Automatic Tablet Dispensing Machine, their outer and inner packages have to be removed manually.**(Step 1)** The medications of a

specific patient would be automatically distributed to a plastic bag and which would be printed with labels (e.g. hospital name, ward, bed number, patient name and ID, name, strength dosage and quantity of medication, and route of administration)**(Step 2).** All the prescriptions in one ward could be finished within a few minutes. The unit doses have to be checked by pharmacists for correct identity, dose, strength and integrity.**(Step 3).** In Peking Union Medical College Hospital, the checking process is done by a machine as well. The problematic unit doses would be corrected by cutting open the plastic bag, replaced with the correct drugs and sealing with plastic tape. After verification, the unit doses would be rolled into big rolls according to ward number and sent to the specific ward.

***Step 1.*** *Manually remove the packages*



***Step 2.*** *Automatically generate the unit doses*

***Step 3.*** *Checking and correcting by pharmacists*

## PARTICIPATION BY HONG KONG PHARMACISTS

Mrs. Mary Cheng, Vice President of PSHK **(Picture 6)** was one of the moderators for 3 sessions after the Opening Ceremony. She co chaired the sessions with Mr. Zhao Yun Sun on the talks on “Reform of health care system toward a superaged society - Expanding role of Pharmacists” by Yasuo Takeda, Japan; Human health needs:Drug.Pharmacy.Pharmacist by Paul Sinclair, Australia and 2017 hot spot- Pharmaceutical care for diabetes and complication by Huande Li, China.


***Picture 6.*** *Mrs. Mary Cheng, Vice President of PSHK as moderator*

Four of our Hong Kong pharmacists were invited to give stimulating talks and seminars to exchange ideas in this special occasion. We understand more about pharmacists’ roles and how they contribute greatly to the healthcare team to provide better pharmaceutical care.

The first talk on the topic “Safety and Care: Experience in Oncology Clinical Pharmacy Service” was delivered by Mr. Vincent Tsui, who is a Board Certified Oncology Pharmacist (BCOP) from Queen Elizabeth Hospital. **(Picture 7)** He shared his valuable experience on medication reviews in oncology ward rounds, clinical screening of chemotherapy orders and counseling of new patients. One impressive audit result revealed was that prescriptions screened by clinical pharmacists were less likely to require intervention in the subsequent dispensing process, which highlighted the importance and significance of clinical pharmacists. Ms. Florence Kwan, from Prince of Wales Hospital, **(Picture 8)** shared to us another big area in pharmacy - clinical drug trials. The importance of clinical research pharmacy includes promoting patient safety and enhancing the quality of IMP (Investigational Medicinal Product) in compliance with international guidelines, regulatory requirements as well as institution management policies. The establishment of CUHK-NTEC Clinical Research Pharmacy (CRP) has also greatly ensured the quality management of IMPs of phase 2 to 4 clinical trials.

***Picture 7.*** *Mr. Vincent Tsui, Board Certified Oncology Pharmacist from Queen Elizabeth Hospital*

***Picture 8.*** *Ms. Florence Kwan, pharmacist from Prince of Wales Hospital*

Prof. Joyce You from the Chinese University of Hong Kong **(Picture 9)** inspired us in her expert area of infectious diseases. Experiences of antimicrobial stewardship programs in optimizing antimicrobial use in inpatient setting were covered. Key interventions include pre-authorization, prospective audit, intravenous-to-oral antibiotic conversion etc. Multi-disciplinary collaboration with other healthcare team members including microbiologist, epidemiologist, information system specialist and physicians was also emphasized.

***Picture 9.*** *Prof. Joyce You from the Chinese University of Hong Kong*

Mr. Benjamin Kwong from the Hospital Authority **(Picture 10)** represented Hong Kong to exchange ideas with delegates from mainland China and Taiwan on home pharmaceutical care. An example of visiting pharmacists in old aged homes in Hong Kong was used. Challenges and common drug issues in institutions were also discussed. The forum marked the end of our fruitful journey in Beijing in the past few days.


***Picture 10.*** *Mr. Benjamin Kwong, Hospital Authority*

## COMPARISON OF PHARMACY SYSTEMS IN HONG KONG AND OTHER COUNTRIES

For outpatient dispensing system, the majority of hospitals in Hong Kong adopt manual picking, packing and labelling of medications by dispensers. The Outpatient Pharmacy Automation System (OPAS) in Singapore has given us insights on how we can improve the outpatient dispensing system.

After the prescriptions are reviewed by pharmacists in the pharmacy, the prescriptions are placed into RFID baskets which are run on conveyor belts. This triggers the automatic dispensing process. Different dosage forms of medications can be dispensed automatically. Tablet blisters and boxes of different sizes can also be picked and packed into re-sealable bags. The Robotic Bottle Dispensing System (BDS) can auto-load bottles from cartons, and directly affix labels onto the bottles. The labels affixed on bottles are innovative flag labels which are water-, tear- and scratch-proof.

All the packed medications are put into the RFID baskets automatically. The system can detect that the prescription has been filled, and the baskets are assembled and delivered to pharmacists at front dispensing counters. OPAS improves prescription packing time during peak hours, productivity and capacity of dispensing and staff satisfaction.

For the busy pharmacy environment and long waiting time for medications of patients, Hong Kong can take Singapore as a reference to automize a part of its dispensing system in order to speed up the dispensing procedures.

For the dispensing of medications after hospitalization or hospital visits, patients in Hong Kong obtain their medications either from hospital pharmacies or community pharmacies. In Japan, home pharmacist has been proposed to provide centralized medication management to dispense medications to patients in a community.

In a community, no matter which hospitals the patients have consulted, they will obtain their medication in the home pharmacy in that community. Even if the patients have consulted multiple hospitals, medications are dispensed in the home pharmacy. This can provide a centralized medication management as home pharmacists manage the whole medication history of patients. Moreover, home pharmacy provides a 24-hour telephone consultation in case of adverse drug reaction or medication mistakes occur in patients during non-business hours. Home pharmacists also actively participate in health-care home visit to manage remaining medications.

Same as Japan, Hong Kong has an aging population. It is foreseeable that an enhanced medication care should be provided for the elders in Hong Kong. Hong Kong can take Japan as a reference to reform its medication care system.

## REFLECTION ON THE WHOLE TRIP

The whole trip was indeed a very valuable experience for us four, not only in terms of exposing ourselves to different pharmacy practices of various countries, but also in terms of meeting pharmacy professionals from different sectors. To be honest, we have never thought that the forum would be so large in scale when I first glanced at the invitation email. After attending the forum in person, I was amazed by the diversity of the participants and the topics that they have delivered. Some of the topics cover the current situation in countries such as Japan, India and Lebanon, which we would never have known without attending the Forbidden City International Forum.

The trip was well-managed and packed with learning activities. Two hospital pharmacy visits were arranged on the day we arrived Beijing. The dispensing process in Peking Union Medical College Hospital is very advanced. There were robotic arms that pick medications in the shelf, which aids the dispensing process. Under such circumstances, pharmacists have more time to provide more comprehensive services. Before the visits, we have never thought of this high level of automation in hospitals in China. We were astonished by the large scale of auto-dispensing in these hospitals. We have also discovered these hospitals also dispense proprietary Chinese medications. That was challenging for pharmacists to watch out for drug-herb interactions.

At the first night of the forum, there was a welcoming dinner. The performances include Peking Opera, traditional Chinese paper cutting, Indian and Spanish Flamenco dance, which were all truly enjoyable. We also gave a performance by singing “red sun”, a song of the Hong Kong singer Hacken Lee. The song was meaningful and inspiring, which had given a good start for the forum on the next day.

## CONCLUSION

This trip was not all about the forum, we also had a chance to know the historical and cultural side of Beijing by visiting tourist attractions and wandering about the city. In short, although the trip was short, however, the experience acquired withstands the test of time.

**Author’s background**
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# The PSHK to host FAPA 2020 in Hong Kong
# The MOU signing ceremony in Kuala Lumpur Malaysia on 12 May 2017

**Reported by Ms S C Chiang**
*BPharm (Hons)., MHA, FHKCHSE, FACHSM, FCPP*


*Front row (from left to right):*
*Mr Andy Wong, Ms S C Chiang, Mr Philip Chiu, Mr Jospeh Wang, Mr Mohamed Dani Pratomo, Dr Yolanda Robles*

Mr Philip Chiu, President of the Hong Kong Pharmaceutical Society of Hong Kong, and Mr Joseph Wang who is the President of FAPA (Federation of Asian Pharmaceutical Associations) were in Kuala Lumpur, Malaysia on 12th May 2017 signing the MOU that Hong Kong will host the FAPA Congress in 2020.

This historic event was witnesses by Ms S C Chiang and Mr Andy Wong who are serving council members of PSHK. Yes, for the information of our pharmacists in HK, the FAPA Congress is a biannual event which has the following hosting arrangement:

| Date | No. | Place | Theme |
|---|---|---|---|
| November 3-8, 2010 | 23rd Congress | Taipei, Taiwan | Pharmacy and Society |
| September 13-16, 2012 | 24th Congress | Bali, Indonesia | Culture & Medicines |
| October 09-12, 2014 | 25th Congress | Sabah, Malaysia | Expanding the Pharmacists' Role in Wellness and Sustainable Health |
| November 09-13, 2016 | 26th Congress | Bangkok, Thailand | Integrating Asian Pharmacy Wisdom for Better Global Health |
| 2018 | 27th Congress | Manila, Philippines | *To be updated* |

Mr Joseph Wang who was inaugurated as FAPA President in year 2014 has pledged that he will make FAPA bigger, better and stronger.

The FAPA is working on several projects now:

- Membership Expansion
- Good Pharmacy Practice
- Antimicrobial Resistance (AMR)
- Disaster Management
- Non-communicable Disease (NCD)
- Separation of Dispensing and Prescribing Practice (SDP)

On the last topic, which may be dear to the hearts of our local pharmacists, FAPA organized and held the Stakeholders' Forum on Addressing the Medication Safety challenges in Asian Countries: Separation of Dispensing and Prescribing Practices in Hotel Istana Kuala Lumpur Malaysia on 12-13 May 2017. The event was co-hosted by the Malaysian Pharmaceutical Society (MPS) celebrating its 50th anniversary with a MPS conference and trade exhibition.

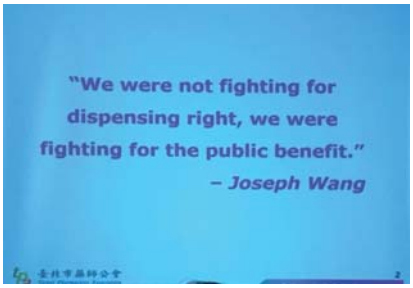

**PART 1**
**Friday Afternoon – May 12, 2017**
**Achieving Separation in Dispensing and Prescribing (SDP): The Asian Experience**

| Time | Activity | Speaker |
|---|---|---|
| 13:30-14:00 | Registration | |
| 14:00-14:10 | Introductory Address | ***Mr. Joseph Wang*** *President, Federation of Asian Pharmaceutical Associations (FAPA)* |
| 14:10-15:00 | Japanese Experience in Achieving SDP | ***Mr. Atsushi Toyomi*** *Director, Japan Pharmaceutical Association (JPA)* |
| 15:00-15:50 | Taiwanese Experience in achieving SDP | ***Ms. Mandy Fan*** *General Secretary, Taipei Pharmacists Association* |
| 15:50-16:20 | Tea Break | |
| 16:20-17:10 | Korean Experience in Achieving SDP | ***Dr. Wan Gyoon Shin*** *Professor, Seoul National University* |
| 17:10-18:00 | Panel Discussion | |
| 18:00-18:10 | Synthesis of Part 1 FAPA Action Statement | ***Dr. Yolanda Robles*** *General Secretary, Federation of Asian Pharmaceutical Associations (FAPA)* |

**PART 2**
**Saturday Afternoon – May 13, 2017**
**Ensuring Patient Safety through Separation of Dispensing and Prescribing**

| Time | Activity | Speaker |
|---|---|---|
| 13:30-14:00 | Registration | |
| 14:00-14:10 | Welcome Message | ***Mr Amrahi Buang,*** *President Malaysian Pharmaceutical Society,(MPS)* |
| 14:10-14:20 | Opening Remarks | ***Mr. Joseph Wang*** *President, Federation of Asian Pharmaceutical Associations (FAPA)* |
| 14:20-14:40 | Video Presentation | *JPA, KPA, TPA* |
| 14:40-15:10 | Responding to the WHO Global Patient Safety Challenge on Medication Safety in Asia | ***Dr. Yolanda Robles*** *General Secretary, Federation of Asian Pharmaceutical Associations (FAPA)* |
| 15:10-15:40 | Impacts of Separation of Dispensing and Prescribing on Patient Safety: Japanese Consumer's Perspective | **Ms. Nanako Kamei** *Japanese Consumer Representative* |
| 15:40-16:10 | Impacts of Separation of Dispensing and Prescribing on Patient Safety: Korean Consumer's Perspective | **Ms. Yoon Mi Cho** *Co-representative, C& I Consumer Research Centre* |
| 16:10-16:40 | Impacts of Separation of Dispensing and Prescribing on Patient's Safety: Malaysian Consumer Perspective | **Ms Narinder Kaur** *Consumer Association of Penang* |

*The 2 Day Medication Safety Forum invited speakers from Korea, Japan and Taiwan to share their journeys to achieve the SDP and also covered the impacts of SDP on the health care system in terms of patients' accessibility to use the pharmacists knowledge, the costs of the overall drug expenditures, the recent development on Family Pharmacists and the response from the consumers about SDP. Not a single place said it was an easy journey but it was all agreed that it took joint efforts to convince the Government, the doctors, the patients and the public that it was for benefits for all that SDP must be implemented.*




It was a pleasant two days listening to the different speakers from Taiwan, Japan and Korea who came forward to share with us how it was like before the SDP was implemented and what were the specific positive impacts and evidences of the SDP on patients particularly in the areas of patient safety and other economical outcomes and what were their recommendations in improving health care team dynamics in the SDP implementation.

I was asked what was being done in Hong Kong by the pharmacists when they learnt that a place like HK is still like Malaysia, Thailand and Cambodia where there is no road map yet for SDP. It was a subject too complicated to be explained and I would hence like to conclude by inviting our local pharmacists to:

- See beyond Hong Kong on Pharmacy Practice
- Learn what other pharmacists are doing
- Own the pharmacy practice development as your responsibility
- Think how we as an individual can contribute to make a difference
- Do what you can no matter how small a step it is to better shape the local pharmacy practice
- Join in as teams and work together to make small steps into bigger steps
- Participate in activities now to put up a good show in 2020 for FAPA Congress Hong Kong

# The Society of Hospital Pharmacists of Hong Kong (SHPHK) Office Bearers 2017/18

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**The Drug Education Resources Centre (DERC) 2016/17**

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## PRAXBIND®
**(Boehringer Ingelheim)**

*Prepared by Fiona Yuen and edited by Ivy Chan*

**Active Ingredient:**
Idarucizumab

**Presentation:**
Each mL of solution for injection/infusion contains 50 mg idarucizumab.
Each vial contains 2.5 g idarucizumab in 50 mL.

**Pharmacological Properties:**
Idarucizumab is a specific reversal agent for dabigatran. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran with very high affinity, approximately 300-fold more potent than the binding affinity of dabigatran for thrombin. The idarucizumab-dabigatran complex is characterised by a rapid on-rate and extremely slow off-rate resulting in a very stable complex. Idarucizumab potently and specifically binds to dabigatran and its metabolites and neutralises their anticoagulant effect.

**Indications:**
Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:
- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding

**Dosage & Administration:**
Restricted to hospital use only.
The recommended dose of Praxbind is 5 g (2x2.5 g/50 mL).
In a subset of patients, recurrence of plasma concentrations of unbound dabigatran and concomitant prolongation of clotting tests have occurred up to 24 hours after administration of idarucizumab.

Administration of a second 5 g dose of Praxbind may be considered in the following situations:
- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

Relevant coagulation parameters are activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT).
A maximum daily dose has not been investigated.
Praxbind (2x2.5 g/50 mL) is administered intravenously as two consecutive infusions over 5 to 10 minutes each or as a bolus injection.

**Contraindications:**
None.

**Precautions:**
Idarucizumab binds specifically to dabigatran and reverses its anticoagulant effect. It will not reverse the effects of other anticoagulants.
Praxbind treatment can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

*Hypersensitivity*
The risk of using Praxbind in patients with known hypersensitivity (e.g. anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Praxbind should be discontinued immediately and appropriate therapy initiated.
*Hereditary fructose intolerance*
The recommended dose of Praxbind contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function, and death. Therefore, in patients with hereditary fructose intolerance the risk of treatment with Praxbind must be weighed against the potential benefit of such an emergency treatment. If Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required.
*Thromboembolic Events*
Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.
*Urinary protein testing*
Praxbind causes transient proteinuria as a physiologic reaction to renal protein overflow after bolus/short term application of 5g idarucizumab intravenously. The transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing.
*Sodium content*
This medicinal product contains 2,2 mmol (or 50 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

**Drug Interactions:**
No formal interaction studies with Praxbind and other medicinal products have been performed. Based on the pharmacokinetic properties and the high specificity in binding to dabigatran, clinically relevant interactions with other medicinal products are considered unlikely.

Preclinical investigations with idarucizumab have shown no interactions with
volume expanders.
coagulation factor concentrates, such as prothrombin complex concentrates (PCCs, e.g. 3 factor and 4 factor), activated PCCs (aPCCs) and recombinant factor VIIa.
other anticoagulants (e.g. thrombin inhibitors other than dabigatran, Factor Xa inhibitors including low-molecular weight heparin, vitamin K-antagonists, heparin). Thus idarucizumab will not reverse the effects of other anticoagulants.

**Side Effects:**
The safety of Praxbind has been evaluated in 224 healthy subjects as well as 123 patients in an ongoing phase III trial, who had uncontrolled bleeding or required emergency surgery or procedures and were under treatment with Pradaxa (dabigatran etexilate).

No adverse reactions have been identified.

**Forensic Classification:**
P1S1S3

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