HONG KONG PHARMACEUTICAL JOURNAL

VOL 32 NO 2 May - Aug 2025 ISSN 1727-2874

News & Short Communications

Expedited Over-the-Counter Drug Registration Pathway – Case Studies in the United States and Canada

Review of Current CAR-T Therapy for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Adults: Tisagenlecleucel (Kymriah®) and Axicabtagene Ciloleucel (Yescarta®)(2 CE Units)

Hepatitis B Screening and Management in Primary Healthcare: Global Models and the Expanding Role of Community Pharmacies in Hong Kong

Highlights from PHARM+Excellence 2025: Driving Standards and Innovation in Primary Healthcare Pharmacy

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

HONG KONG PHARMACEUTICAL JOURNAL

VOL 32 NO 2 May - Aug 2025 ISSN 1727-2874

All communications and enquiries should be directed to:
The Secretary, Hong Kong Pharmaceutical Journal, Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.

For all enquiries regarding advertisement, please contact:
Mrs. Mary CHENG (Tel. 9839 2395) or Ms. Yvonne Li (Tel: 2376 3090) at the following email address: ***admin@pshkk.hk***

INSTRUCTIONS FOR AUTHORS

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

- Pharmacy Education & Practice
- Drugs & Therapeutics
- Primary Care, OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

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

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

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

e-mail: ***editor@hkpj.org***
address: ***Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.***

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

Editorial

News & Short Communications

Pharmacy Education & Practice

Drugs & Therapeutics

Primary Care, Over-the-Counter & Health

Driving Innovation and Collaboration in Healthcare: Insights from Regulatory Advances, Cutting-Edge Therapies, and Community Engagement

Welcome to this issue of Hong Kong Pharmaceutical Journal, where we showcase a collection of articles that reflect the dynamic and evolving landscape of healthcare. From regulatory advancements and cutting-edge therapies to public health strategies and professional collaboration, this edition offers valuable insights into addressing contemporary challenges and shaping the future of healthcare delivery.

Our first article explores the potential for Hong Kong to establish an expedited over-the-counter (OTC) drug registration pathway, drawing on lessons from the United States and Canada. The article highlights the benefits of enhanced regulatory efficiency, reduced costs for manufacturers and improved public health outcomes through greater access to safe OTC medications. However, it also underscores the challenges, including quality control, safety concerns and consumer education. The critical role of pharmacists in this transition, alongside stakeholder collaboration, is emphasized as a cornerstone for success. This piece serves as a timely discussion on how regulatory innovation can balance accessibility and safety in healthcare.

Next, we delve into the groundbreaking field of chimeric antigen receptor T-cell (CAR-T) therapy, a revolutionary approach to treating relapsed/refractory large B-cell lymphoma. The review focuses on tisagenlecleucel and axicabtagene ciloleucel, examining their mechanisms of action, efficacy, safety profiles and expanding clinical applications. With only tisagenlecleucel currently registered in Hong Kong, the article discusses how emerging data and comparative analyses may influence regulatory and clinical decisions, including the potential expansion of axicabtagene ciloleucel's role. This review not only highlights the promise of CAR-T therapy but also underscores the importance of monitoring and managing adverse reactions to ensure patient safety.

Addressing a persistent public health challenge, our third article focuses on chronic hepatitis B (CHB) and the untapped potential of community pharmacies in screening and management. Despite global efforts to eliminate hepatitis B by 2030, gaps in screening and linkage to care remain significant, particularly in high-prevalence regions like Hong Kong. Drawing on international case studies and local pilot programs, the article outlines a framework for expanding the role of pharmacists in hepatitis B care. Recommendations include regulatory reform, standardized protocols and integration with primary healthcare systems. This piece advocates for leveraging community pharmacies as accessible, person-centered hubs for preventive care and chronic disease management.

Finally, we present a report on the PHARM+Excellence 2025 conference, a landmark event that brought together healthcare professionals, academics, policymakers and social service providers to advance the role of pharmacists in primary healthcare. Under the theme "Shaping the Future of Primary Healthcare Pharmacy: Quality Standards, Research, and Interprofessional Collaboration," the conference emphasized quality standards, research and interprofessional collaboration. The event served as a catalyst for actionable strategies, including policy translation, capacity building, stakeholder engagement and international collaboration. This report marks a milestone in elevating the role of pharmacists within primary healthcare and signals a path toward more integrated, patient-centered care.

Together, these articles reflect the multifaceted nature of healthcare innovation, from regulatory frameworks and advanced therapies to community-based interventions and professional development. They highlight the importance of collaboration, evidence-based practice and adaptability in addressing both current and emerging healthcare challenges. As we navigate this ever-evolving landscape, these contributions offer valuable guidance for policymakers, practitioners and researchers alike.

We hope this issue inspires thoughtful discussion and action, driving progress toward a healthier and more equitable future for all. Thank you for joining us on this journey of discovery and innovation.

May P S Lam
Editor-in-Chief
5 September 2025

Prepared by Candice Leung, Branson Fok & Anne Ng

Monthly Mepolizumab Prevents Exacerbations among COPD Patients with Eosinophilic Phenotype

Date: May 1, 2025

Chronic Obstructive Lung Disease (COPD) is a progressive lung disease characterized by chronic bronchitis and/or emphysema, with an estimated 20 to 40% of patients presenting signs of eosinophilic inflammation. Alternations resulting from eosinophilic inflammation are possible to worsen existing COPD symptoms and leads to exacerbations requiring hospitalization. Mepolizumab, a humanized monoclonal antibody targeting interleukin-5, is thus considered as a potential treatment option for COPD patients with eosinophilic phenotype.

The multi-centre, double-blind, randomized and placebo-controlled MATINEE trial recruited 804 COPD patients with eosinophilic phenotype and had episode(s) of moderate or severe exacerbations 12 month before screening. Eligible participants were then randomly assigned in 1:1 ratio to receive either subcutaneous 100mg mepolizumab (n=403) or placebo (n=401) injection every 4 weeks as add-on to their ongoing triple inhaled therapy for up to 104 weeks. The primary end point was the annualized rate of moderate or severe COPD exacerbations. Time to the moderate or severe exacerbation and patient-reported outcome measures were regarded as secondary end points.

The annualized rate of moderate or severe exacerbations in the mepolizumab and placebo group were 0.80 and 1.01 events per year (rate ratio=0.79, 95% confidence interval [CI], 0.66-0.94; P=0.01) respectively. The Kaplan-Meier median time to the first moderate or severe exacerbation was 419 days (95% confidence interval [CI], 332-530 days) in the mepolizumab group, while the median time to first exacerbation was 321 days (95% confidence interval [CI], 262-396 days) in the placebo group. The incidence of adverse or serious adverse event during or after the treatment period was similar for both groups.

To conclude, monthly subcutaneous injections of mepolizumab helps to prevent moderate or severe exacerbations when added to background triple inhaled therapy among COPD patients with eosinophilic phenotype.

Source: www.nejm.org

Obicetrapib Lowers LDL-C and Improves Outcomes in High-Risk Cardiovascular Patients

Date: May 07, 2025

Obicetrapib is a highly selective cholesteryl ester transfer protein (CETP) inhibitor that have shown promising results in early trials to lower low-density lipoprotein (LDL) cholesterol levels and increase high-density lipoprotein (HDL) cholesterol levels. However, the full efficacy and safety profile of obicetrapib among patients at high risk for cardiovascular events is unknown.

In this multinational, randomized, placebo-controlled trial (BROADWAY), patients with heterozygous familial hypercholesterolemia or a history atherosclerotic cardiovascular disease (ASCVD) who were receiving maximum tolerated doses of statin therapy, with or without ezetimibe, bempedoic acid or PCSK9 inhibitors and were at high risk for cardiovascular events were recruited. Eligible patients were randomly assigned in a 2:1 ratio to receive oral obicetrapib (10mg) once daily or matching placebo for 365 days. The primary efficacy endpoint was the percent change in the LDL cholesterol level from baseline to day 84.

A total of 2530 patients spanning 188 sites in China, Europe, Japan, and the United States, were randomly assigned to receive obicetrapib (n = 1686) or placebo (n = 844). The least-squares mean percent change from baseline to day 84 in the LDL cholesterol level was −29.9% (95% confidence interval [CI], −32.1 to −27.8) in the obicetrapib group, as compared with 2.7% (95% CI, −0.4 to 5.8) in the placebo group, for a between-group difference of −32.6 percentage points (95% CI, −35.8 to −29.5; P<0.001). The incidence of adverse events appeared to be similar in the two groups.

In conclusion, obicetrapib has demonstrated greater reduction in LDL cholesterol levels than placebo among patients with ASCVD or heterozygous familial hypercholesterolemia who were on maximum tolerated doses of lipid-lower therapy and were at high risk for cardiovascular events.

Source: www.nejm.org

Intravenous Tenecteplase Before Thrombectomy Shows Improved 90-day Functional Outcomes

Date: May 21, 2025

In patients with acute ischemic stroke due to large vessel occlusion, administering thrombolysis prior to thrombectomy may enhance reperfusion outcomes. While alteplase remains the standard tissue plasminogen activator (tPA) for intravenous thrombolysis before thrombectomy, more studies suggest that tenecteplase offers significant time and cost advantages over alteplase.

A recent randomized, open-label trial conducted in China included patients who were eligible for thrombolysis and presented within 4.5 hours of symptom onset. Participants were assigned to receive either intravenous tenecteplase followed by thrombectomy or thrombectomy alone. The primary outcome measured was functional independence at 90 days, assessed using the modified Rankin scale (scores of 0 to 2, from a range of 0 to 6). Secondary outcomes focused on successful reperfusion rates and safety metrics, including symptomatic intracranial hemorrhage and mortality.

The trial enrolled 550 patients, with 278 assigned to the tenecteplase-thrombectomy group and 272 to the thrombectomy-alone group. 52.9% of patients in the tenecteplase group achieved functional independence at 90 days compared to 44.1% in the control group, indicating a statistically significant improvement (Unadjusted risk ratio, 1.20; 95% confidence interval, 1.01 to 1.43; P= 0.04). Successful reperfusion rates prior to thrombectomy were 6.1% in the tenecteplase group versus 1.1% in the control group, while post-thrombectomy rates were 91.4% and 94.1%, respectively. The incidence of symptomatic intracranial hemorrhage within 48 hours and death within 90 days did not differ significantly between the groups.

In conclusion, the addition of intravenous tenecteplase to thrombectomy demonstrates significant improvement in functional independence of patients with acute ischemic stroke due to large vessel occlusion.

Source: www.nejm.org

Amendment to Dangerous Drugs Ordinance: Etomidate Analogues Classified as Dangerous Drugs

Date: July 16, 2025

On July 16th, The Hong Kong Drug Office announced that all analogues of etomidate—specifically isopropoxate, metomidate, and propoxate—along with six other drugs, will now be classified as dangerous drugs under Part 1 Schedule 1 of the Dangerous Drugs Ordinance (DDO). This update expands the previous legislation, which only included etomidate.

Etomidate, often referred to as the “space oil drug,” began circulating among high-risk groups in 2024. According to the Central Registry of Drug Abuse maintained by the Narcotics Division, there were 493 recorded “space oil drug” abusers from 2023 to May 31, 2025, with 356 of them being young people under 21. Etomidate is primarily used as a short-acting intravenous anesthetic for inducing anesthesia. However, misuse of etomidate and its analogues can lead to dependence and serious health issues, making them susceptible to criminal exploitation to evade legal consequences. Overdose symptoms may include tremors, hallucinations, irreversible nerve damage, and respiratory arrest.

Recent scientific analysis has indicated that certain analogues of etomidate, which was yet classified as dangerous drugs, may potentially be abused. In an proactive measure against the misuse of etomidate, the DDO has now included its analogues and established a general definition for them. This aims to combat the possession and trafficking of these substances by prohibiting public consumption and use, thereby enhancing public safety and health.

Source: www.info.gov.hk

Tarlatamab Prolongs Overall Survival in Small-Cell Lung Cancer Patients Resistant to Platinum-Based Chemotherapy

Date: July 24, 2025

Small-cell lung cancer is an aggressive cancer with rapid rates of metastasis and recurrence. Although most patients respond to first-line platinum-based chemotherapy, etoposide and programmed death ligand 1 (PD-L1) inhibitor therapy recommended by clinical guidelines, poor prognosis is often noted in small-cell lung cancer patients with progression during or after initial platinum-based chemotherapy. Tarlatamab is a bispecific T-cell engager immunotherapeutic agent targeting delta-like ligand 3 on small-cell lung cancer cells to trigger tumour-cell lysis.

The multinational, open-label and randomized phase 3 trial recruited patients with small-cell lung cancer that had progressed during or after first-line platinum-based chemotherapy and with an Eastern Cooperative Oncology Group performance-status score of 0 or 1. A total of 509 patients were then randomly assigned in 1:1 ratio to receive intravenous tarlatamab (n=254) or second-line chemotherapy (n=255) based on pre-defined treatment protocol as active control. Choices of second-line chemotherapy include topotecan, lurbinectedin or amrubicin. The primary end point was overall survival defined as the time from randomization to death from any cause.

As of the data cut-off date in January 2025, the median overall survival was 13.6 months in the tarlatamab group and 8.3 months in the control group (Stratified hazard ratio for death=0.60, 95% confidence interval [CI], 0.47-0.77; P<0.001). The estimated restricted mean progression-free survival at 12 months was 5.3 months in the tarlatamab group and 4.3 months in the chemotherapy group (Piecewise weighted average hazard ratio=0.71; 95% confidence interval [CI], 0.59-0.86, P=0.002). The most common treatment-related adverse events associated with tarlatamab treatments were cytokine release syndrome, dysgeusia and pyrexia. Yet, the incidence of adverse events of grade 3 or higher was lower with tarlatamab (54%) than the active control (80%).

In conclusion, tarlatamab immunotherapy prolongs overall survival than second-line chemotherapy in small-cell lung cancer patients whose disease had progressed despite platinum-based chemotherapy.

Source: www.nejm.org

Finerenone-Empagliflozin Leads to Greater Reduction in Urinary Albumin-to-Creatinine Ratio in Patients with Chronic Kidney Disease and Type 2 Diabetes

Date: August 7, 2025

Individuals suffering from both chronic kidney disease and type 2 diabetes are known as one of the high-risk groups for various cardiovascular diseases and kidney failure. The current clinical approach for such patient population involves the use of renin-angiotensin system blockers, sodium-glucose cotransporter-2 inhibitors (SGLT2i), finerenone, and glucagon-like peptide-1 receptor agonists. Yet, the effect regarding the concurrent use of finerenone and SGLT2i on reducing risk of chronic kidney disease and cardiovascular complications remains unknown.

In this double-blind, randomized, active-controlled CONFIDENCE trial, 800 patients having both type 2 diabetes with chronic kidney disease and albuminuria (with a urinary albumin-to-creatinine ratio between 100-5000) were recruited. Participants were randomly assigned in 1:1:1 ratio to receive oral (1) finerenone and empagliflozin-matching placebo (n=264), (2) empagliflozin and finerenone-matching placebo (n=267) or (3) finerenone-empagliflozin combination therapy (n=269) for 180 days. The primary endpoint was the relative change in log-transformed mean urinary albumin-to-creatinine ratio. Safety outcomes including the change in eGFR and its reversibility with stopping the therapy, or any known adverse events related to finerenone and empagliflozin use were assessed.

The reduction in the urinary albumin-to-creatinine ratio with combination therapy at day 180 was 29% greater than that with finerenone alone (least-squares mean ratio of the difference in the change from baseline=0.71, 95% confidence interval [CI], 0.61-0.82; P<0.001) and 32% greater than empagliflozin monotherapy (least-squares mean ratio of the difference in the change from baseline=0.68, 95% confidence interval [CI],0.59-0.79; P<0.001). None of the treatment groups had unexpected adverse events and the incidence of known adverse events leading to treatment discontinuation were uncommon.

To summarize, oral finerenone-empagliflozin therapy leads to a greater reduction in the urinary albumin-to-creatinine ratio than either treatment alone, which may further lower risk of cardiovascular diseases and kidney failure in patients with both chronic kidney disease and type 2 diabetes.

Source: www.nejm.org

Expedited Over-the-Counter Drug Registration Pathway – Case Studies in the United States and Canada

LAU, Kristy Sin Tung[a]; CHAN, Philip Pan[a]*

[a] Fortune Pharmacal Co. Ltd., Block A & Block B, 50-68 Wang Lok Street, Yuen Long Industrial Estate, Yuen Long, New Territories, Hong Kong, China

*(*Corresponding author)*

ABSTRACT

This article draws lessons from the established systems in the United States and Canada to inform the development of an expedited over-the-counter (OTC) drug registration pathway in Hong Kong. It explores the potential benefits of implementing this pathway, which include enhancing regulatory efficiency, reducing research and development costs for manufacturers, and improving public health outcomes through increased access to safe OTC medications. However, it also presents challenges, including potential quality and safety concerns and consumer confusion resulting from a wider range of available products.

Implementing this pathway in Hong Kong requires careful consideration of regulatory adaptations, comprehensive OTC monographs, and robust post-market surveillance systems. Pharmacists will play a crucial role in this transition by providing expertise in regulatory framework development, public education, and safety monitoring. Ultimately, stakeholder engagement and collaboration among regulators, industry representatives, and healthcare providers are essential for fostering a regulatory environment that promotes the safe and effective use of OTC medications.

Keywords: *Over-the-Counter Drugs, Expedited Registration Pathway, United States, Canada*

INTRODUCTION

Over-the-counter (OTC) drugs are defined by the US Food and Drug Administration (FDA) as drug products marketed for use by consumers without the need for intervention from healthcare professional.(1) This classification empowers individuals to manage minor health issues independently, thereby enhancing their ability to make informed health decisions. The convenience of OTC medications allows consumers to access treatments for common ailments, such as headaches, colds, and allergies, without requiring a prescription. This accessibility is crucial for promoting self-care and reducing the burden on healthcare systems.

In contrast, Hong Kong's current drug registration policy, as outlined by the Department of Health (DH), categorizes drug registration pathways into three main types: Generic Products, New Chemical or Biological Entities, and Biosimilar Products. (2) However, there is a notable absence of specific application pathways for OTC drugs, creating a significant gap in the regulatory framework for non-prescription medications. This lack of dedicated pathways may hinder timely access to safe and effective OTC products, limiting consumer choices and potentially impacting public health.

Countries such as the United States, Canada, and Australia have recognized the need for expedited OTC registration pathways to simplify market access for these essential products. By streamlining the approval process, these countries aim to enhance public health by providing consumers with a broader range of self-care options, ultimately fostering a healthier society. Establishing a similar pathway in Hong Kong could significantly improve access to OTC medications, supporting the population's health and well-being.

This article aims to examine the expedited OTC drug registration pathways in the United States and Canada to inform the development of relevant pathways in Hong Kong. It also discusses the potential benefits and drawbacks, the challenges of implementation, and the role of pharmacists in facilitating such pathways.

EXPEDITED OTC DRUG REGISTRATION PATHWAY IN THE UNITED STATES

a) Background

In the United States, the regulation of OTC drugs is overseen by the FDA, which provides two main pathways for bringing these non-prescription medications to market: the drug application process and the Over-the-Counter Drug Monograph. Under the drug application process, a sponsor of a nonprescription drug submits a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) to FDA for approval.(3) Each pathway serves a distinct purpose and has specific requirements, allowing for a variety of products to reach consumers.

The NDA process is comprehensive, requiring sponsors to submit detailed information about a new drug, including its safety, efficacy, labeling, and manufacturing processes. This application is crucial for obtaining FDA approval before a drug can be marketed. Notably, an NDA can be submitted to market a new drug directly as an OTC product through a direct to over-the-counter (direct to OTC) approach, without first receiving approval as a prescription drug. Typically, many OTC drugs currently available were changed from prescription status through the prescription-to-over-the-counter (Rx-to-OTC) switch process. This transition is often based on a thorough evaluation of the drug's safety and efficacy data, as well as consumer understanding of the proposed labeling and indication through consumer studies.(3)

To secure FDA approval of an NDA for an OTC product, sponsors must submit a complete electronic

Common Technical Document (eCTD) dossier which typically includes extensive clinical trial data, safety data, chemistry, manufacturing and controls (CMC) data, possibly preclinical data, as well as data from consumer studies to demonstrate the consumer can safely and effectively use the product without the supervision of a healthcare professional.[3] The eCTD format standardizes the submission of quality, safety, and efficacy information across different regulatory regions, including the United States, Europe, and Japan. It consists of five modules: Module 1 covers administrative information; Module 2 provides drug summaries; Module 3 outlines drug quality information; Module 4 includes non-clinical study reports; and Module 5 contains clinical study reports. [4] This structured approach ensures that all necessary information is presented clearly and comprehensively, facilitating the review process. (See Figure 1)

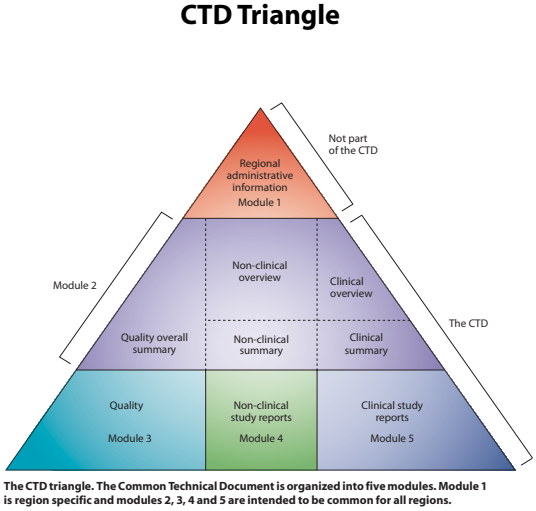


***Figure 1**: The CTD Triangle*[5]

In addition to the NDA process, the ANDA pathway is specifically designed for the approval of generic drugs. This pathway allows sponsors to leverage existing data on the safety and efficacy of a reference drug, expediting the approval process. Unlike NDAs, ANDAs generally do not require preclinical (animal) and clinical efficacy (human) data; instead, they focus on demonstrating bioequivalence to the original product, ensuring that the generic formulation performs similarly in terms of absorption and bioavailability.[6]

In contrast to the NDA and ANDA processes, the OTC Drug Monograph offers a more streamlined approach for bringing OTC drugs to the market. Under this system, products that comply with established OTC monographs do not require an approved application from the FDA.(1) An OTC drug monograph serves as a regulatory standard that outlines the conditions under which a drug is generally recognized as safe and effective (GRASE) for its intended use. If a product adheres to the standards outlined in the applicable OTC monograph and other applicable requirements as stipulated in Section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and complies with the labeling requirements specified in the Code of Federal Regulations (CFR) Title 21 Section 201.66, it can be marketed by submitting a drug listing containing the label and manufacturing information to the FDA.[7]

b) OTC Monograph in the United States

The OTC monograph system, established in 1972, serves as a key regulatory framework for the marketing of OTC drugs in the United States. The monograph functions as a "recipe book", outlining the conditions under which specific active ingredients can be marketed, including their dosage strengths, routes of administration, indications, warnings, directions for use, and testing requirements.[8]

The system underwent significant changes with the enactment of the Coronavirus Aid, Relief, and Economic Security (CARES) Act in March 2020. This legislation introduced Section 505G to the FD&C Act, modernizing the framework for regulating OTC monograph drugs.[7]

The monograph system categorizes OTC drugs into therapeutic classes, each assigned an OTC monograph number. Currently, there are 32 therapeutic classes, including M012 for Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drugs, and M013 for Internal Analgesic, Antipyretic, and Anti-rheumatic Drugs.[9] Each monograph specifies the allowed active ingredients, their permissible doses, intended use, and labeling requirements. For instance, the "Analgesic-Antipyretic Drug Products" section in M013 includes Acetaminophen, Aspirin, and others, detailing their labeling requirements (e.g., statement of identity, indication, warnings, and directions) and testing procedures (e.g., dissolution and drug release testing).[10]

Moreover, the monograph system enables OTC drug products to contain multiple active ingredients, in specific cases, from different therapeutic categories. For example, a product like Coltalin-DM, which is manufactured by Fortune Pharmacal Co., Ltd, contains four ingredients — Acetaminophen, Chlorpheniramine Maleate, Dextromethorphan HBr, and Phenylephrine HCl — across two therapeutic classes (M012 and M013).[11] The respective OTC monograph specifies whether certain ingredient combinations (within a therapeutic class or across different therapeutic classes) are permitted and under what conditions, such as dosage limits.[10,12]

Compliance with the final specifications of the OTC product, including the identity and strength of each active ingredient, is regulated by Good Manufacturing Practices (GMP). Generally, manufacturers are not required to provide ingredient assay and stability results, however the data must be generated, archived and available. Sponsors are responsible for ensuring that each batch meets the specifications before release, and this compliance is assessed during GMP inspections.[13]

OTC monographs are not static; they are updated through administrative orders. This flexibility allows the FDA to respond to new safety data, emerging scientific evidence, and changes in consumer needs effectively. This process, introduced by the CARES Act, replaces the previous lengthy rulemaking process, enabling the FDA to make timely updates to monographs and address urgent safety issues more efficiently.

c) From Three-Phase Public Rule Making to Administrative Order to Manage OTC Monograph

Before the enactment of the CARES Act in March 2020, OTC drug regulation in the United States relied on a cumbersome three-phase public rule-making process. This process aimed to evaluate the safety and effectiveness of OTC drug products marketed in the U.S. before May 11, 1972. The three phases included issuing an Advance Notice of Proposed Rulemaking followed by a public comment period, then release of a Tentative Final Monograph followed by a public comment period, and finally, the publication of a Final Monograph.[14]

While this process could ensure thorough evaluation and public involvement, it often resulted in significant

delays, with many monographs remaining unfinalized for decades. This hindered FDA's ability to quickly address emerging safety concerns and incorporate new scientific evidence into existing monographs, and posed challenges for manufacturers to innovate or introduce new formulations.[8]

To address the inefficiencies, the CARES Act reformed the OTC monograph system by replacing the traditional rule-making process with a more efficient Administrative Order process for issuing, revising, and amending OTC monographs. This change reduces the regulatory burden on both the FDA and industry, allowing for a more agile response to public health needs.[8]

Under the new process, both the FDA and industry stakeholders can initiate updates to OTC monographs by filing an OTC Monograph Order Request (OMOR). For FDA-initiated order, the Agency issues a proposed order for public comment, allowing a 45-day window for public comment. After the public comment period, the FDA can issue a final order to update the monograph, thereby expediting the regulatory process.[7]

Industry-initiated orders follow a similar procedure, but they require the submission of an OMOR for FDA review before a proposed order is issued for public comment. This dual approach ensures that both the FDA and industry can actively participate in the regulatory process, fostering collaboration and innovation.[7]

The CARES Act established two types of OMORs: Tier 1 and Tier 2. Tier 2 OMORs address minor changes to existing monographs, such as reordering information in the drug facts label and changing ingredient nomenclature. In contrast, Tier 1 OMORs encompass requests that involve significant changes which are not determined to be Tier 2 OMOR, such as adding new active ingredients or new indications for use.[1]

The introduction of the Administrative Order process has significantly improved the management of OTC monographs, allowing more timely updates and adaptations to the regulatory framework.

d) OTC Drug Package Labeling Requirements in the United States

The labeling of OTC drugs in the United States is regulated by 21 CFR 201.66. It ensures that product labels are clear and easy to understand by providing essential information in a standardized format. This allow consumers to make informed healthcare decisions and enhance the safe and effective use of medications.[15]

A key component is the Drug Facts Label, which is included on the outer retail package. It summarizes important drug information in a concise and organized manner. The label must include specific headings and content, starting with the title "Drug Facts" in a font size no smaller than 8-point type in standard format.[15]

The Drug Facts label includes several essential sections. The "**Active Ingredients**" section lists the active components and their quantities, helping consumers understand the pharmacological agents they are using. Following this, the "**Purpose**" section outlines the general pharmacological categories of the product, providing context for its intended use. The "**Uses**" section specifies the intended indications, helping consumers identify whether the medication is appropriate for their symptoms.[15]

Important safety information is also included. The "**Warnings**" section alerts consumers to potential product risks, such as contraindications and side effects, enhancing safe use of the medication. The "**Directions**" section provides clear instructions on usage, including recommended dosages and administration routes, ensuring appropriate use of the product without professional oversight. The "**Inactive Ingredients**" section lists out inactive ingredients, promoting transparency for those with allergies or sensitivities and thereby facilitating safe usage.[15] (See Figure 2)

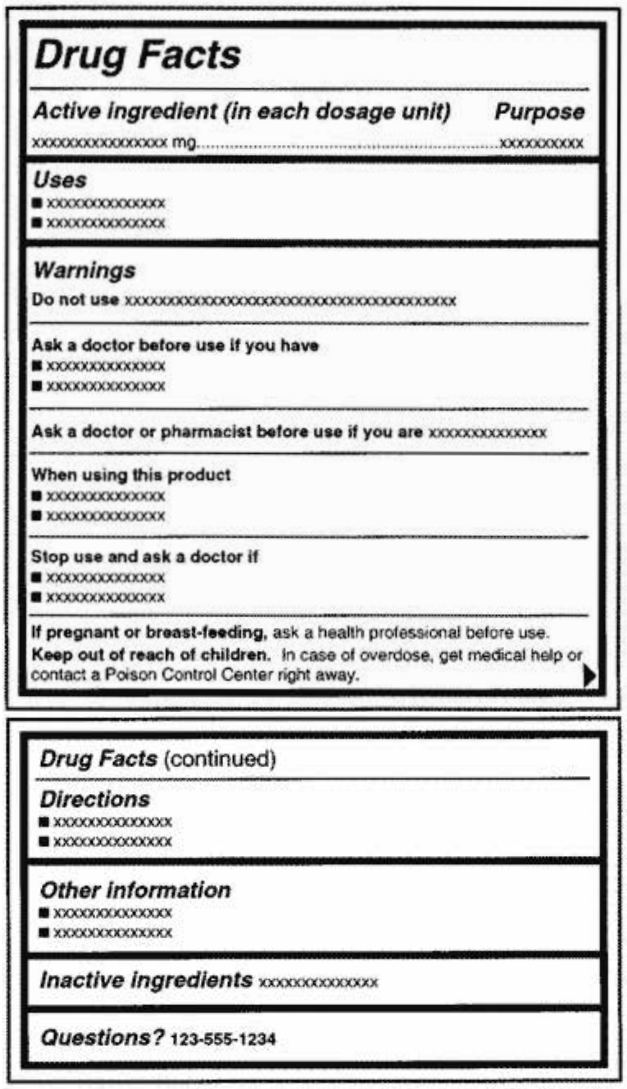


***Figure 2**: Drug Facts Label Outline in the United States*[16]

The FDA emphasizes standardized labeling through detailed requirements for font size, format, and the sequence of information presented on the Drug Facts label. Such standardization creates a uniform format across all OTC drug products, making it easier for consumers to compare similar medications and make informed choices.[17] It is particularly beneficial for populations with lower health literacy, such as older adults and individuals with limited English proficiency.[18]

The Drug Facts label is not merely a regulatory requirement; it significantly enhances consumer understanding and compliance. Research has indicated that the standardized format outperforms previous labeling systems in readability and consumer preference. Studies have also demonstrated that consumers can acquire information more quickly and accurately with the Drug

Facts label, ultimately leading to safer and more effective use of OTC medications.[18]

EXPEDITED OTC DRUG REGISTRATION PATHWAY IN CANADA

a) Background

The regulation of OTC drugs in Canada is overseen by Health Canada, the country's health authority. The requirements for OTC drug registration in Canada share similarities with those established by the U.S. FDA. Manufacturers in Canada can utilize several pathways to bring their products to market, including the New Drug Submission (NDS) for new chemical entities and the Abbreviated New Drug Submission (ANDS) through the Health Products and Food Branch (HPFB).[19]

In addition to these standard pathways, Health Canada has implemented an Expedited Review process for OTC Drug Identification Number (DIN) applications, managed by the Natural and Non-Prescription Health Products Directorate (NNHPD).[19] Similar to the U.S. system, OTC drug products seeking approval through this expedited review must comply with established monographs, referred to as "Labeling Standards", along with specific labeling requirements.[20,21]

A key distinction between the Canadian and U.S. expedited OTC registration pathways is the requirement for pre-market review and approval by Health Canada. While the expedited review in Canada requires this pre-approval, it still significantly reduces the timeline compared to the standard NDS and ANDS pathways.[22] Industry experience shows that the expedited drug registration process requires only the submission of the product label and master formula, facilitating very short approval timelines and quick market access. Approval timeline can be as short as two months for single-ingredient products and up to six months for products containing two active ingredients.

This expedited pathway in Canada aims to ensure the safety and efficacy of OTC drugs while providing timely access for consumers. By leveraging the NNHPD's review process and the established monograph system, Health Canada facilitates efficient introduction of OTC drugs into the market without compromising safety standards.

b) Monograph / Labeling Standard and Labeling Requirements

In Canada, the monograph or labeling standard serves as a scientific benchmark that contains essential information about a specific ingredient, product, or class of products. This information includes the ingredient properties, its acceptable uses, recommended dosages, duration of use, and associated risks. The establishment of these monographs allows the expedited review process for OTC drug products, as the NNHPD has already pre-cleared the safety, efficacy, and quality information of medicinal ingredients included in the monographs.[22] This pre-clearance is vital for facilitating quicker access to OTC products while maintaining consumer safety.

Health Canada has developed monographs for various common OTC drugs, with 33 labeling standards currently in place. These standards cover widely used medications, including acetaminophen, cough and cold remedies, and anti-flatulent products.[20]

The monograph system functions like a recipe book, allowing OTC drug products to contain multiple active ingredients from different monographs. For example, Coltalin Cold & Allergy Tablets (DIN: 02244263), contains three active ingredients: Acetaminophen, Chlorpheniramine Maleate, and Phenylephrine HCl.[23] These ingredients fall under two different labeling standards: the "Acetaminophen Labelling Standard"[24] and the "Nonprescription Oral Pediatric Cough and Cold Labelling Standard"[25]. Each monograph provides guidelines on permissible ingredient combinations and any conditions that must be met, such as dosage limits.

Manufacturers seeking to market new OTC products that do not conform to existing monographs can submit evidence to the NNHPD to demonstrate the safety, efficacy, and quality of their product under proposed conditions. This is particularly relevant for new drugs or active ingredients that are not yet included in the established labeling standards.[20] The ability to submit such evidence fosters innovation while maintaining the regulatory oversight to protect public health.

Similar to the U.S. FDA, compliance with OTC product specifications is regulated by GMP and verified through inspections.[26]

Health Canada shares a similar approach to labeling requirements as the U.S. FDA, emphasizing the importance of a standardized format (i.e. the Drug Facts Table) to enhance consumer understanding. Health Canada has issued guidance documents, such as the "Guidance Document: Drug Facts Table for Non-Prescription Drugs"[27] and the "Labeling Requirements for Non-Prescription Drugs Guidance Document"[21]. These documents outline the necessary labeling requirements, including label design, format, font size, and font style, ensuring that the information presented is clear and accessible to consumers. (See Figure 3)

Drug Facts

Active ingredient (in each tablet) **Purpose**
Ingredient A xxx mg……Xxxxxxxxxxxx

Uses
Relief of •xxxxxxxxx •xxxxxxx •xxxxxxxxxx

Warnings
Allergy alert May cause a severe allergic reaction.

Do not use if •xxxxxx •xxxxxx •xxxxxxxxxxxxxxxx •xxxxxxxxxx

Ask a doctor or pharmacist before use if you •have •xxxxxx xxxxx •xxxxxx •take •xxxxxx •xxxxxx •xxxxxx •are pregnant or breastfeeding

When using this product do not drive a motor vehicle or operate machinery. This product may cause drowsiness or excitability.

Stop use and ask a doctor if •xxxxxx •xxxxxxxxxxxxxxxxxxx •xxxxxxxxx •xxxxxxxx xxxxxxx •xxxxxxxxxxxxxxxxxxxxxxx •xxxxxxx xxxx

Keep out of the reach of children. In case of an overdose, call a poison control centre or get medical help right away. ▼

Drug Facts (continued)

Directions
Do not chew tablets.

Children under 6 years		Ask a doctor
Children 6-12 years	x tablet(s) every y hours as needed	Do not take more than Z tablets in 24 hours
Children over 12 years, and adults	X tablets every Y hours as needed	Do not take more than Z tablets in 24 hours

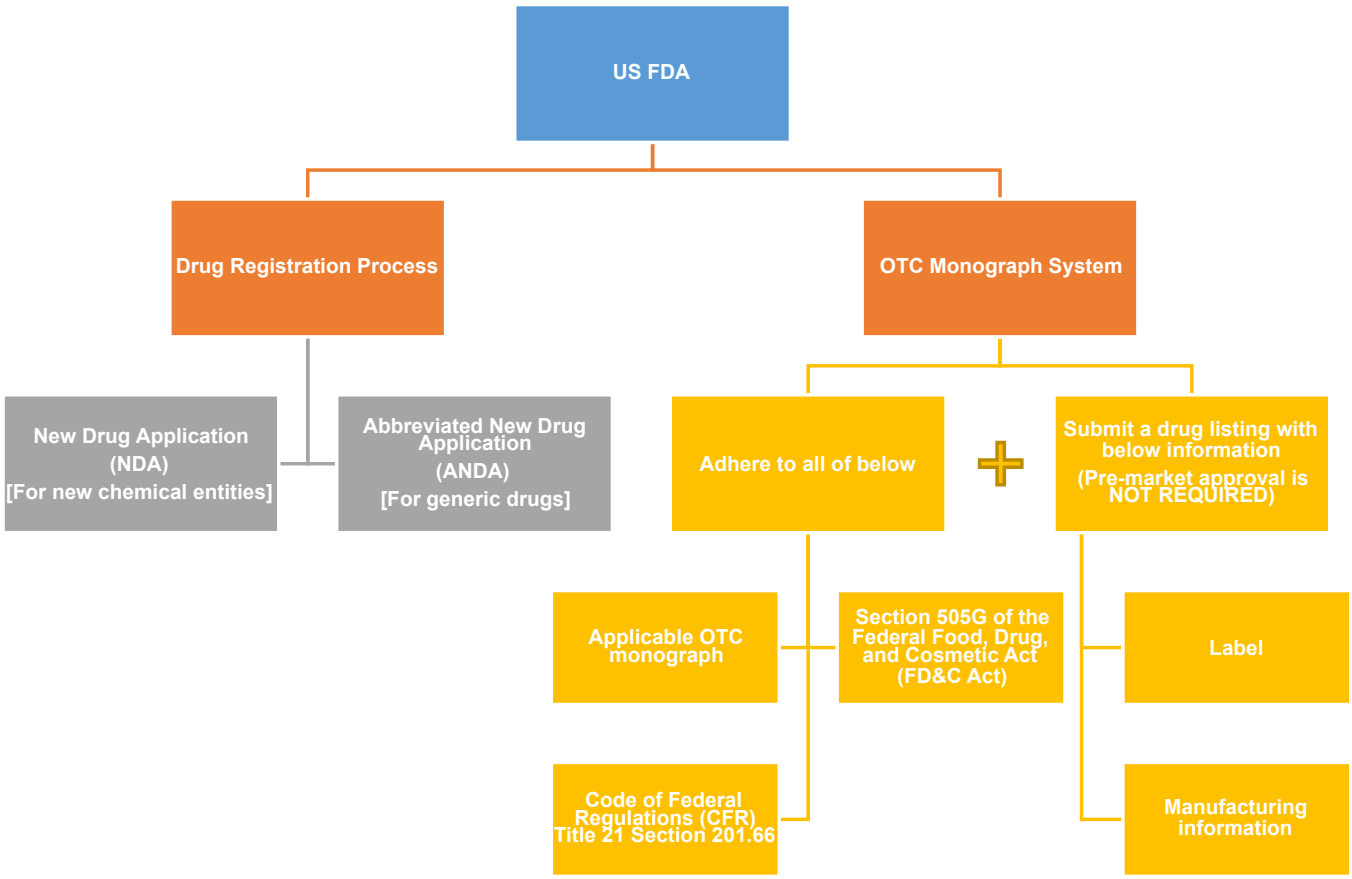
Other information
Store at room temperature (15-30° C).

Inactive ingredients
List of NMIs List of NMIs List of NMIs NMIs List of NMIs

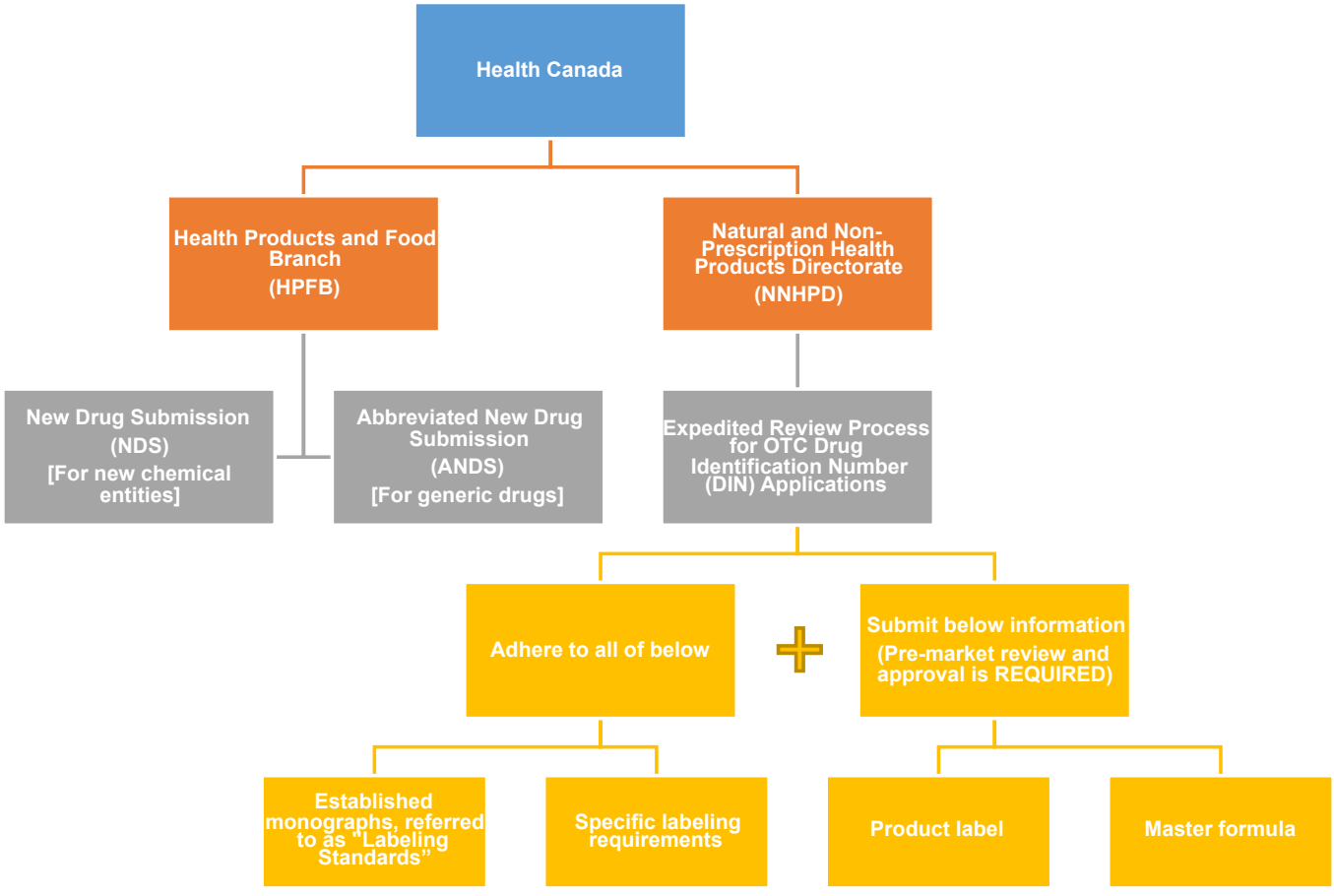
Questions? Call 1-8XX-XXX-XXXX

***Figure 3**: Drug Facts Label Outline in Canada*[28]

SUMMARY



Drug Registration Pathway in the US



Drug Registration Pathway in Canada

POTENTIAL BENEFITS AND DRAWBACKS OF EXPIDITED OTC REGISTRATION PATHWAY

The expedited OTC registration pathway offers several potential benefits that can significantly enhance the pharmaceutical landscape. One primary advantage is increased regulatory efficiency; by streamlining the approval process for OTC products, regulatory agencies can allocate more resources to review applications for new chemical entities, generic prescription drugs, and biosimilar products. This efficiency can lead to faster market access for a broader range of medications.

Economic benefits for drug manufacturers are also notable, as the shortened approval process can reduce research and development costs associated with bringing OTC products to market. This financial relief can encourage companies to invest more in innovation, leading to the development of new formulations or combinations of established ingredients. Furthermore, enhanced public health outcomes can result from increased market access, potentially leading to more competitive pricing for consumers. Standardized labeling can also facilitate better understanding of OTC products, empowering individuals to make informed choices about self-care.

However, the expedited pathway is not without drawbacks. There are potential quality and safety concerns, particularly with increased access to OTC products. Inadequate regulatory oversight, particularly in post-marketing surveillance and manufacturing inspections, raises the possibility of substandard products entering the market, which may compromise consumer safety and undermine public trust in OTC medications. Furthermore, the significant increase in product options may confuse consumers, making it challenging for them to identify the most suitable medications for their needs. This confusion can undermine the intended benefits of increased access and self-care, highlighting the need for effective education and clear labeling to guide consumers in their decisions.

IMPLEMENTATION CONSIDERATION IN HONG KONG

Implementing an expedited OTC registration pathway in Hong Kong necessitates several key considerations to ensure its effectiveness and alignment with local needs. First and foremost, the existing regulatory framework must be adapted to accommodate the new pathway. This includes modifying current drug registration regulations and potentially enacting legislative changes to establish the necessary legal basis for expedited processes. These adaptations should harmonize with international standards while remaining relevant to Hong Kong's unique market context.

The development and regular evaluation of comprehensive OTC monographs and standards are essential. These monographs should cover various OTC drug categories and be updated with the latest scientific evidence. Striking a balance between specificity and flexibility in monograph requirements is vital to ensure that they are robust and adaptable to new information.

Post-market surveillance systems must also be established to monitor the safety and efficacy of products approved through the expedited pathway. This involves ensuring timely identification and response to adverse events while balancing the need for expedited access to OTC drugs.

Industry readiness is another critical factor. Pharmaceutical companies must be educated about the new pathway to facilitate a smooth transition. Addressing potential resistance from companies accustomed to existing processes is important to ensure equitable access for both local and international manufacturers.

Public education and awareness campaigns will be necessary to inform consumers about changes in OTC drug availability and labeling. This includes addressing misconceptions about the safety of expedited approval products and promoting responsible self-medication practices.

Finally, cultural and language considerations must be taken into account. Labeling requirements should accommodate multiple languages, particularly Chinese and English, to ensure clear communication of drug information across Hong Kong's diverse population. Managing potential market disruptions during the transition and ensuring the continued availability of essential OTC medications is also crucial for maintaining a stable market environment.

ROLES OF PHARMACIST

Pharmacists play a pivotal role in implementing an expedited OTC registration pathway. Their expertise is invaluable in developing and refining OTC monographs and standards. By tailoring international standards to the local context, pharmacists ensure that regulations remain relevant and effective. Additionally, their participation in advisory committees enhances the regulatory development process by incorporating valuable clinical insights.

In developing and updating OTC monographs and standards, pharmacists can contribute their clinical expertise to create comprehensive documents that reflect real-world usage patterns and address patient concerns. They are instrumental in ensuring that the information remains current and scientifically sound, adapting it based on emerging evidence.

Pharmacists can also enhance post-market surveillance by actively monitoring and reporting adverse events related to OTC drugs marketed through the expedited pathway. Their feedback to regulatory bodies on real-world efficacy and safety is vital for maintaining consumer safety. Additionally, their participation in pharmacovigilance networks contributes to a broader understanding of drug safety.

In terms of industry education, pharmacists can act as liaisons between regulatory bodies and pharmaceutical companies, ensuring compliance with the new pathway requirements. They can also assist in developing multilingual labeling and patient information to address cultural and language considerations. Through public education campaigns, pharmacists can raise awareness of responsible self-medication practices and the proper use of OTC drugs, ultimately promoting safer health outcomes in the community. Furthermore, they can provide insights into OTC drug market dynamics, monitoring the availability and pricing of essential medications to mitigate economic impacts.

CONCLUSION

The expedited OTC drug registration pathway represents a significant advancement in the regulation of OTC medications, drawing valuable lessons from the models established in the United States and Canada. Both countries have implemented effective systems that utilize monographs and standards, comprehensive labeling requirements, and streamlined review processes to ensure the safety and efficacy of OTC products while facilitating quicker market access.

For Hong Kong, adopting a similar expedited pathway could increase regulatory efficiency, yield economic benefits for drug manufacturers, enhance public health through improved access to safe OTC medications, and promote innovation in drug formulations.

However, potential drawbacks must be carefully considered. There are risks related to quality and safety, particularly concerning the increased access to OTC products, which could lead to confusion among consumers. Addressing these concerns will require a robust regulatory framework, including the development and regular evaluation of OTC monographs and effective post-market surveillance systems.

Pharmacists will play a crucial role in this transition, leveraging their expertise to address key challenges, educate the public, and ensure compliance within the industry. Their involvement will be essential in fostering awareness and understanding of the new pathway among both healthcare professionals and consumers.

To successfully implement this expedited OTC registration pathway, it is vital to encourage stakeholder engagement and emphasize the importance of continued dialogue and collaboration among regulators, industry representatives, and healthcare providers. By working together, Hong Kong can create a regulatory environment that enhances public health while promoting safe and effective use of OTC medications.

Author's background

LAU, Kristy Sin Tung *is currently the Quality Assurance Pharmacist at Fortune Pharmacal Co. Ltd in Hong Kong. Her email address is kristy.lau@fortunepharm.com*

CHAN, Philip Pan *is currently the Quality Assurance Manager at Fortune Pharmacal Co. Ltd in Hong Kong. His email address is philip.chan.pan@fortunepharm.com*

References

1. U.S. Food and Drug Administration. Small Business Assistance: Frequently Asked Questions on the Regulatory Process of Over-the-Counter (OTC) Drugs [Internet]. 2022 [cited 2024 Sept 4]. Available from: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-regulatory-process-over-counter-otc-drugs
2. Pharmacy and Poisons Board of Hong Kong. Guidance Notes on Registration of Pharmaceutical Products/Substances [Internet]. 2022 [cited 2024 Sept 4]. Available from: https://www.ppbhk.org.hk/eng/files/Guidance_on_Reg_of_Pharm_Prod_Sub_en.pdf
3. U.S. Food and Drug Administration. Drug Application Process for Nonprescription Drugs: New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) [Internet]. 2022 [cited 2024 Sept 5]. Available from: https://www.fda.gov/drugs/types-applications/drug-application-process-nonprescription-drugs
4. U.S. Food and Drug Administration. CTD Triangle [Internet]. [cited 2024 Sept 5]. Available from: https://www.accessdata.fda.gov/cder/eCTD/backgr/backgr/fd_02_01_0030.htm
5. ICH. CTD Triangle [Internet]. 2021 [cited 2024 Sept 4]. Available from: https://admin.ich.org/sites/default/files/2019-05/CTD_triangle.pdf
6. U.S. Food and Drug Administration. Abbreviated New Drug Application (ANDA) [Internet]. 2022 [cited 2024 Sept 5]. Available from: https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda
7. U.S. Food and Drug Administration. OTC Drug Review Process | OTC Drug Monographs [Internet]. 2023 [cited 2024 Sept 5]. Available from: https://www.fda.gov/drugs/otc-drug-review-process-otc-drug-monographs
8. Michele TM. An Exciting New Chapter in OTC Drug History: OTC Monograph Reform in the CARES Act [Internet]. FDA; 2020 [cited 2024 Sept 5]. Available from: https://www.fda.gov/news-events/fda-voices/exciting-new-chapter-otc-drug-history-otc-monograph-reform-cares-act
9. U.S. Food and Drug Administration. Search OTC Monographs [Internet]. [cited 2024 Sept 5]. Available from: https://dps.fda.gov/omuf/monographsearch
10. U.S. Food and Drug Administration. OTC Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use [Internet]. 2022 [cited 2024 Sept 5]. Available from: https://dps.fda.gov/omuf/monographsearch/monograph_m013
11. National Institutes of Health. DailyMed - COLTALIN-DM- acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide, phenylephrine hydrochloride tablet [Internet]. 2024 [cited 2024 Sept 5]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8b1138f2-aad0-43ef-80d4-e36f92fe5e93&audience=professional
12. U.S. Food and Drug Administration. OTC Monograph M012: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use [Internet]. 2022 [cited 2024 Sept 5]. Available from: https://dps.fda.gov/omuf/monographsearch/monograph_m012
13. U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21 Section 211.165 [Internet]. 2024 [cited 2024 Sept 5]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.165
14. Consumer Product Testing Company. Understanding the Over-The-Counter (OTC) Drug Monograph System [Internet]. [cited 2024 Sept 5]. Available from: https://cptclabs.com/understanding-the-over-the-counter-otc-drug-monograph-system/
15. U.S. Food and Drug Administration. Guidance for Industry Labeling OTC Human Drug Products [Internet]. 2009 [cited 2024 Sept 5]. Available from: https://www.fda.gov/media/76481/download
16. U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21 Section 201.66 [Internet]. 2024 [cited 2024 Sept 13]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.66
17. U.S. Food and Drug Administration. OTC Drug Facts Label [Internet]. 2015 [cited 2024 Sept 6]. Available from: https://www.fda.gov/drugs/information-consumers-and-patients-drugs/otc-drug-facts-label
18. Catlin JR, Brass EP. The Effectiveness of Nonprescription Drug Labels in the United States: Insights from Recent Research and Opportunities for the Future. Pharmacy. 2018 Oct 26;6(4):119. doi:10.3390/pharmacy6040119
19. Government of Canada. Guidance Document: The Management of Drug Submissions and Applications [Internet]. 2022 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry/document.html
20. Government of Canada. Nonprescription Drugs: Labelling Standards - Drug Product [Internet]. 2016 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/nonprescription-drugs-labelling-standards.html
21. Government of Canada. Labelling requirements for non-prescription drugs guidance document [Internet]. 2022 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription/legislation-guidelines/guidance-documents/labelling-requirements-non-prescription-drugs.html#a2
22. Government of Canada. How Drugs are Reviewed in Canada [Internet]. 2015 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html
23. Government of Canada. Product Information: Coltalin Cold & Allergy Tablets [Internet]. 2024 [cited 2024 Sept 6]. Available from: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition
24. Government of Canada. Revised Guidance Document: Acetaminophen Labelling Standard [Internet]. 2016 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/revised-guidance-document-acetaminophen-labelling-standard.html
25. Government of Canada. Guidance Document: Nonprescription Oral Paediatric Cough and Cold Labelling Standard [Internet]. 2009 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/nonprescription-drugs-labelling-standards/nonprescription-oral-paediatric-cough-cold-labelling-standard.html
26. Government of Canada. Good manufacturing practices guide for drug products (GUI-0001) [Internet]. 2020 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001/document.html
27. Government of Canada. Guidance Document: Drug Facts Table for Non-prescription Drugs [Internet]. 2017 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/natural-health-products/guidance-document-drug-facts-table-non-prescription-drugs.html#a1
28. Government of Canada. Non-prescription drug labels [Internet]. 2018 [cited 2024 Sept 6]. Available from: https://www.canada.ca/en/health-canada/topics/buying-using-drug-health-products-safely/non-prescription-drug-labels.html

Review of Current CAR-T Therapy for Relapsed/Refractory Diffuse Large B-Cell Lymphoma in Adults: Tisagenlecleucel (Kymriah®) and Axicabtagene Ciloleucel (Yescarta®)

YUEN Sheung Shing[a]; CHENG Wing Yan[a]; KWOK Wai Shing[a]; LAM Chun Kwan[a]; WONG Yin Chun[a]; YICK Chau Ho[a]; TAI Bik Wai Bilvick[a]*

*[a] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China (*Corresponding author)*

ABSTRACT

Chimeric antigen receptor T-cells (CAR-T) therapy is an advanced therapy product which involves the modification and reprogramming of T cells to generate new fusion protein for combating cancer cells. CAR-T therapy is a recognised immunotherapy for treating relapsed/ refractory large B-cell lymphoma, in combination with conditioning chemotherapy and leukapheresis. Two of the early established CAR-T products, tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), were approved by the U.S. Food and Drug Administration for such lymphoma. The pivotal JULIET trial of tisagenlecleucel, had demonstrated a high response rate in patients and high tendency of reaching relapse-free. Common adverse reactions identified including cytokine release syndrome (CRS), neurotoxicity, and abnormal blood count. Two landmark trials, ZUMA-1 and ZUMA-7, had shown that axicabtagene ciloleucel might prolong the survival of patients with presenting adverse reactions of CRS and neurologic toxicity. More studies have been conducted to examine the efficacy and expanding roles of axicabtagene ciloleucel. Currently, only tisagenlecleucel is registered in Hong Kong since March 2020. In view of these findings and the increasing recognition and utilization of the two CAR-T therapy products, this review highlights the mechanism of action as well as efficacy and safety profile of tisagenlecleucel and axicabtagene ciloleucel. The newer data on efficacy contributing to their expanded indications, different monitoring parameters and management of adverse reactions are discussed. The comparative analysis of both CAR-T products and potential role of axicabtagene ciloleucel in Hong Kong are addressed in the context of this review.

Keywords: *Relapsed/ Refractory Large B-Cell Lymphoma, CAR-T Therapy, Tisagenlecleucel, Axicabtagene ciloleucel, Kymriah®, Yescarta®*

INTRODUCTION

Disease Background - Refractory/Relapsed Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a cancer type that affects the lymphatic system, specifically the B lymphocytes. The uncontrolled growth of abnormal B cells in patients causes formation of solid tumors in various parts of the body. DLBCL, of note, is the most common type of non-Hodgkin lymphoma (NHL), accounting for approximately 25% to 30% of NHL worldwide[1].

The etiology of DLBCL remains largely unknown[2]. However, certain risk factors have been identified, including increased age and weakened immune system [3]. Genetic factors and certain chromosomal abnormalities, including translocation and mutations, have also been associated with an increased risk of developing DLBCL[4]. Conventional chemotherapy, the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), can be given as the initial treatment[1]. However, approximately 40% of DLBCL patients experience disease relapse or are refractory to first-line chemoimmunotherapy, which indicates the failure of first-line chemotherapy causing refractory or relapsed DLBCL (R/R DLBCL)[5].

Introduction of CAR-T Therapy

Chimeric antigen receptor T-cells (CAR-T) therapy is an immunotherapy used to treat different NHL disorders. In R/R DLBCL, the process starts by collecting T-cells from peripheral blood cells from individual patients[6]. Since the cancer cells may disguise themselves as healthy cells, autologous T cells may not be capable of eradicating the cancer cells, hence require modification. After harvesting the patient's own T cells, the genetic information is modified to express a chimeric antigen receptor on their cell surface. The modified T cells will be readministered back to the patient, which allows for the more effective recognition of cancer cells (B cells) and targeting specific antigens present on them resulting in cancer cell death[6].

The first CAR-T therapy launched was tisagenlecleucel (tisa-cel), which was approved by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of refractory/ relapsed B cell precursor acute lymphoblastic leukemia (R/R BCP-ALL) in pediatric and young adult[7]. Since then, CAR-T therapies have been developed and approved for other cancers, including DLBCL and follicular lymphoma[7,8]. Eligibility for CAR-T therapy depends on various factors, including type and stage of cancer, previous treatments, and individual health status[9]. However, CAR-T therapy is considered for patients

who have not responded to standard treatments or have relapsed after previous therapies[9]. CAR-T therapy is still new and complex. Ongoing research and clinical trials are carrying on to improve and assess its effectiveness and safety, with the aim to expand its use to other types of cancer.

CAR-T Therapy Options for R/R DLBCL

Tisa-cel and axicabtagene ciloleucel (axi-cel) are CAR-T therapies that obtained approvals for the indication of R/R DLBCL[8]. Clinical trials have demonstrated remarkable response rates and remissions in adult patients with R/R DLBCL. Despite demonstrating impressive efficacy, the use of CAR-T therapy also exhibits drawbacks. Cytokine release syndrome (CRS) and neurologic toxicities are its significant adverse events, so patients require management and monitoring closely [10]. Additionally, the high cost and complexity of CAR-T therapy lead to barriers to widespread use[11].

TISAGENLECLEUCEL (KYMRIAH®)

Mechanism of Action in R/R DLBCL

Pharmacologically, tisa-cel involves a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR) and hence reprogram patient's T cells[12]. A CAR is made from a single-chain antibody fragment (scFv) which targets the CD19 of the B cells. The scFv is connected by a linker with a CD8α hinge, which is to stabilize CAR expression, and a transmembrane domain, which is for transduction of ligand recognition signals [12,13,14]. After readministering the modified T cells into the patient's bloodstream, modified T cells recognize CD19-expressing target cells, and the intracellular domains then activate the downstream signaling cascades that result in T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines that kill cancer cells[15].

EFFICACY OF TISAGENLECLEUCEL

Pivotal Study for Tisagenlecleucel

In July 2015, the pivotal study JULIET (ClinicalTrials.gov Identifier: NCT02445248) was initiated to evaluate the efficacy and safety of tisa-cel in patients with R/R DLBCL[16]. It is a phase two, single-arm, multicenter, international study that enrolled 165 patients. Patients recruited in the study were at least 18 years of age and had priorly received at least two lines of therapy containing rituximab and anthracycline; and were ineligible for, or relapse after, receiving autologous transplantation. The exclusion criteria included having received CD-19-directed therapy or allogeneic transplant before, or active central nervous system (CNS) involvement in DLBCL and primary mediastinal DLBCL. Among the enrolled patients, 93 of them received the infusion and were evaluated for efficacy. The primary endpoint for the study was the overall response rate (ORR) using Lugano classification. The various efficacy-associated secondary endpoints included response duration, time to response, safety, cellular kinetics data, and overall survival (OS).

A propitious result was identified in the study[16]: a best ORR of 52% was seen (95% CI, 41 – 62) in which 40% of the patients achieved complete response (CR) and 12% of them achieved partial response. Although the median duration of response was not established in the study, the estimated relapse-free probability at different time frames was developed. It was estimated that at 12 months, 63.4% of patients were likely to be relapse-free. The OS was measured in the study as well[17]: the percentages of survival at 12, 36, and 60 months were 48.2%, 36.6%, and 31.7% respectively; and the median month of survival was reported to be 11.1 (95% CI, 6.6 - 23.9). In view of the efficacy profile derived from the JULIET study, the FDA approved the use of tisa-cel in adult patients with large B-cell lymphoma, with requirements similar to those stated in the study (e.g. adult patients who received at least two lines of therapy previously)[18].

Newer Efficacy Data in Treating R/R DLBCL

A newer BELINDA (ClinicalTrials.gov Identifier: NCT03570892) trial started in 2019 also aimed at studying the efficacy of tisa-cel among patients with DLBCL, as well as those with other diseases subtypes such as high grade B-cell lymphoma and primary mediastinal B-cell lymphoma[19]. The patient demographics showed over 60% of enrolled patients were diagnosed with DLBCL, reflecting it was the most common type of aggressive B-cell lymphoma in the study, and the trial results can provide valuable insights on the efficacy evaluation of tisa-cel in this review.

The BELINDA trial was a phase three, double arm, randomized, open label, multicenter trial which compared the efficacy of tisa-cel with standard care. The standard care group received platinum-based chemotherapy followed by conditioning chemotherapy with autologous hematopoietic stem cell transplantation (HSCT) depending on the response.

The study result did not indicate that tisa-cel has superiority in reference to the standard care group. The hazard ratio for any event or death for tisa-cel group compared to standard care was found to be 1.07 (95% CI, 0.82 – 1.40, P = 0.61). The median event-free survival (EFS) was 3 months in both treatment arms. The response at week 6 among the tisa-cel patients was 38.3% compared to 53.8% in standard care patients. Finally, progressive disease was seen in 25.9% of patients from the tisa-cel group compared to 13.8% in the standard care group. Based on these results, the BELINDA trial did not demonstrate superiority of utilizing tisa-cel as a replacement for the standard chemotherapy and autologous HSCT.

Evaluation

The abovementioned studies showed mixed results about the therapeutic efficacy of tisa-cel in R/R DLBCL. It is noted that the number of studies evaluating the efficacy of tisa-cel compared with standard care is scarce, and the superiority of tisa-cel over standard care cannot yet be determined. Therefore, additional studies are warranted to address this issue seen in the existing trials.

The differences in setting or protocol between trials can also inadvertently affect the outcome measure in the studies. In the JULIET trial, 92% of the patients received a combination of chemotherapy like rituximab, gemcitabine, and etoposide before infusion, while 82.7% of patients in the BELINDA trial received platinum-based systemic bridging therapy. More patients received bridging therapy in JULIET, and the medication regimens used in the two trials were also

not consistent. The use of bridging therapy before tisa-cel infusion may impose an effect on the study outcome, and this is a particular problem when there is no clear description about the amount of bridging therapy used in the trials. Additionally, the JULIET trial excluded the patients with primary mediastinal large B-cell lymphoma (a subtype of DLBCL) while they are included in the BELINDA trial. Thus, there is a possibility that the JULIET trial overestimated the efficacy of tisa-cel.

Ongoing studies include a prospective cohort study assessing the effectiveness of tisa-cel in Brazilian patients with B-cell malignancy (ClinicalTrials.gov Identifier: NCT05541341) and a Novartis-sponsored single arm interventional trial (ClinicalTrials.gov Identifier: NCT04094311). A more comprehensive clinical benefit profile of tisa-cel can be obtained after these studies are completed.

SAFETY OF TISAGENLECLEUCEL

Adverse Events

The adverse events of tisa-cel are summarized with data from the JULIET study, PR(AG)404/2020 study (a retrospective study with data collected from 10 Spanish institutions), and a match comparison study (an analysis of a retrospective French registry study comparing tisa-cel and axi-cel in matched populations) **(Table 1)**[16,20,21]. Other common adverse events associated with tisa-cel in the JULIET study are also shown **(Table 2)**. Cautions should be exercised when interpreting the adverse event rates as varied clinical criteria were used for reporting adverse event across the three studies, and the summarized rates in this review is only intended to provide a general picture of the incidence of these adverse events.

Table 1: Rates of adverse events in patients receiving tisa-cel therapy

Adverse Events	JULIET study[a] (N=111) (%)	PR(AG)404/2020 study[b] (N=75) (%)	Matched comparison study[c,d] (N=209) (%)
Cytokine release syndrome (CRS)	58	71	75.6
Neurological toxicity[e]	21	15	22
Infection	34	28	N/A
Cytopenia	44	N/A	39.2
Anemia	48	N/A	27.8
Neutropenia	20	N/A	27.3
Thrombocytopenia	13	N/A	29.7

N/A: not available / not reported
[a] Medical Dictionary for Regulatory Activities (version 20.1) and Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) were used for reporting adverse events
[b] CRS and neurotological toxicity were reported using American Society for Transplantation and Cellular Therapy (ASTCT) criteria or Lee criteria
[c] Hematologic toxicity in the matched comparison study was reported according to CTCAE (version 5.0)
[d] Only adverse events >20% are shown
[e] Neurological toxicity refers to "neurologic events" in JULIET and "immune effector cell-associated neurotoxicity syndrome (ICANS)" in PR(AG)404/2020 and the matched comparison study

Table 2: Other common adverse events of tisa-cel in JULIET

Adverse Events[a]	Incidence Rate (%)[b]
Pyrexia	35
Diarrhea	32
Nausea	29
Hypotension	26
Fatigue	25
Headache	23
Hypokalemia	23

[a] Medical Dictionary for Regulatory Activities (version 20.1) and Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) were used for reporting adverse events
[b] Only adverse events with incidence rate >20% are shown

In all three studies, CRS had the highest occurrence. CRS is a common adverse event reported in CAR-T therapy, as activated CAR-T cells release cytokines, followed by subsequent activation of endogenous immune cells, namely monocytes and macrophages, resulting in further release of cytokines[22]. Due to the high occurrence of CRS, a specific treatment algorithm is required. Moreover, it is noted that the incidence of CRS of any grade in a real-life setting is even higher than that recorded in the pivotal trial, so it is deemed important to counsel patients on the possible CRS signs and symptoms such as fever, hypoxia, and hypotension, and to briefly address the management approach[22].

A type of neurological toxicity known as immune effector cell-associated neurotoxicity syndrome (ICANS) is another significant adverse event observed in CAR-T therapy patients. ICANS is closely related to and results from CRS: increased cytokine level in the systemic system indirectly causes blood-brain-barrier disruption, allowing myeloid cell infiltration into the brain parenchyma and triggering CNS immune response together with resident microglia[23]. Therefore, the key to managing ICANS is resolving CRS.

Abnormal blood cell count and infectious complications were also frequently observed in the three studies. The mechanism of blood cell abnormality is still poorly understood based on current state of knowledge. Infections in patients are caused by their immunosuppression and cytopenia status[24], and fatal infection had occurred with the use of tisa-cel in R/R DLBCL patient.

For adverse events of higher severity, CRS, ICANS, hematotoxicities, and infections were the ones with higher occurrence **(Table 3)**. It is noteworthy that adverse events of grade ≥ 3 were generally lower in real-world studies compared to the pivotal trial, especially for CRS and ICANS. The possible reasons include earlier and more extensive use of tocilizumab (an interleukin-6 receptor antagonist) and corticosteroids, the standard medications for CRS management, along with more clinical experience in CAR-T therapy patient management[21].

Table 3: Rates of Adverse Events ≥ Grade 3 in patients receiving tisa-cel

Adverse Events ≥ Grade 3	JULIET (N=111) (%)	PR(AG)404/2020 (N=75) (%)	Matched comparison study (N=209) (%)
Cytokine release syndrome (CRS)[a]	22	5	9.1
Neurological toxicity[b]	12	1	2.9
Cytopenia[c]	32	N/A	12.4
Neutropenia[c]	15	N/A	12.4
Thrombocytopenia[c]	12	N/A	9.1
Infection	20	N/A	N/A

N/A: not available / not graded / not reported
[a] CRS was graded by University of Pennsylvania Grading Scale in JULIET; and by the American Society for Transplantation and Cellular Therapy (ASTCT) criteria or Lee criteria in PR(AG)404/2020; and by ASTCT criteria in the matched comparison study
[b] Neurotological toxicity was graded by ASTCT criteria in PR(AG)404/2020 and the matched comparison study
[c] Haemotological toxicity was graded by CTCAE (version 5) in the matched comparison study

Management and monitoring for adverse reactions

Certain approaches have been adopted to treat the adverse reactions upon the administration of tisa-cel, and the ones for CRS, ICANS, cytopenia, and infections are reviewed here.

CRS

CRS, if suspected, should be managed based on the recommendations[25] (**Table 4**).

Table 4: Standard CRS Treatment Algorithm

CRS Grade[a]	Treatment
Grade 1	Exclude other causes of symptoms and treat specific symptoms (e.g. antipyretic for low grade fever, antiemetic). Tocilizumab is not applicable unless the patient experiences persistent (>3 days) or refractory fever. If so, manage as grade 2 CRS. Corticosteroid is not applicable.
Grade 2	Administer antipyretics, oxygen, IV fluids, and/or low-dose vasopressor if needed. Administer tocilizumab IV over 1 hour. Dose: 8mg/kg if ≥30 kg (max: 800mg); 12 mg/kg if <30 kg. Repeat every 8 hours until improvements are shown (max: 3 doses in 24 hours, a total of 4 doses). If no improvement is shown with tocilizumab after 24 hours, administer 2 mg/kg/day methylprednisolone IV once daily (or equivalent), until vasopressor and oxygen can be discontinued. Gradually taper off methylprednisolone.
Grade 3	Administer high-flow oxygen, IV fluids, and high-dose or multiple vasopressors. Identify specific organ toxicities and manage with local guidelines. Administer tocilizumab as per grade 2, and switch to alternative therapy if the patient is non-responsive.b Administer methylprednisolone or equivalent as per grade 2, and proceed to grade 4 if no improvement.
Grade 4	Provide mechanical ventilation. Administer IV fluids and high-dose vasopressor(s). Identify specific organ toxicities and manage according to local guidelines. Administer tocilizumab as per grade 2, and switch to alternative therapy if the patient is non-responsive.b Administer methylprednisolone 1000mg IV once or twice daily for 3 days. If the patient is non-responsive, increase the dosing frequency to twice or thrice daily. Continue with methylprednisolone until CRS grade 1 is achieved, then gradually taper off.

[a] Grading according to Lee criteria
[b] Alternative therapy refers to anti-cytokine and anti-T cell treatments according to local guidelines. Drug choices registered in Hong Kong include siltuximab, ruxolitinib, cyclophosphamide, and IV immunoglobulin.

ICANS

Treatment approaches of ICANS depends on assessment of its severity, and whether the patient has any concurrent CRS [25]. For patients without CRS, treatment options include supportive care with IV hydration and corticosteroid. For patients with CRS, tocilizumab and corticosteroid should be considered. Mechanical ventilation is reserved for severe patients who require airway protection, and non-sedating anticonvulsant (e.g. levetiracetam) should be considered for selected patients who are at risk of seizure disorder (e.g. those with seizure history and CNS disease).

Cytopenia

There is no standard protocol for cytopenia management, and individuals are managed based on their clinical manifestations[26]. Current clinical practice includes blood transfusion and administration of hematopoietic growth factors including granulocyte colony-stimulating factor (G-CSF) and thrombopoietin (TPO)[27]. TPO receptor agonists and sirolimus are also used for mitigation[27]. Monitoring patients' blood count is essential, and G-CSF should be provided when ANC is < 0.5 x 109/L[28]. Transfusion is given to maintain a hemoglobin level of ≥ 8 g/dL when symptomatic anemia is observed or hemoglobin level is < 6 g/dL[28]. Erythropoietin (EPO) can be given for anemia control and to minimize the need for blood transfusion[28]. As for platelet count, when platelet level is < 10 x 109/L or bleeding is observed, either TPO or platelet transfusion is provided[28]. When fibrinogen is < 100 mg/dL, administer cryoprecipitate[28].

Infections

Tisa-cel should not be initiated in patients with active uncontrolled infection until the infection is resolved. Clinicians should also be aware of febrile neutropenia and evaluate for infection, and inform the patients to report any signs and symptoms of an infection such as fever and chills[25]. Infections are managed based on individual species of bacterium, fungus or virus according to the local guidelines[21]. As infection risk increases with prolonged cytopenia, cytopenia should be managed as mentioned[28].

AXICABTAGENE CILOLEUCEL (YESCARTA®)

Mechanism of Action in R/R DLBCL

Axi-cel fuses chimeric antigen receptors onto the T-cells after genetic modification and exhibits the same elimination effect of the abnormal B-cells as tisa-cel. It is composed of a scFv which targets the CD-19 of B-cells. The differences between the two CAR-T products are the subtype of hinge and transmembrane domain, which are both CD-28 subtypes[29]. These signals can increase the expansion, longer-term persistence and potency of CAR-T cells. When the scFv binds to CD19-expressing B-cells, the CAR transmits a signal to promote T-cell expansion, activation and hence elimination of the excess B-cells[13].

EFFICACY OF AXICABTAGENE CILOLEUCEL

Pivotal study for axicabtagene ciloleucel

In April 2015, the ZUMA-1 trial (ClinicalTrials.gov Identifier: NCT02348216) was started to evaluate the safety and efficacy of axi-cel with refractory aggressive non-Hodgkin lymphoma[30]. This single-arm, multi-center, phase 1 and 2 clinical trial recruited 108 patients with R/R DLBCL, other non-Hodgkin lymphomas, or chemotherapy-refractory disease. Subsequently, the FDA approved axi-cel to be a treatment for adult patients with R/R DLBCL after two or more lines of systemic therapy based on the study results[31]. Among the 101 patients evaluated, the ORR was 72% and the complete remission rate was 51% (95% CI: 41%, 62%). The patients with the best overall response with complete remission had a longer duration of response than those with partial response. A new alternative option was provided for patients as a third-line treatment. The study continued to collect patient data in follow-ups and more efficacy data was published until 2021. The progression-free survival (PFS) and OS in Phase 2 (Pivotal Study) cohort 1 were 5.1 months and 11.5 months respectively. Due to the potential of axi-cel being utilized as a more front-line treatment, more refinement of the design of ZUMA-1 trial had been made and new clinical trials arose in the next decade.

Newer efficacy data in treating R/R DLBCL

A new pivotal ZUMA-7 trial (ClinicalTrials.gov Identifier: NCT02601313) was launched in 2018 after the first approval of axi-cel. The efficacy of axi-cel versus standard care as second-line therapy in patients with R/R DLBCL was compared[32]. This international, randomized, open-labeled, multi-centered, phase 3 clinical trial recruited 359 patients above 18 years old with histologically proven DLBCL and had relapsed or refractory disease after conditioning chemotherapy without a history of autologous or allogeneic stem cell transplantation, and were randomized on 1:1 basis to receive either axis-cel or standard care treatment. This is unique since previous clinical trials only included one intervention and did not have side-by-side comparisons with conventional treatment options. Among the 359 randomized patients, the median ORR in the axi-cel group was 83%, which is significantly higher than 50% identified in the standard care group. In terms of duration of response, the median month in the axi-cel group was 26.9, which is longer than median 8.9 months found in the standard care group[32]. Another study analyzing the same trial highlighted the survival indices between the two treatment arms[32]. In terms of EFS, it was significantly longer in the axi-cel group (8.3 months) than in the standard care group (2.0 months) with a hazard ratio of 0.40. Moreover, the estimated 18-month EFS rate of the axi-cel arm and the standard therapy arm was 41.5% and 17% respectively.

With the clear improvement and superiority of axi-cel in terms of EFS and the percentage of patients with a response, the FDA further approved axi-cel for adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy in April 2022, which widened its utilization and more patients with R/R DLBCL having the eligibility to access axi-cel[34].

At the end of the ZUMA-7 trial, the PFS and death rate between the two intervention groups have been analyzed. In the axi-cel treatment group, the PFS at a median of 47.2 months of follow-up was 14.7 months [32], while that in the standard care group was 3.7 months. The final OS rate could not be evaluated since the median and upper limit of CI of OS were not reached due to an insufficient number of events for both treatment arms. In summary, this trial revealed that the

axi-cel treatment arm had a higher response rate and survival rate than the standard care group for R/R DLBCL patients as treatment after failing chemotherapy. This underlines a clinical advantage of axi-cel as administering CAR T-cells earlier in the treatment course may be beneficial to patients, which suggests that it can potentially be a promising treatment option.

Expanding role of axicabtagene ciloleucel for patients who are ineligible for autologous stem cell transplantation (ASCT)

ZUMA-7 trials excluded patients who were ineligible for ASCT due to frailty, age, co-existing medical conditions, history of hepatitis B or other infections, and more, causing about half of patients with R/R DLBCL to be considered unfit to receive axi-cel in clinical practice. A one-of-a-kind clinical trial, ALYCANTE (ClinicalTrials.gov Identifier: NCT04531046) was initiated in March 2021[35]. It was the first-ever study to evaluate the effectiveness of axi-cel in patients with R/R DLBCL who were ineligible for ASCT. This was a single-arm, open-label, multi-centered, phase 2 clinical trial that recruited 62 patients to receive a single axi-cel infusion. The primary outcome was measured after 3 months of the infusion and the results, which were encouraging, were published in late 2022. The complete metabolic response and ORR were 71.0% (95% CI, 58.1–81.8%) and 75.8% (95% CI, 63.3–85.8%) respectively. Follow-ups have been conducted to evaluate the survival rate of the participants. The median EFS rates at 6 and 12 months were 66.7% and 51.2% respectively, whereas the PFS rates at 6 and 12 months were 67.7% and 48.8% respectively. The estimated OS rate and median duration of response were not reached and would be statistically determined in the 3-year follow-up in 2025[35].

Comparing the results from ALYCANTE with that from ZUMA-7, the results were consistent in terms of response rate and survival rate, providing a new insight into expanding the role of axi-cel to more suitable patients. However, ALYCANTE was different from ZUMA-7 trials in terms of study design, eligibility criteria, sample size, and demographics of participants, etc. For instance, the median age of patients in the ALYCANTE study was 70 years, which was older than that in the ZUMA-7 (59 years). The advanced age might influence the duration of survival or safety profile. Most notably, the study was a single-arm design with no active control group, which made the study prone to selection bias. Although the ALYCANTE study investigators supported axi-cel as second-line treatment for R/R DLBCL patients ineligible for ASCT based on the optimistic study results, the study itself was constrained by its own study limitations.

On a related note, lisocabtagene maraleucel (liso-cel) is a CAR-T agent that can be used for R/R DLBCL patients who are medically unfit for ASCT. Detailed discussion about liso-cel is beyond the scope of this review, but the trials evaluating the efficacy of axi-cel and liso-cel in R/R DLBCL patients ineligible for ASCT are summarized for comparison purpose **(Table 5)**.

Table 5: Studies of CAR-T therapy in patients with R/R DLBCL who are ineligible for ASCT

Journal	Description of the study	Treatment arm	Control arm (or 2nd treatment arm)	Condition/ Disease	Results/ Conclusion
Study Title: CAR T in patients with large B-cell lymphoma not fit for autologous transplant[36]					
British Journal of Haematology	Patients who were less fit in autologous transplant, received treatment of either axi-cel or tisa-cel as CAR-T treatment, and were analyzed by the UK National CAR T Clinical Panel, according to fitness for ASCT. A total of 81 participants underwent evaluation. The outcome measures were response rate, PFS, and OS	Axicabtagene ciloleucel	Tisagenlecleucel	Relapsed or refractory large B-cell lymphoma	The response rate, PFS, and OS were similar in both treatment arms. CAR-T therapy was well tolerated in ASCT-unfit patients. The adverse events CRS and neurotoxicity were 2% and 11%, respectively.
Study Title: Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study[37]					
The Lancet Oncology	Patients who were not intended for hematopoietic stem cell transplantation received liso-cel. A total of 61 participants received this newer CAR-T option in the US. The outcome measures were the overall response rate and any Treatment-Emergent Adverse Events (TEAE). Follow-ups are on-going.	Lisocabtagene maraleucel		Relapsed or refractory large B-cell lymphoma	49 patients (80%) had a complete or partial response. 5 patients had stable disease condition and 9 patients encountered progressive disease or not evaluable. 13 patients (21%) reported TEAE and no treatment-related death was shown.

SAFETY OF AXICABTAGENE CILOLEUCEL

Safety concerns of axi-cel

The pharmaceutical company that developed axi-cel highlighted CRS and neurotoxicity as its two principal life-threatening toxicities, and the two toxicities are now included as boxed warnings in the prescribing information [38,39].

CRS

Being the dose-limiting toxicity, similar to tisa-cel, occurrence of CRS was prevalent in axi-cel in both ZUMA-7 and ALYCANTE studies [32, 35], which is due to overactivated immunological cells and cytokines. The median onset time of CRS was 1.5 days and could last for 5 days. The majority of patients had mild (grade 1 or 2) cases of CRS, and only 6% patients were categorized in grade 3 or above.

Neurotoxicity

Occurrence of ICANS, a type of neurotoxicity in ALYCANTE study, was slightly less than CRS, whilst the severity was higher in both ZUMA-7 and ALYCANTE trials[32,35]. Neurotoxicity is caused by the systemic capillary leak in the blood-brain barrier, facilitating infiltration of immune cells into the CNS, hence a cascade of inflammatory responses will occur inside the brain. The median onset time was 4 days after infusion with a resolution time of 5 days[40]. Neurological issues were mostly resolved, and none of the cases from the ZUMA-7 trial reported death due to neurological issues.

Comparison of various trials

Fludarabine and cyclophosphamide were included as conditioning chemotherapeutics agents in the ZUMA-7 trial[32]. As an anti-metabolite, fludarabine can cause peripheral neuropathy while cyclophosphamide is not typically associated with either CRS or neurotoxicity[41]. Use of fludarabine in the ZUMA-7 trial might explain the increased risk of neurotoxicity.

Apart from CRS and neurotoxicity, the ZUMA-7 trial also evaluated different adverse events. Different from the dose-limiting toxicities of axi-cel, the prevalence and severity of hematological adverse events was significantly higher. Neutropenia, anemia, and thrombocytopenia were among the most commonly reported adverse events in the axi-cel group, and there was large proportion of patients who experienced these adverse events of grade 3 or above. Hematological monitoring should be considered for patients receiving axi-cel treatment. The frequency of the hematological and other common adverse events in patients using axi-cel in the ZUMA-7 trial are shown **(Table 6)**.

Table 6: Hematological and other common adverse events in 170 patients using axi-cel in ZUMA-7 trial

Adverse Events[a]	Any Grade (%)	Grade 1-2 (%)	Grade 3 or above (%)
Pyrexia[b]	93	84	9
Neutropenia	71	2	69
Hypotension[b]	44	33	11
Diarrhea	42	40	2
Anemia	42	12	30
Tachycardia[b]	34	32	2
Thrombocytopenia	29	14	15
Chills[b]	28	27	1
Hypoxia[b]	22	13	9
Vomiting	19	19	0

[a] Adverse events were graded by Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03)
[b] Isolated adverse events; not considered as part of CRS

Management of adverse events

Since axi-cel and tisa-cel share similar mechanisms of action and adverse events profiles which primarily consist of CRS, neurotoxicity, and hematotoxicity, the toxicity management strategies are also similar. For specific adverse events such as pyrexia and emesis, supportive care (e.g. antipyretic and antiemetic) can be provided accordingly for symptomatic relief.

OVERALL COMPARISON OF TISAGENLECLEUCEL AND AXICABTAGENE CILOLEUCEL AND IMPLICATION FOR HONG KONG

Both tisa-cel and axi-cel show impressive clinical activities in R/R DLBCL. Although they belong to the same treatment category, there are differences between them in terms of evidence on therapeutic efficacy, adverse events, and patient eligibility criteria for use.

First, axi-cel has a higher risk of causing fatal toxic effects than tisa-cel. Apart from the JULIET, ZUMA, and ALYCANTE trials, a comprehensive analysis of the toxicity profiles between tisa-cel and axi-cel has been conducted using Vigilyze-VigiBase, the World Health Organization (WHO) database for global incidents of adverse drug reactions[42]. The analysis showed that 10%, 14%, and 29% more patients treated with axi-cel experienced immune system disorders, CRS, and nervous system disorders respectively than those treated with tisa-cel. This suggests that tisa-cel has a relatively less fatal safety profile than axi-cel. However, with close monitoring, the mortality rate of these fatal adverse events can be significantly lowered in both therapies[42].

Second, medical literature shows a better performance for tisa-cel than axi-cel. The real-life matched comparison study also evaluated the efficacy of tisa-cel in patients with R/R DLBCL in France[21]. The study analyzed the outcomes of 809 patients who were assigned to either tisa-cel or axi-cel groups. The ORR was 66% and the complete response rate was 42% in the tisa-cel group (P<0.001). The 1-year PFS was found to be 33.2% after a median follow-up time of 11.7 months. This highlights the clinical benefit of tisa-cel in terms of durable response in R/R DLBCL patients.

However, for patient eligibility criteria, axi-cel has a higher potential for expanded usage in Hong Kong. axi-cel is eligible as a second-line therapy for patients with R/R DLBCL failing the first-line therapy[34], and can serve as an alternative treatment option at an earlier stage for R/R DLBCL compared with tisa-cel. According to the ZUMA-7 trial, the 24-month EFS of the axi-cel group and standard-care group was 41% and 16% respectively. This shows that by using axi-cel in the earlier treatment, more R/R DLBCL patients can benefit from axi-cel, improving the overall chance of remission.

Tisa-cel received the FDA approval in May 2018 for treating R/R DLBCL after two or more lines of systemic therapy; while axi-cel received the FDA approval in October 2017 for treating R/R DLBCL after two or more lines of systemic therapy[18,31]. Axi-cel, under the trade name Yikaida, also received China's approval and became the first CAR-T therapy product for use in June 2021, and now with an indication for treating R/R DLBCL after receiving second-line or above systemic therapy in the country[43,44]. At present, tisa-cel is the only CAR-T therapy product registered in Hong Kong. There is potential that axi-cel will become the second registered CAR-T therapy product with expanded use in Hong Kong, providing a valuable treatment option for R/R DLBCL with data supported by pharmacoeconomic analysis in Hong Kong in the future.

CONCLUSION

Tisagenlecleucel and axicabtagene ciloleucel are approved CAR-T therapy products for patients with R/R DLBCL, demonstrating significant efficacy in response rate and survival rate shown in recent studies. Adequate monitoring and supportive care have been outlined as the management approach to resolve the adverse reactions issue encountered by the patients. The FDA has approved high priority of axi-cel utilization in R/R DLBCL patients, while newer trials are investigating whether axi-cel will have a greater role in ASCT ineligible patients. The adoption of this second CAR-T therapy product in Hong Kong can be considered.

Author's background

YUEN, Sheung Shing *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: aaron.yuen2003@gmail.com.* ***CHENG, Wing Yan*** *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: chengwingyanb@gmail.com.* ***LAM, Chun Kwan*** *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: lamck0911@gmail.com.* ***KWOK, Wai Shing*** *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: vincentwskwok@yahoo.com.hk.* ***WONG, Yin Chun*** *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: rachelwong201202@gmail.com.* ***YICK, Chau Ho*** *is a fourth year Bachelor of Pharmacy student of The Chinese University of Hong Kong. Her email address is: judeyick1302@gmail.com.* ***TAI, Bik Wai Bilvick*** *is a lecturer of School of Pharmacy, The Chinese University of Hong Kong. He is the corresponding author and his email address is: bwtai@cuhk.edu.hk.*

References

1. Padala SA, Kallam, A. Diffuse Large B Cell Lymphoma. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557796/#:~:text=Healthcare%20Team%20Outcomes-
2. Martelli M, Ferreri AJM, Agostinelli C, Rocco AD, Pfreundschuh M, Pileri SA. Diffuse Large B-Cell Lymphoma. Crit Rev Oncol Hematol, 2013 Aug 87(2):146-71.
3. Gibson TM, Engels EA, Clarke CA, Lynch CF, Weisenburger DD, & Morton LM. (2014). Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States. Am J Hematol. 2014 Jul;89(7):714-20.
4. Pasqualucci L, Dalla-Favera R. (2018). Genetics of diffuse large B-cell lymphoma. Blood. 2018 May 24;131(21):2307-2319.
5. Moore DC, Peery MR, Tobon KA, Raheem F, Hwang GS, Alhennawi L, & Hughes ME. New and emerging therapies for the treatment of relapsed/refractory diffuse large B-cell lymphoma. J Oncol Pharm Pract. 2022 Dec; 28(8):1848–1858.
6. Hernández-López A, Téllez-González MA, Mondragón-Terán P, & Meneses-Acosta A. Chimeric Antigen Receptor-T Cells: A Pharmaceutical Scope. Front Pharmacol. 2021 Aug 20:12:720692.
7. Mitra A, Barua A, Huang L, Ganguly S, Feng Q, He B. From bench to bedside: the history and progress of CAR T cell therapy. Front Immunol. 2023 May 15;14:1188049.
8. Awasthi R, Maier HJ, Zhang J, & Lim S. Kymriah® (tisagenlecleucel) – An overview of the clinical development journey of the first approved CAR-T therapy. Hum Vaccin Immunother. 2023 Dec 31;19(1):221046

9. Dana-Farber Cancer Institute. CAR T Cell Therapy. Dana-Farber Cancer Institute Internet. Available from: https://www.dana-farber.org/cancer-care/treatment/cellular-therapies/car-t-cell-therapy#:~:text=Eligibility%20Cr iteria%20for%20CAR%20T. Accessed 2025 Jun 30
10. Adkins S. CAR T-Cell Therapy: Adverse Events and Management. J Adv Pract in Oncol. 2019 May-Jun; 10(Suppl 3):21-28.
11. Gajra A, Zalenski A, Sannareddy A, Jeune-Smith Y, Kapinos K, Kansagra A. Barriers to Chimeric Antigen Receptor T-Cell (CAR-T) Therapies in Clinical Practice. Pharmceut Med. 2022 Jun; 36(3):163-171.
12. DrugBank. DB13881: Kymriah. DrugBank Internet. Available from: https://go.drugbank.com/drugs/DB13881. Accessed 2025 Jun 30
13. Benmebarek MR, Karches CH, Cadilha BL, Lesch S, Endres S, & Kobold S. Killing Mechanisms of Chimeric Antigen Receptor (CAR) T Cells. Int J Mol Sci. 2019 Mar 14;20(6):1283.
14. Nucleus Biologics. Kymriah vs Yescarta. Nucleus Biologics Internet. Available from: https://nucleusbiologics.com/educational-content/kymriah-vs-yescarta/ Accessed 2025 Jun 30
15. Zhang C, Durer S, Thandra KC, & Kasi A. (2022). Chimeric Antigen Receptor T-Cell Therapy. In StatPearls. StatPearls Publishing.
16. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
17. European Medicines Agency. Kymriah EPAR product information. European Medicines Agency Internet. Available from: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf Accessed 2025 Jun 30
18. U.S. Food and Drug Administration. FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma. U.S. Food and Drug Administration Internet. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma Accessed 2025 Jun 30
19. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, at al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-39.
20. Iacoboni G, Villacampa G, Martinez-Cibrian N, Bailén R, Lopez Corral L, Sanchez JM, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. Cancer Med. 2021;10(10), 3214-3223.
21. Bachy E, Le Gouill S, Di Blasi R, Sesques P, Manson G, Cartron G, et al. A real-world comparison of Tisagenlecleucel and Axicabtagene Ciloleucel Car T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154.
22. Balagopal S, Sasaki K, Kaur P, Nikolaidi M, & Ishihara J. Emerging approaches for preventing cytokine release syndrome in CAR-T cell therapy. J Mater Chem B. 2022;10(37), 7491-7511.
23. Xiao X, Huang S, Chen S, Wang Y, Sun Q, Xu X, & Li Y. Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. J Exp Clin Cancer Res. 2021 Nov 18;40(1):367.
24. Stewart AG, & Henden AS. Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis. 2021 Au 24:8:20499361211036773.
25. Novartis. Safety profile of Kymriah in diffuse large B-cell lymphoma in adults. Novartis Internet. https://www.hcp.novartis.com/products/kymriah/diffuse-large-b-cell-lymphoma-adults/safety-profile/. Accessed 2025 Jun 30
26. Sharma N, Reagan PM, & Liesveld JL. Cytopenia after CAR-T cell therapy—a brief review of a complex problem. Cancers (Basel). 2022 Mar 15;14(6):1501.
27. Zhang X, Zhu L, Zhang H, Chen S, & Xiao Y. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. Front Immunol. 2022 Jun 10:13: 927153.
28. Si X, Gu T, Liu L, Huang Y, Han Y, Qian P, et al. Hematologic cytopenia post CAR T cell therapy: Etiology, potential mechanisms and perspective. Cancer Lett. 2022 Dec 1:550:215920.
29. DrugBank. DB13915: Axicabtagene ciloleucel. DrugBank Internet. Available from: https://go.drugbank.com/drugs/DB13915 Accessed 2025 Jun 30
30. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1–2 trial. Lancet Oncol. 2019 Jan 20(1):31–42.
31. U.S. Food and Drug Administration. FDA approves axicabtagene ciloleucel for large B-cell lymphoma. U.S. Food and Drug Administration Internet. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-large-b-cell-lymphoma Accessed 2025 Jun 30.
32. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022 Feb 17;386(7):640–654.
33. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med. 2023 Jul 13;389(2):148–157.
34. U.S. Food and Drug Administration. FDA Disco Burst Edition: FDA approval of Yescarta (axicabtagene ciloleucel) for adult patients with large B-cell lymphoma. U.S. Food and Drug Administration Internet. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-yescarta-axicabtagene-ciloleucel-adult-patients-large-b-cell#%3A~%3Atext%3DOn%20April%201%2C%202022%2C%20the%2Cmonths%20of%20first%2Dline%20chemoimmunotherapy. Accessed 2025 Jun 30.
35. Houot R, Bachy E, Cartron G, Gros F-X, Morschhauser F, Oberic L, et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. Nat Med. 2023 Oct;29(10):2593–2601.
36. Kuhnl A, Kirkwood AA, Roddie C, Menne T, Tholouli E, Bloor A, et al. CAR T in patients with large b-cell lymphoma not fit for autologous transplant. Br J Haematol. 2023 Jul;202(1):65–73.
37. Sehgal A, Hoda D, Riedell PA, Ghosh N, Hamadani M, Hildebrandt GC, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol. 2022 Aug;23(8):1066–1077.
38. Yescarta. Managing side effects. Available from: https://www.yescarta.com/managing-side-effects. Accessed 2025 Jun 30.
39. Gilead Sciences, Inc. Yescarta (axicabtagene ciloleucel) prescribing information. Available from: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf. Accessed 2025 Jun 30.
40. Gust J, Taraseviciute A, Turtle CJ. (2018). Neurotoxicity associated with CD19-targeted car-T cell therapies. CNS drugs. 2018 Dec;32(12):1091-1101.
41. Fraiser LH, Kanekal S, Kehrer JP. Cyclophosphamide Toxicity. Drugs. 1991 Nov;42(5):781-95.
42. Cai C, Tang D, Han Y, Shen E, Abdihamid O, Guo C, et al. A comprehensive analysis of the fatal toxic effects associated with CD19 CAR-T cell therapy. Aging (Albany NY). 2020 Sep 24;12(18):18741-18753.
43. Lu J, Jiang G. The journey of CAR-T therapy in hematological malignancies. Mol Cancer. 2022 Oct 8;21(1): 194.
44. Li N, Lei J, Zhang J, Cai H, Zheng B, Yang T, et al. Cost-effectiveness analysis of axicabtagene ciloleucel as a second-line treatment for diffuse large B-cell lymphoma in China and the United States. Ther Adv in Hematol. 2023 May 23;14:20406207231168215.

Questions for Pharmacy Continuing Education Program

2 CE Units

Review of Current CAR-T Therapy for adults Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Tisagenlecleucel (Kymriah®) and Axicabtagene Ciloleucel (Yescarta®)

1. ***Which of the following about CAR-T therapy is correct?***
   a. It is considered as a chemotherapy
   b. It cannot be used in elderly patients
   c. It is a genetically modified allogeneic T cell therapy
   d. It is prepared from the patient's peripheral blood cells

2. ***What type of cancer cells do tisagenlecleucel and axicabtagene ciloleucel target?***
   a. HLA-DR-expressing cancer cells
   b. CD-19-expressing cancer cells
   c. CD-20-expressing cancer cells
   d. PAX5-expressing cancer cells

3. ***Based on the US FDA approved indication of tisagenlecleucel, which of the following patients can receive tisagenlecleucel for treating B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse?***
   a. 21-year-old patient
   b. 42-year-old patient
   c. 63-year-old patient
   d. 84-year-old patient

4. ***Which study supported the US FDA approval of tisagenlecleucel for treating adults with relapsed or refractory large B-cell lymphoma?***
   a. ZUMA-1
   b. ZUMA-7
   c. JULIET
   d. ALYCANTE

5. ***Which of the following is correct about BELINDA study?***
   a. It was a phase 2, double-blinded trial that was only conducted in the US.
   b. It compared the efficacy of tisagenlecleucel and lisocabtagene maraleucel for B-cell lymphomas.
   c. Its primary endpoint was the occurrence of neurotoxicity associated with CAR-T therapy.
   d. Diffuse large B-cell lymphoma was the most common disease subtype in the study population.

6. **Which of the following is NOT a sign or symptom of cytokine release syndrome?**
   a. Fever
   b. Hypertension
   c. Tachycardia
   d. Hypoxia

7. ***Which of the following is the most appropriate treatment for Grade 2 cytokine release syndrome?***
   a. Mechanical ventilation, IV fluid, low-dose vasopressor, tocilizumab, methylprednisolone
   b. Antipyretic, oxygen, IV fluid, low-dose vasopressor, tocilizumab, methylprednisolone
   c. Antipyretic, antiemetic
   d. IV fluid, high-dose vasopressor, tocilizumab, methylprednisolone

8. ***Which of the following is correct about immune effector cell-associated neurotoxicity syndrome (ICANS) associated with CAR-T therapy?***
   a. Treatment options for ICANS are the same across different severities.
   b. Corticosteroid should be avoided in ICANS patients with concurrent cytokine release syndrome.
   c. Levetiracetam should be considered for seizure prophylaxis in ICANS patients with seizure history.
   d. It is only associated with tisagenlecleucel but not axicabtagene ciloleucel.

9. ***Which of the following patients on CAR-T therapy should receive evaluation for infection risk?***
   a. Those with peripheral neuropathy
   b. Those with edema
   c. Those with aphasia
   d. Those with febrile neutropenia

10. ***Which of the following is the only registered CAR-T therapy product in Hong Kong as of June 2025?***
    a. Tisagenlecleucel
    b. Axicabtagene ciloleucel
    c. Lisocabtagene maraleucel
    d. Obecabtagene autoleucel

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 321(D&T)

Overview of Pharmacologic Treatment of Motor Fluctuations in Parkinson's Disease

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

Hepatitis B Screening and Management in Primary Healthcare: Global Models and the Expanding Role of Community Pharmacies in Hong Kong

LEE, Marco Tsun[a]; CHEUNG, Vernon Ka Chun[a]; LEE, Judy Siu Har[b]; MAK, Loey Lung Yi[c]*

[a] *Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China*

[b] *The Hong Kong Society for Rehabilitation, Hong Kong SAR, China*

[c] *Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China (*Corresponding author)*

ABSTRACT

Chronic hepatitis B (CHB) remains a major public health challenge, particularly in the Asia-Pacific region. Despite effective antiviral therapy and World Health Organisation (WHO) targets to eliminate hepatitis B by 2030, gaps in screening and linkage to care persist globally. Community pharmacies, due to their accessibility and public trust, are increasingly recognized for their role in preventive care. This review explores international experiences in pharmacy-based hepatitis B screening and synthesizes key enablers for implementation. Case studies from the United States, Australia, the United Kingdom, and China illustrate varied levels of integration and policy support for pharmacy-led models. A 2024 systematic review further affirms the feasibility and acceptability of viral hepatitis testing in pharmacy settings, particularly when combined with outreach, training, and structured referral pathways. In Hong Kong, where CHB prevalence remains high, particularly among individuals aged over 35, screening is largely confined to opportunistic detection in hospital settings. Community pharmacies remain underutilized in hepatitis B care despite their widespread presence and emerging roles in chronic disease management. A recent pilot study demonstrates public receptiveness to pharmacist-linked point-of-care (POC) screening. Drawing on global evidence and local capacity, this article outlines a framework to expand the role of pharmacists in hepatitis B screening, vaccination, education, and linkage to care. Recommendations include pilot programs, regulatory reform, standardized protocols, and integration with the territory's evolving primary healthcare system. Leveraging community pharmacies offers a scalable and person-centered pathway to address longstanding gaps in hepatitis B prevention and management in Hong Kong.

Keywords: *Chronic Hepatitis B, Community Pharmacy, Community Pharmacist, Point-of-Care Testing, Primary Healthcare, Hong Kong*

INTRODUCTION

Chronic hepatitis B (CHB) caused by hepatitis B virus (HBV) remains a significant public health challenge globally, particularly in the Asia-Pacific region. The World Health Organization (WHO) has set ambitious goals to eliminate viral hepatitis as a major public health threat by 2030, targeting a 90% reduction in new infections and a 65% reduction in related mortality.[1] Achieving these goals requires robust screening, early diagnosis, linkage to care, and long-term management, which are the components traditionally centered in specialist settings.[2] However, with the shift toward person-centered primary healthcare systems, there is growing interest in decentralizing aspects of CHB care to primary healthcare providers, including community pharmacists. Hong Kong has one of the highest CHB prevalence rates among high-income jurisdictions, with an estimated 5.6% of the population affected.[3] Most of these individuals were born before the universal neonatal hepatitis B vaccination program was introduced in 1988, and many remain unaware of their infection status or are not engaged in ongoing care. While the public healthcare system provides antiviral treatment and specialist management through specialist clinics operated by the Hospital Authority, the gap in early-stage screening and community-based engagement limits the effectiveness of the current care cascade. Community pharmacies, as accessible and trusted healthcare touchpoints, are increasingly recognized for their potential role in public health interventions, including chronic disease management, medication management services and smoking cessation service.[4] This review explores global models of hepatitis B management involving community pharmacies and proposes a locally adapted approach for Hong Kong within the context of its Primary Healthcare Blueprint.

GLOBAL EXPERIENCES IN COMMUNITY PHARMACY-BASED HEPATITIS B SCREENING

United States: From Risk-Based to Potential Universal Pharmacy Screening

In the United States, hepatitis B screening and vaccination have seen major policy advancements in recent years. In 2023, the Centers for Disease Control and Prevention (CDC) adopted a universal screening recommendation for all adults at least once in their lifetime, replacing the previous risk-based approach that often failed to identify asymptomatic carriers.[5] Similarly, the Advisory Committee on Immunization Practices (ACIP) now recommends universal hepatitis B vaccination for all adults aged 19 to 59, regardless of risk factors.[6] These changes present important opportunities to expand hepatitis B services beyond traditional healthcare settings. Community pharmacies, already established as key providers of vaccinations and chronic disease management, are well-positioned to support public health outreach. While pharmacists in many states are authorized to perform Clinical Laboratory Improvement Amendments (CLIA)-waived point-of-care (POC) testing through collaborative practice agreements, there are currently no FDA-cleared CLIA-waived tests for hepatitis B surface antigen (HBsAg).[7] This regulatory limitation means that pharmacy-based screening for hepatitis B remains largely aspirational, in contrast to established roles in human immunodeficiency virus (HIV) and hepatitis C virus (HCV) testing. Despite some challenges, community pharmacies have emerged as accessible and acceptable primary healthcare service points, providing promising sites expanding hepatitis B services, especially for underserved and hard-to-reach populations.

Australia: Growing Potential for Community Pharmacy in Hepatitis B Screening

Australia has laid foundational infrastructure for community-based hepatitis B services, although large-scale pharmacy-led screening is not yet mainstream. The country has experience in POC testing and community pharmacy–based harm reduction programs, including models for HIV and HCV.[8] While dedicated hepatitis B screening pilots remain limited, several feasibility studies and policy discussions suggest pharmacies could expand into this space. In jurisdictions like Queensland and New South Wales, expanded pharmacist scope has already authorized pharmacists to deliver hepatitis B vaccination under an expanded scope of practice.[9,10] Although no formal national framework exists for HBV testing in pharmacies, the infrastructure, workforce readiness, and public trust suggest strong potential for pilot programs to be adapted for hepatitis B, especially in underserved and rural populations.

United Kingdom: Limited Pilots on Hepatitis B Screening in Community Pharmacies

In the United Kingdom, community pharmacy–based hepatitis B screening is not widely implemented, with only isolated pilot programs demonstrating feasibility. Screening efforts have been limited to small-scale pilots, often integrated within broader blood-borne virus (BBV) testing services. There is no universal or large-scale pharmacy-led HBV screening program in either country. In 2014, a dry blood spot testing pilot conducted across 22 community pharmacies on the Isle of Wight offered screening for HIV, HCV, syphilis, and HBsAg among people with risk factors. Over the nine-month pilot, 186 tests were performed and 13 HCV-positive cases identified. Although HBV test results were not separately reported, the initiative demonstrated feasibility and the potential of community pharmacies as low-barrier access points for BBV screening within a broader testing framework.[11] This pilot targeted high-risk groups, such as people who inject drugs, and showed that community pharmacies can be effective low-barrier access points. However, HBV testing remains localized, with no national rollout or formal commissioning pathway.

China: Potential of Community Pharmacies for Hepatitis B Screening

China bears one of the heaviest global burdens of chronic hepatitis B, with an estimated 86 million people living with HBV, yet community pharmacy–based screening remains undeveloped.[12] Recent community-based initiatives, such as the Community-Based HBV Infection Detection and Vaccination (HBVIDV) programme in Beijing's Chaoyang District, demonstrated feasibility of non-hospital vaccine and screening interventions.[13] The programme was implemented in nearly 43 communities, significantly increasing HBV vaccination and immunity rates. However, the initiative was centrally managed by public health authorities, not via community pharmacy platforms. As of 2020, China boasted over 550,000 community pharmacy outlets, highlighting rapid expansion of retail pharmacy access nationwide.[14] China's extensive network of community pharmacies, which are highly accessible and trusted by the public, presents an underutilized but promising platform to support hepatitis B screening and management.

GLOBAL SYNTHESIS: THE CASE FOR PHARMACY-LED HEPATITIS B SCREENING

While hepatitis B screening through community pharmacies remains limited globally, emerging evidence supports the feasibility and acceptability of this approach in select settings. A 2024 systematic review synthesizing 42 studies on pharmacy-based viral hepatitis testing revealed that pharmacies are viable and acceptable venues for POC testing, particularly when integrated with outreach, education, and linkage-to-care services.[15] Although most evidence centered on hepatitis C, four studies reported hepatitis B screening outcomes. These included pilots from England, Portugal, and Sierra Leone using dried blood spot (DBS) tests conducted among individuals with elevated risk. Program evaluations, primarily conducted in the context of hepatitis C, consistently highlighted high acceptability among both clients and pharmacy staff. Pharmacists expressed willingness to continue offering viral hepatitis services, provided they received appropriate training and system support. Clients found pharmacies accessible, convenient, and acceptable as

testing venues, especially when confidentiality and trust were preserved. However, time constraints, workload, and stigma-related concerns were identified as barriers. Structured training programs enhanced pharmacists' confidence in providing testing, counselling, and referrals. The experience of hepatitis C programs offers transferable insights. Core enablers such as pharmacist training, integration into existing workflows, availability of rapid diagnostic tools, and clear referral pathways are equally relevant to hepatitis B. As countries progress toward the WHO 2030 elimination targets, these findings underscore the untapped potential of community pharmacies in expanding equitable access to hepatitis B screening and early care, especially among underserved or stigmatized populations.

HONG KONG: LOCAL BURDEN, SYSTEM GAPS, AND MISSED OPPORTUNITIES

Local Epidemiology and Care Landscape

Hong Kong bears a substantial burden of CHB, with an estimated prevalence of 5.6%, equating to over 400,000 affected individuals.[2] The disease burden is particularly concentrated among those born before 1988, prior to the introduction of universal neonatal hepatitis B vaccination. Notably, prevalence remains as high as 8.4% among individuals aged over 35, highlighting the priority of targeted interventions in this demographic.[3] Other high-risk groups include immigrants, under-screened adults, and those with occupational exposure. At present, CHB management is primarily delivered through specialist outpatient clinics (SOPCs) under the Hospital Authority, offering confirmatory testing, liver function monitoring, antiviral therapy, and hepatocellular carcinoma (HCC) surveillance. However, this specialist-led model creates bottlenecks, with long waiting times and access barriers, particularly for those requiring follow-up or early-stage evaluation.[16,17] Conversely, primary healthcare settings remain underutilized in CHB screening and longitudinal care. Community pharmacies, despite being widely accessible and frequently visited by the public, currently lack a structured framework for offering POC testing, formal referral mechanisms, or systematic participation in hepatitis B care pathways. At present, no publicly commissioned programme or regulatory framework explicitly supports community pharmacists to conduct hepatitis B screening, reflecting a missed opportunity for broader community-based engagement.

Gaps in the Current Cascade of Care

Despite the high disease burden and the availability of effective antiviral treatment, many individuals living with hepatitis B in Hong Kong remain undiagnosed.[3] The existing system relies heavily on opportunistic detection, such as through antenatal screening, blood donation, or pre-employment health checks, rather than proactive or population-based screening efforts.[18] As a result, significant gaps persist across the cascade of care. Community-based screening remains limited thus missing opportunities to identify asymptomatic individuals. Public awareness also remains suboptimal, with ongoing misconceptions about transmission and social stigma associated with the condition, especially among older adults.[19] Furthermore, there is a systemic overreliance on specialist clinics for diagnosis and follow-up, with little integration of primary healthcare professionals, including community pharmacists, into the broader management of chronic hepatitis B. These structural limitations result in late diagnoses, fragmented follow-up, and missed opportunities for prevention and early intervention.

A recent pilot study conducted at the primary healthcare setting in Hong Kong further illustrates the feasibility and public receptiveness of pharmacy-linked or community-based POC hepatitis B screening.[20] The study identified significant knowledge gaps, particularly regarding HBV transmission and chronicity. Nevertheless, low stigma and high acceptance were observed, with over 90% of participants reporting high satisfaction across convenience, cost, and disease management dimensions. Importantly, all participants expressed willingness to be screened if recommended by their family doctor. These findings highlight the value of patient education and demonstrate the readiness of the public to engage in POC hepatitis B screening within primary healthcare settings, such as community pharmacies.

Untapped Potential of Community Pharmacies in Hong Kong in Hepatitis B Screening

Community pharmacies in Hong Kong are well positioned to play a more active role in hepatitis B prevention and care. With over 600 registered community pharmacies across districts, they provide convenient, walk-in access to the public without the need for prior appointments. The ongoing expansion of service models under primary healthcare initiatives such as Jockey Club PHARM+ Community Medication Service Network has further demonstrated that community pharmacists can support chronic disease management, health promotion, and preventive care directly within the community setting.[21,22] However, to fully harness their potential in hepatitis B care, including screening, education, vaccination referral, and treatment adherence, further system integration and policy support are required. Community pharmacists already competent to deliver pharmaceutical services such as medication management services, vaccination and osteoporosis risk screening. There is a strong foundation upon which to build structured hepatitis B interventions within community pharmacy practice.

EXPANDED ROLE OF COMMUNITY PHARMACISTS IN HEPATITIS B PREVENTION AND MANAGEMENT

Building on the unmet needs and gaps identified in the local care landscape, community pharmacists in Hong Kong are well placed to contribute across the hepatitis B care continuum. Drawing on international models and local pilot evidence, the

following core functions outline how community pharmacy–based services can be implemented and scaled up.

POC Testing and Linkage-to-Care

Community pharmacies can act as vital access points in the care cascade. Trained community pharmacists can provide risk-based hepatitis B screening using rapid HBsAg test kits under clear and pre-defined protocols. A pharmacist-led model can offer accessible, low-barrier testing, especially for individuals aged over 35 or those from high-risk groups. Testing could be accompanied by risk assessment, counselling, and built-in referral for follow-up care. Besides, community pharmacists can deliver structured pre- and post-test counselling, issue referrals to public or private providers, and support patients in navigating follow-up. Integration with Electronic Health Record Sharing System (eHealth) would further streamline these services.

Health Education and Stigma Reduction

As frontline primary healthcare professionals, community pharmacists can correct misconceptions about hepatitis B transmission and promote prevention through culturally sensitive education. Pharmacy-based health promotion by public education talks, counselling, leaflets, or online platforms can enhance disease literacy, normalize screening, and reduce stigma, especially among older adults and immigrant populations.

Hepatitis B Vaccination Services

As the government plans to launch pharmacist-led vaccination programmes, expanding hepatitis B immunization to include trained community pharmacists is a logical and feasible next step. Community pharmacists in Hong Kong already receive vaccination-related training through accredited programmes offered by local universities, equipping them with the necessary clinical skills and knowledge. With formal authorization, community pharmacists would be well positioned to assess patient eligibility, administer the full vaccine series, monitor for adverse events, and contribute to improving adult vaccination coverage, particularly among under-immunized or high-risk populations.

Adherence and Monitoring Support

For patients on long-term antiviral therapy, community pharmacists can offer adherence counselling, side effect monitoring, and support tools including drug refill reminders. Their routine interaction with patients creates opportunities to reinforce follow-up schedules and improve treatment outcomes. This aligns with community pharmacists' established role in chronic disease management and medication therapy review.

PRACTICE RECOMMENDATIONS FOR HONG KONG

To fully leverage the potential of community pharmacists in hepatitis B screening and management, the following operational enablers are recommended:

Launch Pilot Programs for Pharmacist-Led Screening and Vaccination

Pilot initiatives and commissioned programmes should be implemented in qualified community pharmacies in collaboration with the Hospital Authority and DHCs. These pilots should focus on adults aged over 35 and other high-risk populations, offering point-of-care testing and vaccination services.

Capacity Building by Standardized Protocols and Training

Clear and standardized service protocols should be established for hepatitis B screening, informed consent, counselling, documentation, vaccination, and referral. These protocols must align with existing clinical and infection control guidelines and be supported by consistent patient education materials. In parallel, accredited training programmes should be provided to ensure community pharmacists are equipped with the necessary competencies to deliver these services safely and effectively. To fully enable pharmacist-led care, policymakers should also explore regulatory mechanisms to expand the scope of practice under relevant ordinances.

Enable Sustainable Infrastructure and Integrated Care Pathways

To ensure the long-term viability and effectiveness of pharmacist-led hepatitis B services, a supportive infrastructure must be established. This includes the development of sustainable reimbursement models to incentivize pharmacist participation, such as public-private partnerships, DHC-linked subsidies, per-service reimbursement, or bundled payment schemes. Digital tools should be integrated into pharmacy workflows to facilitate data collection and service monitoring. Key indicators, including screening uptake, positivity rates, referral completion, vaccination coverage, and patient satisfaction, should be routinely tracked to inform quality assurance and continuous improvement. Furthermore, strong cross-sector collaboration is essential. Formal referral and feedback systems should be established between community pharmacists, family doctors, and DHCs. Integration with the eHealth platform would enable real-time communication, shared care planning, and outcome tracking across providers, helping to build a coordinated and person-centered hepatitis B care pathway.

CONCLUSION

Chronic hepatitis B remains a major public health challenge, particularly in high-prevalence regions like the Asia-Pacific. Despite WHO's 2030 elimination goals, persistent gaps

in early detection, vaccination, and linkage to care hinder progress. Community pharmacies, as trusted, convenient, and accessible healthcare providers, remain an underutilized resource in the hepatitis B care cascade. Global evidence supports pharmacy-led models in screening, education, and vaccination as effective complements to traditional healthcare, especially for underserved populations. In Hong Kong, primary healthcare reform presents a timely opportunity to expand the role of pharmacists in hepatitis B services. With the right policy support, training, and integration, community pharmacies can help close critical gaps in the care cascade, reduce stigma, and improve continuity of care. Importantly, this is not only a pragmatic approach, but also an equity-driven one. Embedding hepatitis B services into community pharmacies can engage populations who face barriers to formal care, promoting a more inclusive and person-centered healthcare system. As Hong Kong advances its Primary Healthcare Blueprint, activating the pharmacy sector will be key to achieving hepatitis B elimination and strengthening long-term public health resilience.

Author's background

LEE, Marco Tsun *is the Senior Pharmacist at the Department of Pharmacology and Pharmacy, the University of Hong Kong. His email is marcolt@hku.hk*

CHEUNG, Vernon Ka Chun *was the Bachelor of Pharmacy (BPharm) student at the University of Hong Kong. His email is vernoncheung0802@gmail.com*

LEE, Judy Siu Har *is the Project Coordinator at Central and Western District Health Centre Express, operated by The Hong Kong Society for Rehabilitation. Her email is judy.lee@rehabsociety.org.hk*

Professor MAK, Loey Lung Yi *is the Clinical Assistant Professor at the Department of Medicine, the University of Hong Kong. Her email is lungyi@hku.hk*

References

1. World Health Organization. *Global Hepatitis Report 2024*. Geneva, Switzerland: World Health Organization; 2024. Accessed June 28, 2025.
2. World Health Organization. *Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.* Geneva, Switzerland: World Health Organization; 2024.
3. Department of Health. *Thematic Report on Viral Hepatitis (Population Health Survey 2020–22).* Hong Kong SAR: Government of the Hong Kong Special Administrative Region; 2023. Accessed June 19, 2025.
4. Health Bureau, The Government of the Hong Kong Special Administrative Region. *Primary Healthcare Blueprint.* December 19, 2022. Accessed August 5, 2025.
5. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations — *United States, 2023. MMWR Recomm Rep 2023*; 72(No. RR-1):1–25. DOI: http://dx.doi.org/10.15585/mmwr.rr7201a1
6. Weng MK, Doshani M, Khan MA, et al. Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. *MMWR Morb Mortal Wkly Rep 2022*;71:477–483. DOI: http://dx.doi.org/10.15585/mmwr.mm7113a1
7. Klepser ME, Adams AJ, Srnis P, Mazzucco M, Klepser D. U.S. community pharmacies as CLIA-waived facilities: Prevalence, dispersion, and impact on patient access to testing. *Res Social Adm Pharm.* 2016;12(4):614-621. doi:10.1016/j.sapharm.2015.09.006
8. McMillan SS, Chan H, Hattingh LH. Australian Community Pharmacy Harm-Minimisation Services: Scope for Service Expansion to Improve Healthcare Access. *Pharmacy (Basel).* 2021;9(2):95. Published 2021 Apr 26. doi:10.3390/pharmacy9020095
9. Health NSW. Pharmacist initiation and administration of vaccines under clause 48A (Poisons and Therapeutic Goods Regulation 2008, NSW): expanded authorisation includes hepatitis B vaccine. Updated April 17, 2025. Accessed August 2025.
10. Queensland Health. Extended Practice Authority—Pharmacists: inclusion of hepatitis B vaccine under EPA framework. Medicines and Poisons (Medicines) Regulation 2021, amended SL 2023 No 0152. Effective July 1, 2025. Accessed August 2025.
11. Buchanan R, Hassan-Hicks P, Noble K, Grellier L, Parkes J, Khakoo S. Integrating community pharmacy testing for hepatitis C with specialist care. *Clinical Pharmacist.* Published online January 1, 2016. doi:10.1211/cp.2016.20201549
12. Hui Z, Yu W, Fuzhen W, et al. New progress in HBV control and the cascade of health care for people living with HBV in China: evidence from the fourth national serological survey, 2020. *Lancet Reg Health West Pac.* 2024;51:101193. Published 2024 Sep 14. doi:10.1016/j.lanwpc.2024.101193
13. Liu X, Qiu W, Liang Y, et al. Effect of a Community-Based Hepatitis B Virus Infection Detection Combined with Vaccination Program in China. *Vaccines (Basel).* 2021;10(1):19. Published 2021 Dec 24. doi:10.3390/vaccines10010019
14. Feng Z, Ye Y, Ye H, Tang Z. Changes in pharmaceutical retail market and regional inequality of community pharmacists accessibility in mainland China: a retrospective cross-sectional study. *BMJ Open.* 2022;12(11):e063739. Published 2022 Nov 21. doi:10.1136/bmjopen-2022-063739
15. Hayes MJ, Beavon E, Traeger MW, et al. Viral hepatitis testing and treatment in community pharmacies: a systematic review and meta-analysis. *EClinicalMedicine.* 2024;69:102489. Published 2024 Feb 27. doi:10.1016/j.eclinm.2024.102489
16. Viral Hepatitis Control Office, Department of Health. *Management of Adult Patients with Chronic Hepatitis B in Primary Care.* Hong Kong SAR: Government of the Hong Kong Special Administrative Region. Published September 2023. Accessed August 5, 2025.
17. Hospital Authority. Hospital Authority: *Waiting Time for New Case Booking for Specialist Out-patient Services.* Accessed August 5, 2025.
18. Viral Hepatitis Control Office, Department of Health. *Mother-to-child Transmission of Hepatitis B.* Hong Kong SAR: Government of the Hong Kong Special Administrative Region. Published 2023. Accessed May 25, 2025. https://www.hepatitis.gov.hk/english/mtct/maternal_transmission_of_hepatitis_b.html.
19. Chan HLY, Wong GLH, Wong VWS, Wong MCS, Chan CYK, Singh S. Questionnaire survey on knowledge, attitudes, and behaviour towards viral hepatitis among the Hong Kong public. *Hong Kong Med J.* 2022;28(1):45-53. doi:10.12809/hkmj219463
20. Lee MT, Lee JS, Cheung CL, Mak LL. Knowledge and perception of chronic hepatitis B infection and attitude towards point-of-care testing among the general population in primary care settings in Hong Kong [abstract]. Presented at: EASL Congress 2025; May 10, 2025; Amsterdam, The Netherlands.
21. Lee KHT, Cheung GD, Law KKK, Lee MT, Cheng FJT, Wan EYF, Wong ICK. Jockey Club PHARM+ Community Medication Service Network - Roundtable Meeting on Scope of Community Pharmacy Services in Evolving Primary Healthcare Model. *HKPharm J.* 2025;32(1):24. https://hkpj.org/en/blog-detail.php?id=89
22. So SPY, Yung JCH, LiAYT, Lee MT, Wong JKT, Cheng FWT, Lam MPS, Chiu PKL, Wong ICK. Primary Care Pharmacy – A Review of Current Situation and Future in Hong Kong. *HKPharm J.* 2024;31(1):21-28. https://www.hkpj.org/en/blog-detail.php?id=62&vol=75

Highlights from PHARM+Excellence 2025: Driving Standards and Innovation in Primary Healthcare Pharmacy

Theme: Shaping the Future of Primary Healthcare Pharmacy: Quality Standards, Interprofessional Collaboration and Research

LEE, Marco Tsun[a†]; LAW, Kitty Kit Ki[a†]; Tommy Ka Ho[a]; CHEUNG, Gladys Daphne[a]; CHENG, Franco Wing Tak[a]; HUNG, Anchor Tak Fung[a]; NG, Vanessa Wai Sei[a]; YIU, Hei Hang Edmund[a]; WAN, Eric Yuk Fai[a,b]; WONG, Ian Chi Kei[a*] *([†]Co-first authors with equal contributions) (*Corresponding author)*

[a] Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[b] Department of Family Medicine and Primary Care, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

1. EXECUTIVE SUMMARY

PHARM+Excellence 2025: Driving Standards and Innovation in Primary Healthcare Pharmacy was successfully held on 21 June 2025 at the HKUMed Campus. The conference brought together over 370 participants, including healthcare professionals, academics, policymakers, and social service providers, to explore strategies for advancing community pharmacy services in primary healthcare.

Under the theme "Shaping the Future of Primary Healthcare Pharmacy: Quality Standards, Research, and Interprofessional Collaboration", the event featured a comprehensive programme of keynote speeches, expert panels, interactive symposiums, poster presentations, and a pre-conference community pharmacy tour. These sessions highlighted innovations in service delivery, evidence-based practices, interprofessional education, and policy alignment.

The conference served as a pivotal platform for cross-sector dialogue, professional development, and collaborative action, reinforcing the critical role of pharmacists in achieving accessible, integrated, and patient-centered primary healthcare. Notably, over 90% of participants agreed that the conference was a valuable learning experience, affirming its impact and relevance to current primary care challenges and reform directions.

The conference also served as a catalyst for post-event actions, with key strategic directions identified:

I. Translating Insights into Policy and Practice
   - Consolidating conference learnings to inform clinical guidelines, service standards, and ongoing policy consultations supporting the Government's Primary Healthcare Blueprint.

II. Strengthening Professional Capacity and Service Quality
   - Consolidating conference learnings to inform clinical guidelines, service standards, and ongoing policy consultations supporting the Government's Primary Healthcare Blueprint.

III. Sustaining Stakeholder Engagement
   - Leveraging the PHARM+ Network to co-develop new care models, share knowledge, and address emerging community needs.

IV. Fostering International Collaboration
   - Building global partnerships for joint research, training exchanges, and service benchmarking.

The success of PHARM+Excellence 2025 marks a key milestone in the ongoing efforts to elevate the role of pharmacists in the primary healthcare system.

2. OBJECTIVES OF THE CONFERENCE

- To promote the development and implementation of quality standards in community pharmacy services within the primary healthcare setting.
- To showcase innovative service models, research findings, and best practices in primary healthcare pharmacy both locally and internationally.
- To strengthen interprofessional collaboration and education across healthcare, academic, and social service sectors for holistic patient care.
- To align community pharmacy services with governmental healthcare policies and reform directions, contributing to an integrated primary healthcare system.
- To foster professional development and capacity building among pharmacists and primary healthcare providers through knowledge exchange and strategic dialogue.
- To cultivate a platform for networking, collaboration, and stakeholder engagement that supports the continuous advancement of people-centered care.

3. CONFERENCE HIGHLIGHTS

The PHARM+Excellence 2025 featured a robust and multidisciplinary programme that highlighted the evolving role of pharmacists in Hong Kong's primary healthcare system. The event provided a timely platform to reflect on the achievements of the Jockey Club PHARM+ Community Medication Service Network (JC PHARM+ Project), and to explore pathways for scaling up pharmacist-led services as part of healthcare reform.

Opening Ceremony

The ceremony opened with remarks from leaders in academia, government officials, and healthcare, affirming the critical role of pharmacy in primary healthcare transformation. Professor Chak Sing Lau, Dean of Li Ka Shing Faculty of Medicine, The University of Hong Kong, welcomed participants, followed by welcome speeches from Dr. Fei-chau Pang (Commission for Primary Healthcare, Health Bureau, Hong Kong SAR Government), Professor Sophia Chan (Convenor, Advisory Committee, JC PHARM+ Project), and Professor Ian Wong

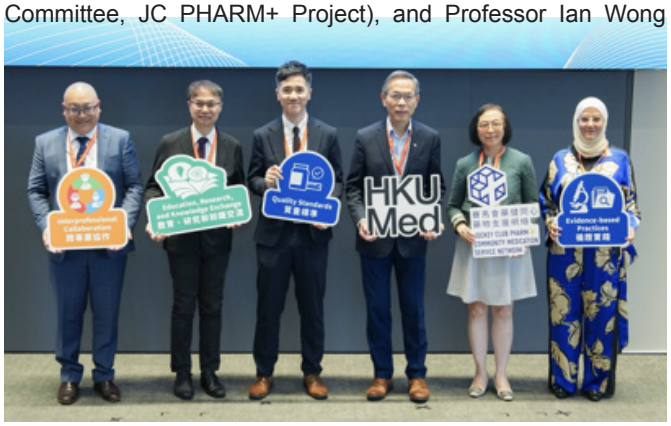


***Photo 1**. Opening Ceremony of PHARM+Excellence 2025*

***Photo 2**. Opening Ceremony of PHARM+Excellence 2025*

(Principal Investigator, JC PHARM+ Project). Collectively, the speakers reaffirmed that strengthening pharmacy practice is central to achieving the government's Primary Healthcare Blueprint, particularly in preventive care, chronic disease management, and care continuity at the community level. **(Photo 1 & 2)**

Keynote Speeches

Dr. Tony Ha, Assistant Commissioner for Primary Healthcare 2, Health Bureau, Hong Kong SAR Government, presented the government's roadmap for integrating community pharmacies into Hong Kong's primary healthcare system. He highlighted the pressing need to address an ageing population and rising chronic disease burden through accessible, pharmacist-led care in the community. Citing the Chronic Disease Co-Care (CDCC) Pilot Programme, Dr Ha illustrated how community pharmacy can support early detection, improve health outcomes, and reduce system costs. A key focus was the development of service models and quality standards under the Primary Healthcare Commission, including a Guideline of Practice for Community Pharmacy, a sub-directory for pharmacists under the Primary Care Directory (PCD), and a Community Drug Formulary (CDF). These initiatives will be piloted within DHC networks and progressively scaled. He emphasized the role of digital health tools such as eHealth+ in supporting service integration. **(Photo 3)**

***Photo 3**. Keynote Speech by Dr. Tony Ha*

Professor Timothy Chen, Professor of Medication Management, School of Pharmacy, The University of Sydney and International Advisor of JC PHARM+ Project, provided an international perspective on advancing quality standards in pharmacy-led primary care. Drawing on models from Australia, the UK, the USA, and Japan, he emphasized the global trend toward expanded roles for pharmacists in delivering medication management, chronic disease services, and preventive care. He underscored the importance of establishing measurable structures, processes, and outcomes using the Donabedian model, and highlighted quality indicators and system-level enablers such as workforce training, digital readiness, and medicines policy. Professor Chen advocated for continuous quality improvement based on the ECHO (Economic, Clinical, Humanistic Outcomes) model and called for greater integration of pharmacists into team-based primary care to improve health outcomes and service sustainability. **(Photo 4)**

***Photo 4**. Keynote Speech by Professor Timothy Chen*

These keynotes set the tone for the conference by aligning policy priorities with on-the-ground innovation and situating the development of community pharmacy in Hong Kong within a global context.

Panel Discussion: The Future of Quality Standards in Primary Healthcare Pharmacy

Moderated by Professor Sophia Chan, the panel brought together Dr. Tony Ha, Professor Timothy Chen, and Professor Ian Wong to explore how quality in community pharmacy can be defined, measured, and scaled within Hong Kong's evolving primary healthcare landscape. **(Photo 5)**

***Photo 5**. Panel Discussion on The Future of Quality Standards in Primary Healthcare Pharmacy*

Key insights emerged across several key dimensions:

- Professor Timothy Chen reinforced ECHO model as a comprehensive framework for assessing service quality in primary healthcare pharmacy. He emphasized that robust and multi-dimensional outcome measures, including clinical effectiveness, patient satisfaction, and cost-efficiency, are essential for driving quality improvement and demonstrating value to stakeholders.

- Professor Ian Wong highlighted the PHARM+ Network's role as a testbed for quality development, sharing that structured service protocols, real-time patient feedback systems, and internal evaluation mechanisms are being developed to support continuous quality improvement. He also emphasized the profession's ongoing effort to enhance public awareness of primary healthcare and to clarify the expanding role of community pharmacists as integral care providers.

- Dr. Tony Ha reinforced the importance of system-level enablers, such as service commissioning, district-based care models, and sustainable funding, to support pharmacist-led care. He cited the CDCC Pilot Programme as a successful example of how structured primary care services can improve early detection, patient outcomes, and cost-effectiveness. He also emphasized how visibility through accreditation of service providers, guideline development, and quality assurance mechanisms can enhance accountability and encourage participation in government-supported programmes.

Looking ahead, the panel collectively envisioned pharmacists as core members of the primary care team, empowered by clear role definitions, inter professional training, data-sharing infrastructure, and ongoing evaluation. The discussion reinforced that quality in pharmacy must be both evidence-informed and system-supported, with strong alignment to health policy, patient needs, and service sustainability.

Symposium 1: Establishing Quality Standards in Community Pharmacy

This session examined strategies to define, implement, and sustain quality across diverse community pharmacy settings in Hong Kong and Macau.

- Dr. Franco Cheng, Lecturer from Department of Pharmacology and Pharmacy at the University of Hong Kong, shared a structured approach to service standardization, including the development of operational manuals, pharmacist training, and quality management protocols. He emphasized the importance of embedding continuous improvement into everyday practice to uphold care standards.

- Mr. William Chui, Chief Pharmacist at the Hospital Authority, presented the Hospital Authority's accreditation experience and outlined the principles of accreditation, including integrity, transparency, and evidence-based practice, as crucial foundations. He advocated applying these principles to community pharmacy, highlighting patient safety, regulatory compliance, and staff competence as core pillars.

- Ms. Carol Chow, Head of Pharmacy and Research at Gleneagles Hospital Hong Kong, showcased how Gleneagles Hospital Hong Kong adapted private hospital pharmacy standards for its Community Pharmacy. She illustrated a governance model integrating clinical education, HKU oversight, continuous quality improvement of pharmacy services, and regulatory compliance. The Community Pharmacy will support upcoming government primary healthcare initiatives and innovative services development.

- Mr. João Lei, Chefe de Divisão de Farmácia, Serviços de Saúde de Macau, discussed Macau's experience in implementing a drug refill service supported by a centralized IT system for prescription tracking and patient engagement. He described how continuous service improvement can safeguard medication safety and support primary heathcare development in Macau.

Together, the panel underscored the need for a unified quality assurance framework tailored to the community setting, supported by inter professional governance, workforce development, and scalable digital infrastructure. Their experiences collectively pointed toward a future where quality in community pharmacy is standardized, measurable, and embedded within the broader primary healthcare ecosystem. **(Photo 6)**

***Photo 6**. Panel Discussion in Symposium 1: Establishing Quality Standards in Community Pharmacy*

Symposium 2: Interprofessional Education and Collaboration in Primary Healthcare

This session emphasized the importance of team-based care and interprofessional education (IPE) in building an integrated primary healthcare system. Speakers shared successful models of collaboration that position pharmacists as core contributors to holistic patient care.

- Ms. Jody Chu, Senior Lecturer from Department of Pharmacology and Pharmacy at the University of Hong Kong, described how HKUMed's community pharmacy placements expose students to IPE in real-world environments.

- Professor Vivian Lee, Associate Professor from Centre for Learning Enhancement And Research (CLEAR) at The Chinese University of Hong Kong, presented compelling evidence from international and local studies showing how IPE enhances competencies in communication, collaboration, and shared decision-making. She advocated for integrating IPE across the education continuum to foster system-wide impact.

- Dr. Ning Fan, Founder of Health in Action, shared community-based experiences of pharmacists managing social determinants of health. He highlighted that pharmacists, when trained to collaborate with NGOs and social workers, can go beyond dispensing to address complex, patient-centred needs in vulnerable populations.

- Ms. Catherine Wong, Multicultural Pharmacy Service Coordinator of Health in Action, outlined the 5E's approach, including exploration, engagement, education, empowerment, and experience, to experiential pharmacy education, aiming to address multicultural health needs and challenges.

- Mr. Shek Ming Leung, Lecturer from Department of Pharmacology and Pharmacy at the University of Hong Kong, showcased a collaborative mental health service involving pharmacists, nurses, and social workers. Using a structured Medication Management Service, the team successfully deprescribed inappropriate psychotropics for people with intellectual disabilities, showing the power of multidisciplinary input and non-pharmacological strategies. **(Photo 7)**

***Photo 7**. Panel Discussion on Symposium 2: Interprofessional Education and Collaboration in Primary Healthcare*

The symposium concluded with a discussion on how embedding pharmacists into interdisciplinary pathways not only enhances care quality but also supports workforce resilience. A working group under the HKU Comprehensive Primary Healthcare Collaboratory is now developing a new curriculum to deepen interprofessional competencies through experiential learning and professional shadowing across sectors.

Symposium 3: Innovations and Insights from Research in Primary Healthcare

This symposium showcased how evidence from local studies and pilots informs practice transformation and supports policy development in primary care pharmacy.

- Dr. Edmund Yiu, Research Assistant Professor from Department of Pharmacology and Pharmacy at the University of Hong Kong, shared qualitative findings from the PHARM+ Network, highlighting that pharmacist-led services like Minor Ailment Service (MAS) and Medication Management Services (MMS) improved patient engagement and service delivery. He emphasized that cross-sector collaboration, training, and public awareness are essential for scaling these innovations in primary care.

- Professor Eric Wan, Assistant Professor from Department of Pharmacology and Pharmacy and Department of Family Medicine and Primary Care at the University of Hong Kong, presented the interim outcomes of the CDCC Pilot Scheme, showcasing

how the program significantly improved clinical parameters and projected a potential prevention of over 9,000 cardiovascular events and 11,000 deaths over 10 years at just 10% population uptake. He emphasized pharmacists' contributions and the scheme's cost-effectiveness, advocating for its broader adoption across Hong Kong.

- Professor Celine Chui, Assistant Professor from School of Nursing at the University of Hong Kong, introduced the P-CARDIAC model, an AI-powered cardiovascular risk prediction tool tailored for Chinese populations, demonstrating its integration into pharmacist-led services and its potential to enhance risk communication and early prevention in primary care.

- Professor Peter Tanuseputro, Clinical Professor from Department of Family Medicine and Primary Care at the University of Hong Kong, called for a shift from hospital-centric end-of-life care to early, community-based palliative interventions, aligned with patients' preferences to age and die at home. He emphasized the vital role pharmacists can play in home-based care teams, particularly in medication support and symptom relief. **(Photo 8)**

***Photo 8**. Panel Discussion on Symposium 3: Innovations and Insights from Research in Primary Healthcare*

These studies validate the clinical and system-level impact of pharmacist-led services and support further investment in community-based research and evaluation. During the discussion, the speakers believed that policy changes or stakeholder collaboration are essential for scaling up innovations. Key strategies include increasing public awareness, addressing community health needs, establishing referral pathways for interprofessional communication and collaboration, advocating for top-down policy from the Government, and exploring thesuccessful overseas models.

Poster Presentations

The PHARM+Excellence 2025 featured eleven practice abstracts that showcased pioneering efforts in advancing pharmacy services, informatics, and multidisciplinary collaboration in Hong Kong's evolving primary healthcare system. These diverse initiatives reflect growing momentum toward integrating community pharmacy into patient-centred, preventive, and data-informed care. Collectively, these initiatives demonstrate that community pharmacists are increasingly positioned as key contributors to an integrated, person-centered primary healthcare system. From clinical service delivery to public education and digital innovation, the abstracts highlight scalable models that align with Hong Kong's Primary Healthcare Blueprint and global trends in pharmacy-led care. **(Photo 9)**

***Photo 9**. Poster Exhibition in PHARM+Excellence 2025*

4. PRE-CONFERENCE COMMUNITY PHARMACY TOUR

As a prelude to the PHARM+Excellence 2025, a Pre-conference Community Pharmacy Tour was organized on 19–20 June 2025, offering participants the opportunity to gain first-hand insight into the operational models, service delivery innovations, and interdisciplinary collaborations that define Hong Kong's evolving community pharmacy landscape. A total of seven site visits were conducted across the PHARM+ Community Medication Service Network and other NGO-operated pharmacies. Each session was hosted by frontline pharmacists and programme leaders, with tailored walkthroughs and interactive briefings. **(Photo 10 & 11)**

***Photo 10**. Pre-conference Community Pharmacy Tour in PHARM+ Hong Kong Sheng Kung Hui Community Pharmacy*

***Photo 11**. Pre-conference Community Pharmacy Tour in PHARM+ Pok Oi Hospital Community Pharmacy*

5. IMPACT AND FOLLOW-UP ACTIONS

The PHARM+Excellence 2025 served as a catalyst for advancing the role of pharmacists in primary healthcare and reinforced the importance of cross-sector collaboration, evidence-based practice, and service innovation. The positive impact of the conference was reflected in post-event feedback, with over 90% of participants agreeing that the event was a valuable learning experience. Building on the insights shared throughout the conference, several strategic directions have been identified for post-conference action:

Translating Insights into Policy and Practice

Key themes and recommendations from keynote speeches, symposium discussions, and panel dialogue will be consolidated into a summary report to inform ongoing policy consultations, particularly in support of the Government's Primary Healthcare Blueprint. These insights will also guide the development and refinement of clinical guidelines, service standards, and operational protocols for community pharmacy services.
Strengthening Professional Capacity and Service Quality
Targeted training and professional development workshops will be organized under the PHARM+ initiative to upskill pharmacists and frontline staff. Priority areas include minor ailment service delivery, chronic disease management, interprofessional collaboration, and quality assurance. These efforts aim to promote consistency, enhance service quality, and empower community pharmacists to take on expanded clinical roles in primary care.

Sustaining Stakeholder Engagement through the PHARM+ Network

The PHARM+ Network will continue to serve as a collaborative platform for pharmacists, academics, healthcare providers, and NGOs. Post-conference engagement will include follow-up meetings, knowledge-sharing forums, and working groups to co-develop innovative care models, evaluate service outcomes, and pilot new initiatives in response to emerging community needs.

Fostering International Collaboration

Building on the participation of international speakers and collaborators, the PHARM+ team will explore opportunities for joint research, training exchanges, and comparative studies with overseas institutions. These partnerships will support the global benchmarking of local pharmacy services and facilitate the adoption of best practices across borders.

6. Acknowledgements

The Organizing Committee of PHARM+Excellence 2025 extends its sincere thanks to all who contributed to the success of this event. We are especially grateful to our speakers, moderators, panelists, and poster presenters for their invaluable insights, which enriched discussions and advanced the dialogue on the future of primary healthcare pharmacy. We also thank our partners from the University of Hong Kong, the Health Bureau, community pharmacy networks, academic institutions, NGOs, and healthcare professionals for their active engagement and ongoing support. Our heartfelt appreciation goes to the Hong Kong Jockey Club Charities Trust for their visionary support of the JC PHARM+ Project. Their generous funding and strategic guidance have been instrumental in driving innovation, service development, and capacity building in community pharmacy to support primary healthcare development in Hong Kong. Together, we are shaping a more integrated, accessible, and patient-centered primary healthcare system with community pharmacists as key enablers of community care.

Author's background
LEE, Marco Tsun *is the Senior Pharmacist at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is marcolt@hku.hk*
LAW, Kitty Kit Ki *is the Pharmacist at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. Her email is kittylkk@hku.hk*
LEE, Tommy Ka Ho *is the Pharmacist at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is tkhlee@hku.hk*
CHEUNG, Gladys Daphne *is the Pharmacist at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. Her email is gdcheung@hku.hk*
CHENG, Franco Wing Tak *is the Lecturer at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is francowt@hku.hk*
HUNG, Anchor Tak Fung *is the Assistant Project Director at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. Her email is anchor01@hku.hk*
NG, Vanessa Wai Sei *is the Post-Doctoral Fellow at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. Her email is vanwsng@hku.hk*
YIU, Hei Hang Edmund *is the Research Assistant Professor at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is hheyiu@hku.hk*
WAN, Eric Yuk Fai *is the Assistant Professor at the Department of Family Medicine and Primary Care and the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is yfwan@hku.hk*
WONG, Ian Chi Kei *is the Professor at the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong. His email is wongick@hku.hk*