

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

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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)

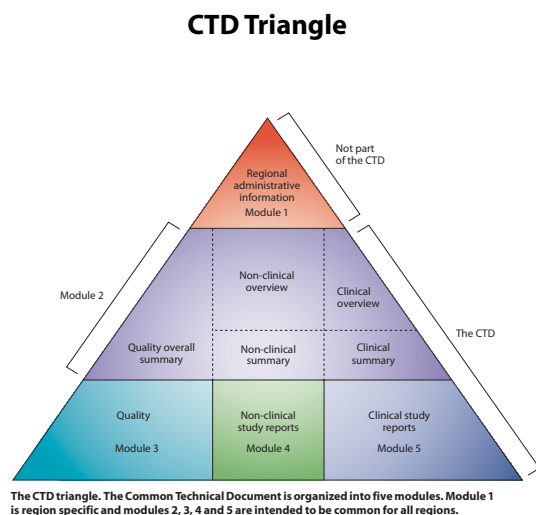


Figure 1: The CTD Triangle⁽⁵⁾

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 Coltalain-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.⁽⁶⁾

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.⁽⁶⁾

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)

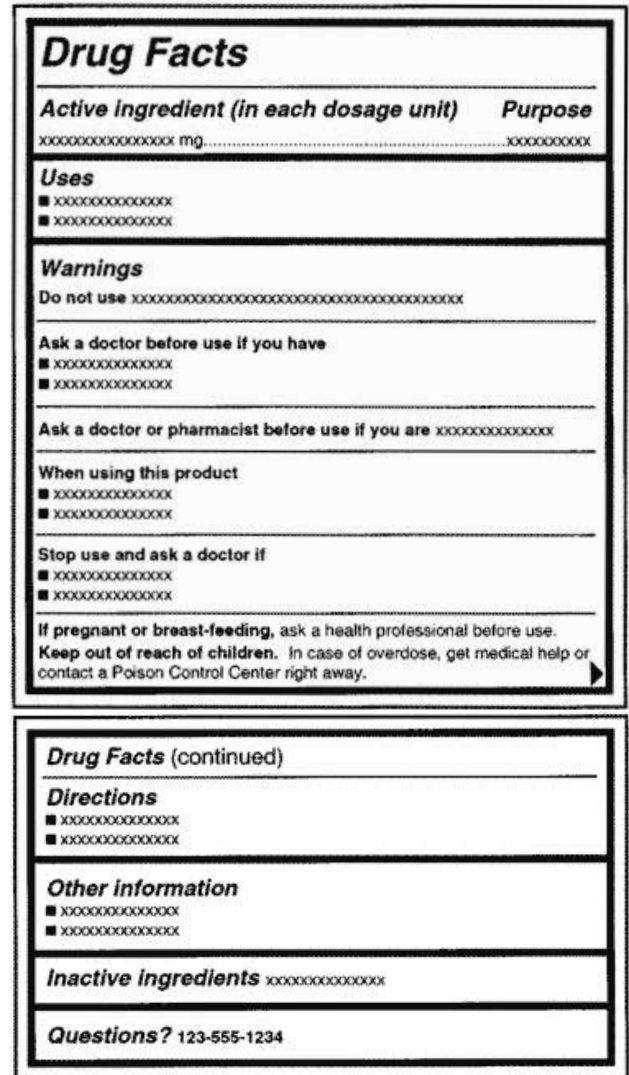


Figure 2: Drug Facts Label Outline in the United States⁽¹⁶⁾

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⁾

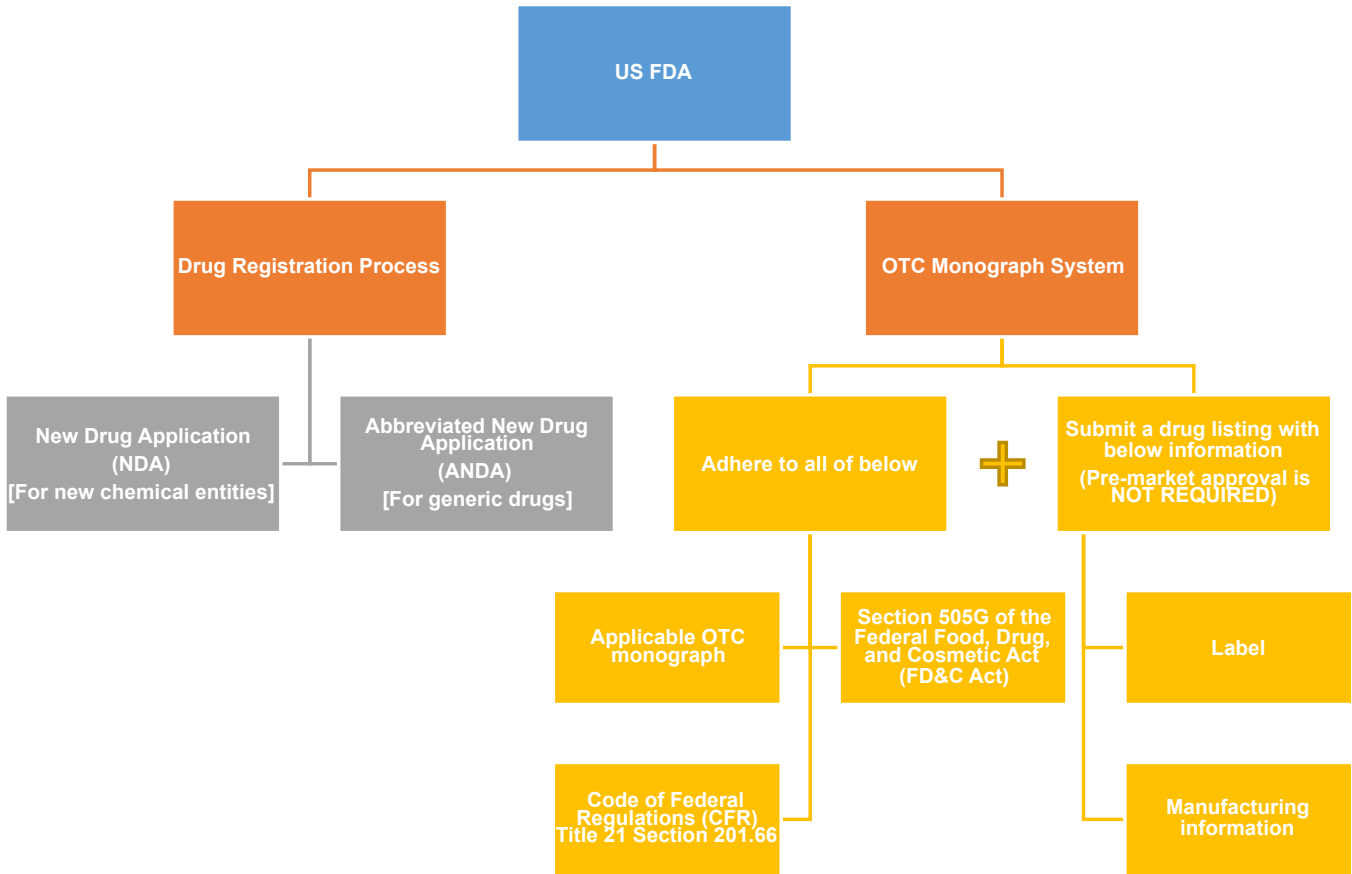
Health Canada shares a similar approach to labeling requirements as the U.S. FDA, emphasizing the importance of a standardized format (i.e. the Drug Facts Table) to enhance consumer understanding. Health Canada has issued guidance documents, such as the "Guidance Document: Drug Facts Table for Non-Prescription 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 *XXXXXXXX *XXXXXX *XXXXXXXXXX	
Warnings	
Allergy alert May cause a severe allergic reaction.	
Do not use if *XXXXXX *XXXXXX *XXXXXXXXXXXXXXXXXXXX *XXXXXXXXXXXX	
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 *XXXXXXXXXXXXXXXXXXXX *XXXXXXXXXX *XXXXXXXXXX XXXXXXXX *XXXXXXXXXXXXXXXXXXXX *XXXXXXXX XXXX	
Keep out of the reach of children. In case of an overdose, call a poison control centre or get medical help right away. ▼	

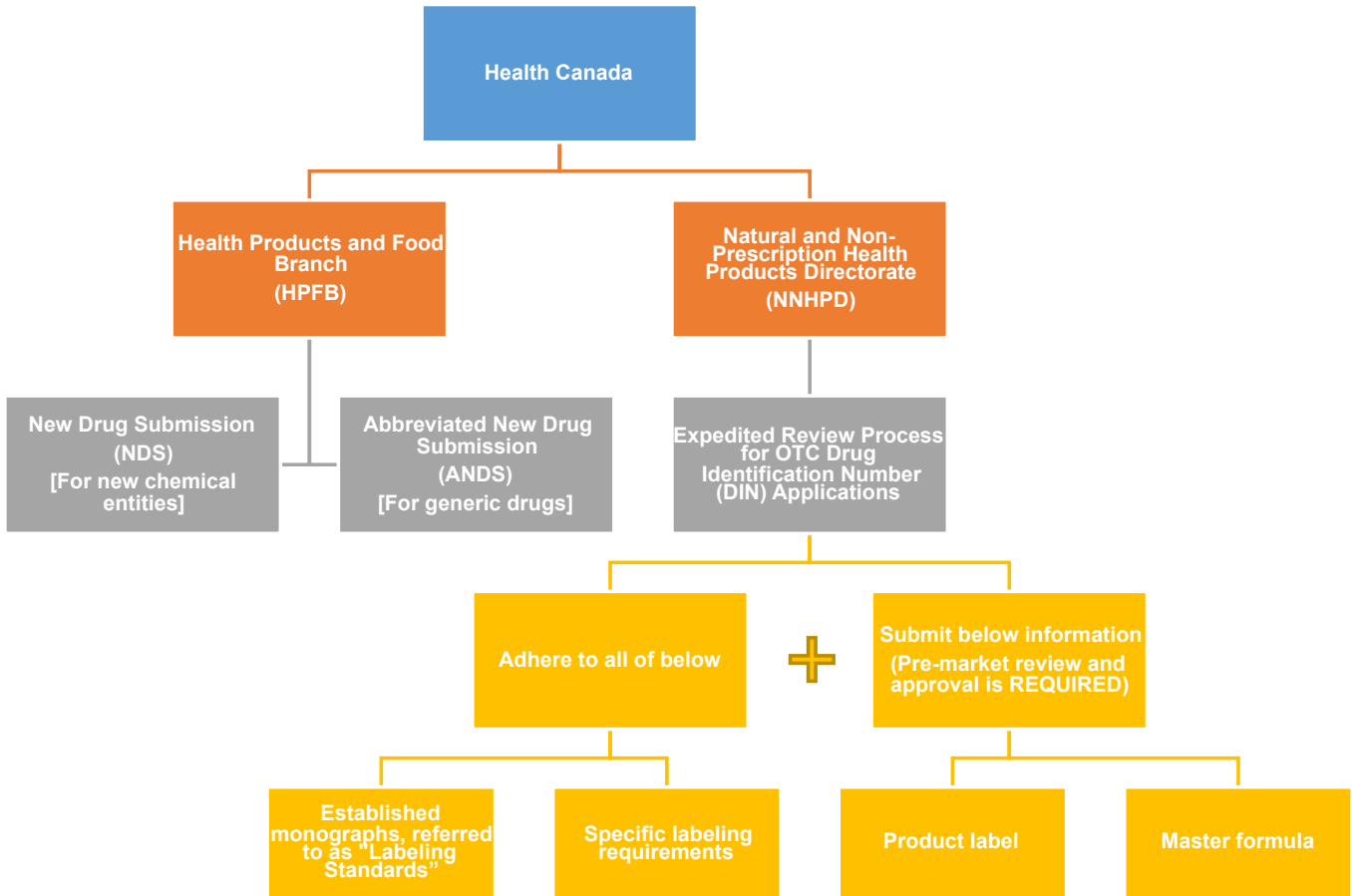
Drug Facts (continued)		
Directions		
Do not chew tablets.		
Children under 6 years		Ask a doctor
Children 6-12 years	x tablet(s) every y hours as needed	Do not take more than Z tablets in 24 hours
Children over 12 years, and adults	X tablets every Y hours as needed	Do not take more than Z tablets in 24 hours
Other information		
Store at room temperature (15-30° C).		
Inactive ingredients		
List of NMI's List of NMI's List of NMI's List of NMI's		
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 EXPEDITED 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.

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