DRUG CLASSIFICATION SCHEME REVIEW AND THE ECONOMIC IMPACT ANALYSIS OF ABANDONING NON-PRESCRIPTION DRUG REIMBURSEMENT IN THAILAND.

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ดวงพร ลีลาวณิชย์ : การทบทวนระบบการแบ่งประเภทยาและการวิเคราะห์ผลกระทบทางเศรษฐศาสตร์ของการยกเลิกการเบิกจ่ายยาที่ไม่ต้องสั่งโดยแพทย์ในประเทศไทย. (DRUG CLASSIFICATION SCHEME REVIEW AND THE ECONOMIC IMPACT ANALYSIS OF ABANDONING NON-PRESCRIPTION DRUG REIMBURSEMENT IN THAILAND.) อ.ที่ปรึกษาหลัก : รศ. ภญ. ร.ต.ท.หญิง ดร.ภูรี อนันตโชติ

ข้อขัดแย้งเกี่ยวกับระบบการแบ่งประเภทยาในประเทศไทยนั้นมีอยู่อย่างต่อเนื่อง ทั้งในเรื่องของจำนวนประเภทยาและการจัดยาเข้าไปในแต่ละประเภทที่หลายคนคิดเห็นว่าไม่เหมาะสม นอกจากนี้ระบบการแบ่งประเภทยาในประเทศไทยยังไม่ถูกนำไปใช้ในการจัดสรรงบประมาณด้านสุขภาพมาก่อน ในขณะที่ในประเทศอื่นมีการนำระบบมาใช้ โดยยกเลิกการเบิกจ่ายยาที่ไม่ใช้ใบสั่งแพทย์ เพื่อที่จะนำรายจ่ายของยาเหล่านี้ไปจัดสรรให้กับยารักษาโรคที่มีค่าใช้จ่ายสูงแทน ดังนั้นการศึกษานี้จึงมีจุดมุ่งหมายเพื่อ (1) ทบทวนระบบการแบ่งประเภทยาในประเทศไทยโดนเปรียบเทียบกับประเทศอื่นๆ (2) ประเมินผลกระทบทางเศรษฐศาสตร์เมื่อยกเลิกการเบิกจ่ายยาที่ไม่ใช้ใบสั่งแพทย์ โดยใช้ยาต้านฮิสตามีนชนิดไม่ง่วงในผู้ป่วยโรคภูมิแพ้จมูกที่มีอาการเป็นช่วงๆเป็นกรณีศึกษา และ (3) พัฒนาระบบการแบ่งประเภทยาแบบใหม่ในประเทศไทยจากผลการศึกษา ในการศึกษาส่วนแรก จะทำการเปรียบเทียบระบบการแบ่งประเภทยาของประเทศไทย กับสหรัฐอเมริกา สหราชอาณาจักร ญี่ปุ่น สิงคโปร์ มาเลเซีย ฟิลิปปินส์ และ แคนาดา ประเภทยาและเกณฑ์การแบ่งถูกศึกษาโดยใช้วิธีทบทวนวรรณกรรมอย่างเจาะจง จากนั้นประเภทยาที่ถูกจัดในแต่ละประเทศของยา 53 ตัว ถูกนำมาเปรียบเทียบ สำหรับการศึกษาในส่วนที่สอง ใช้ decision tree model ในการศึกษาผลกระทบต่องบประมาณที่เกิดขึ้นจากมุมมองระบบสุขภาพ โดยเปรียบเทียบจากการเบิกจ่ายแบบปัจจุบัน (นโยบายที่ 1) กับการยกเลิกการเบิกจ่ายยาต้านฮิสตามีนชนิดไม่ง่วง (นโยบายที่ 2) ผลลัพธ์หลักที่สนใจคือค่าใช้จ่ายที่ลดลง มีการจัดทำการวิเคราะห์ความไว ผลการศึกษาพบว่า ทั้งแปดประเทศที่มีการจัดแบ่งประเภทยาออกเป็นสองกลุ่มหลัก ได้แก่ ยาที่ใช้ใบสั่งแพทย์และยาที่ไม่ใช้ใบสั่งแพทย์ บางประเทศมีการแบ่งยาที่ไม่ใช้ใบสั่งแพทย์ออกเป็นกลุ่มย่อยอีกการศึกษายังพบว่ายาที่นำมาศึกษานั้นมักจัดประเภทเป็นยาอันตราย (ยาที่ต้องจ่ายโดยเภสัชกร) ในประเทศไทย ทั้งยาต้านฮิสตามีน ยาลดความดัน ไปจนถึงวัคซีน ชาวไทยสามารถเข้าถึงยาที่ถูกจัดประเภทเป็นยาที่ต้องใช้ใบสั่งแพทย์ในประเทศอื่นได้ง่ายกว่าเนื่องจากไม่ต้องใช้ใบสั่งแพทย์ ตัวอย่างเช่น ยาปฏิชีวนะและยาลดความดัน สำหรับผลกระทบทางเศรษฐศาสตร์ของนโยบายแบบใหม่ ผลการศึกษาพบว่า เมื่อยกเลิกการเบิกจ่ายยาต้นฮิสตามีนชนิดไม่ง่วงและเมื่อความน่าจะเป็นในการไปพบแพทย์ลดลงจาก 70% มายัง 30% ประเทศไทยจะประหยัดค่าใช้จ่ายไปจำนวน 2.24 พันล้านบาท (72.39 ล้านดอลลาร์สหรัฐ) ตัวแปรที่มีผลต่อผลการศึกษามากที่สุดคือ ความน่าจะเป็นในการไปพบแพทย์ นโยบายที่ 2 จะทำให้ค่าใช้จ่ายลดลงได้ก็ต่อเมื่อความน่าจะเป็นในการไปพบแพทย์ลดลงจนถึงจุดหนึ่ง ขึ้นกับความน่าจะเป็นในการไปพบแพทย์ในนโยบายที่ 1 การศึกษานี้สรุปได้ว่าจำนวนประเภทยานั้นไม่ใช่ปัญหาสำคัญ แต่กลับเป็นการจัดยาเข้าไปในแต่ละ นโยบายการเบิกจ่ายยาแบบใหม่เป็นนโยบายที่ควรมีการนำมาประเมินเพื่อนำมาใช้ต่อไป ระบบการแบ่งประเภทยาแบบใหม่ที่นำเสนอจากการศึกษานี้ควรมีการพัฒนาต่อโดยการปรึกษาผู้เชี่ยวชาญและทำประชาวิจารณ์ และควรมีการรณรงค์ให้ประชาชนตระหนักถึงความสำคัญของการดูแลสุขภาพโดยตนเองต่อไป

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
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6278002833 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY

KEYWORD: drug classification, criteria, prescription, non-prescription, over-the-counter, reimbursement, healthcare policy, non-sedating antihistamines

Doungporn Leelavanich : DRUG CLASSIFICATION SCHEME REVIEW AND THE ECONOMIC IMPACT ANALYSIS OF ABANDONING NON-PRESCRIPTION DRUG REIMBURSEMENT IN THAILAND. . Advisor: Assoc. Prof. Pol.Lt. PUREE ANANTACHOTI, Ph.D.

In Thailand, controversies regarding the drug classification system persist; it was believed that the number of schemes should be changed, and most drugs classified into improper schemes. The system is not also fully used to allocate healthcare budgets, while several other countries cease non-prescription (OTC) drugs reimbursement to allocate this expenditure to catastrophic diseases instead. This study thus aims to (i) review drug classification system in Thailand by comparing to other countries, (ii) evaluate the economic impact of delisting OTC drugs from drug reimbursement list using non-sedating antihistamines (AH) in patients suffering from intermittent allergic rhinitis as a case study, and (iii) formulate an updated Thailand's drug classification system. For the first part; The US, the UK, Japan, Singapore, Malaysia, the Philippines and Canada were selected to compare. The schemes and written criteria were targeted review from each respective country's drug regulatory agency website, available published research, and expert interviews. The actual drug schemes of 53 selected drugs were then compared across different countries. For the second part, a decision tree model was used to conduct budget impact analysis using the healthcare system perspective to compare continuing (policy 1) vs abandoning reimbursement of non-sedating AH (policy 2). The primary outcome was cost-saving. Sensitivity analyses were performed. It was found that all eight countries classify drugs into two major categories: prescription and non-prescription drugs. Some countries further subclassify non-prescription drugs. Most selected drugs in Thailand are behind-the-counter drugs, varied from antihistamines, antihypertensives to vaccines. Thai people easier access to drugs that need prescriptions in other countries since no prescriptions required. For the economic impact, when assuming non-sedating AH were no longer reimbursed, and doctor (MD) visits were decreased from 70% to 30%, Thailand would save 2.24 billion baht (72.39 million USD). The most impact parameter is MD visit probability. Cost-saving can be achieved when decreasing MD visit probability in policy 2 to a particular point, depending on the MD visit probability in policy 1. In conclusion, the number of schemes in the drug classification system is not an issue, but putting drugs in schemes is. The new reimbursement policy of OTC drug is also worth considering policy. The updated system provided in this study should be further developed by expert consultations and public hearing. More campaigns to support self-care culture in Thai populations are required.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
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Doungporn Leelavanich

TABLE OF CONTENTS

LIST OF TABLE

LIST OF FIGURES

CHAPTER 1

Introduction

A drug classification scheme has been used by the governments as a healthcare strategy after drugs have been launched in the market. Regulations; regarding gate keepers, channels of drug distribution, advertisements, and reimbursement policies in certain countries; are differently implemented for each drug scheme.

Drugs are classified into different schemes by their characteristics. Major factors that affect the drug classification are self-diagnosis nature of diseases and safety profile of drugs. Catastrophic disease treatments and minor ailment treatments are usually classified into different schemes, which are prescription drugs and non-prescription drugs, respectively. Drug status can be re-classified downward or upward depending mainly on the safety information [1]. In the UK, diclofenac was re-classified upward from non-prescription to prescription status due to an increased risk of cardiovascular diseases [2]. Conversely, to increase drug accessibility, in the US, loratadine was re-classified from prescription to non-prescription status when its safety information was confirmed after placing on the market for nine years [3]. Besides, due to their limited healthcare budgets, governments in some countries, such as Germany, choose to allocate their budgets to reimburse prescription drugs, but not non-prescription drugs, for patients because they realize that drugs for catastrophic diseases need more financial supports from them than drugs for minor ailments. For example, ondansetron for highly emetogenic cancer chemotherapy is classified as a prescription and eligible for reimbursement, while paracetamol for fever are non-prescription drugs and non-reimbursable [4, 5]. It can be seen that dug regulatory agencies put a lot of efforts to classify drugs into appropriate categories to ensure patient safety, maximize timely access to drugs, and aid healthcare budget allocation.

Thailand's healthcare system was ranked 47th by World Health Organization [6]. Currently, all Thai citizens have been covered under one of the three public health insurance schemes: the National Health Security Office (NHSO), the Social Security Office (SSO) and the Civil Services Medical Benefits Scheme (CSMBS) [7]. The drug reimbursement list in Thailand, known as National list of essential medicines (NLEM), covers various drugs; varied from pain killers, antihistamines to antibiotics and chemotherapies. Thailand has approximately 13,405 public hospitals, 384 private

hospitals, 13,510 clinics, 17,069 type 1 community pharmacies, and 2,865 type 2 community pharmacies [8, 9]. Type 1 community pharmacies sell any types of drugs and require a pharmacist on duty during operating hours. Type 2 community pharmacies sell limited non-prescription drugs and allow other certified non-pharmacists on duty during operating hours. In 2005, the Ministry of Public health no longer authorized new type 2 community pharmacy licensing. The number of type 2 community pharmacies were projected to decline in the future [10].

The Thai FDA has classified drugs into four legal categories. Regulatory details of each drug classification scheme are shown in **Table 1** [11, 12].

Table 1: Current drug classification schemes and their regulatory details in Thailand

Classification scheme	Gate keeper	Prescription Requirement	Distribution channels			Direct-to-consumer advertising
			Hospital	Pharmacy	Retailer	
Controlled drugs	Physician	Yes	Yes	Yes	No	No
Dangerous drugs	Pharmacist	No	Yes	Yes	No	No
Non-dangerous drugs	None	No	Yes	Yes	No	Yes
Household remedies	None	No	Yes	Yes	Yes	Yes

Reference: [11, 12]

As of 2017, Thailand had more than 37,500 drugs registered with the Thai FDA [13]. Drugs in the following three schemes; controlled drugs, dangerous drugs and household remedies, must be enlisted and announced by the FDA. Drugs that not listed in the three mentioned categories are automatically classified as non-dangerous drugs [12]. Nonetheless, some pharmacists proposed that non-dangerous drug scheme should be discontinued. This controversy persists until now since the new Drug Act A.C. 2019 does not resolve this issue [14-16].

Compare to other countries, Thai people relatively easier access to drugs. Having easy access to medicines can initiate irrational use of drugs. Classic irrational drug use's examples are antibiotic resistance from antibiotics overuse; addiction from tramadol overuse; drug misuse, for example using hydrochlorothiazide for weight lost and using brown mixture and dextromethorphan to mixed with beverage or other illicit drugs for recreation purpose [17-20]. In contrary, some other drugs in Thailand are more difficult to access when compared to other countries. In Thailand, cetirizine and ibuprofen were kept behind the counter and must be dispensed by pharmacists, while

both drugs can be sold in retailers without healthcare professionals' involvement in the US and the UK [3, 21, 22].

Although the universal healthcare coverage has been implemented in Thailand; some catastrophic diseases, such as cancer and end stage renal disease; have not yet fully covered due to limited healthcare budgets [23-25]. As previously described that drug classification schemes can aid healthcare budget allocation, Thailand should consider delisting some minor ailment drugs, such as non-sedating antihistamines for intermittent allergic rhinitis. The cost saving from this approach would be further appropriately allocate to catastrophic diseases. This new policy is not a new idea, but already have been used in many countries in Europe, such as Germany and Italy [4, 26].

It can be seen that Thailand's drug classification scheme regulations have some controversies and not yet fully utilize as a financial healthcare strategy. Several research regarding drug classification scheme, but none of them conducted in Thailand's context [27-29]. While, the economic impact were conducted only in unpublished research in one therapeutic area: acute urticaria. This prompts the new research regarding this topic in Thailand. This study were then conducted to obtain the evidences by dividing in two parts: the review of drug classification scheme and the economic impact of delisting non-prescription drugs from NLEM in Thailand using non-sedating antihistamines as a case study.

Objective

1. To compare drug classification scheme across countries.

2. To evaluate the economic impact of the new reimbursement policy of non-prescription drug scheme from healthcare system perspective.

Expected outcome

1. The study intended to obtain the evidence that can be used to improve the drug classification scheme in Thailand.

2. The study intended to evaluate net benefits from new proposed reimbursement scenario for non-prescription drugs by using non-sedating antihistamines for intermittent allergic rhinitis as a case study.

CHAPTER 2

Literature review

1. Drug classification and re-classification system

There are many ways to classify drugs. Some are formal classifications, which are adopted from every countries. For example, classification by pharmacology: penicillin, beta blockers, etc., therapeutic classification: antibiotics, antihypertensives, etc. However, there are some classification that different among countries. Legal drug classification is one of them since each country has drug regulation in their own context.

To control drug use, the legal drug classification system has been used for grouping the drugs that need the similar management after the market approve. In Thailand, there are three bills cover the drug regulation:

- The Thai Drug Act 2019, which regulate general drugs, such as cancer treatments, anti-hypertension, antihistamines

- The Thai Narcotics act B.E.1979, which regulate narcotic drugs, such as opioid.

- The Psychotropic Substances Act, B.E. 2016, which regulate psychotropic drugs such as pseudoephedrine.

In the US, there is the Controlled Substance Act for controlling drugs that has potential to abuse, for example heroin, codeine and ketamine [30, 31]. In Canada, there is the Controlled Drugs and Substances Act, which similar to the Controlled Substance Act in the US [29].

However, legal drug classification whose common use is classification by the distribution channel to patients. Some countries have the same system; some are different. In the US, drugs are classified into Prescriptions (Drugs requiring prescription to be dispensed) and Over-the-counter drugs (Drugs that do not require prescription and can be sold in retailers) [32]. While in the UK, drugs are classified into Prescription-only drugs, Pharmacy-only drugs, and General-sale drugs [22]. In Thailand, there are four classes of drugs: Controlled drugs, which require a prescription; Dangerous drugs, that can be dispensed by pharmacists without prescription; Non-dangerous drugs

that must be sold in pharmacies, but do not require dispensal by pharmacists; and Household remedies that can be sold in retailers [11].

Legal drug classification is the major tool for controlling drug use and drug distribution. The more dangerous, the more stringent control. However, the stringent control can lead to difficult drug accessibility, which increase hospital burden and reimbursement from a government. It can be seen that to classify one drug into the right class is not an easy task.

2. Drug re-classification

After drug licensing for an agreed period, some drugs are reclassified into other classes. Generally, new drug is usually classified into the stringent class, such as prescription drugs in order to limit the distribution and to monitor drug safety and efficacy. If drug information has been gathered enough to confirm the safety and efficacy, that drugs can be reclassified in to less stringent class. The re-classification of prescription to non-prescription drug is usually known as Rx-to-OTC switch.

As far as known, Rx-to-OTC switch was begun in the US. Some antihistamines (for allergy) and decongestant drugs were re-classified into non-prescription drug in 1976. 4 years later, many countries around the world follow the US. They re-classified antihistamines and decongestant drugs to non-prescription drugs too. After that, the UK re-classified ibuprofen (for pain) in 1983. The timeline of Rx-to-OTC switch in the US and the UK has shown in **Figure 1** and details of the timeline are described in **Table 2**. Apart from the US and the UK, ketoconazole in topical preparations for fungal infection were switched in Australia and Canada in 1994. There was a big proportion of Rx-to-OTC switch in Mexican in 1998. Thirty-one drugs were re-classified by international drug class comparison. In New Zealand, influenza vaccine was reclassified to non-prescription status in 2010 due to influenza spreading. This is very unique decision since most countries had never reclassified injection or vaccine for this situation before. Nowadays, many countries are still reviewing prescription drugs to find the potential candidates to re-classified them as non-prescription drugs [31].

Table 2: The details of Rx-to-OTC switch from the timeline (Figure 1).

Year	Country	Active ingredient	Indication
1976	US	Brompheniramine maleate (oral)	Allergy
1976	US	Chlorpheniramine maleate (oral)	Allergy
1976	US	Oxymetazoline HCl (topical aqueous solution)	Decongestant
1983	UK	Ibuprofen (Oral)	Pain
1983	UK	Loperamide (Oral)	Anti-diarrhoeal
1984	US	Ibuprofen (Oral)	Pain
1993	UK	Acyclovir (Oral)	Cold sores
1993	UK	Cetirizine (Oral)	Allergy
1993	UK	Loratadine (Oral)	Allergy
1994	UK	Beclomethasone (Oral)	Hay fever
1995	UK	Fluconazole (Oral)	Vaginal thrush
1995	US	Famotidine (Oral)	Stomach acid relief
1995	US	Ranitidine (Oral)	Stomach acid relief
1996	US	Nicotine (patches and gum)	Smoking cessation
1998	UK	Domperidone (Oral)	Nausea
2001	UK	Levonorgestrel (Oral)	Emergency contraceptive
2002	US	Loratadine (Oral)	Allergy
2004	UK	Omeprazole (Oral)	Heartburn
2006	US	Levonorgestrel (Oral)	Emergency contraceptive
2007	US	Cetirizine (Oral)	Allergy

Year	Country	Active ingredient	Indication
2008	UK	Naproxen (Oral)	Pain
2011	US	Fexofenadine (Oral)	Allergy
2013	UK	Esomeprazole (Oral)	Heartburn
2016	US	Adapalene (topical gel)	Acne
2017	UK	Ibuprofen for children (Syrup)	Pain

References: [3, 22, 31]

However, some drugs were re-classified into a more stringent class, such as prescription drugs. The major reasons are the increased potential risk to patients, increased drug abuse and low sale volume.

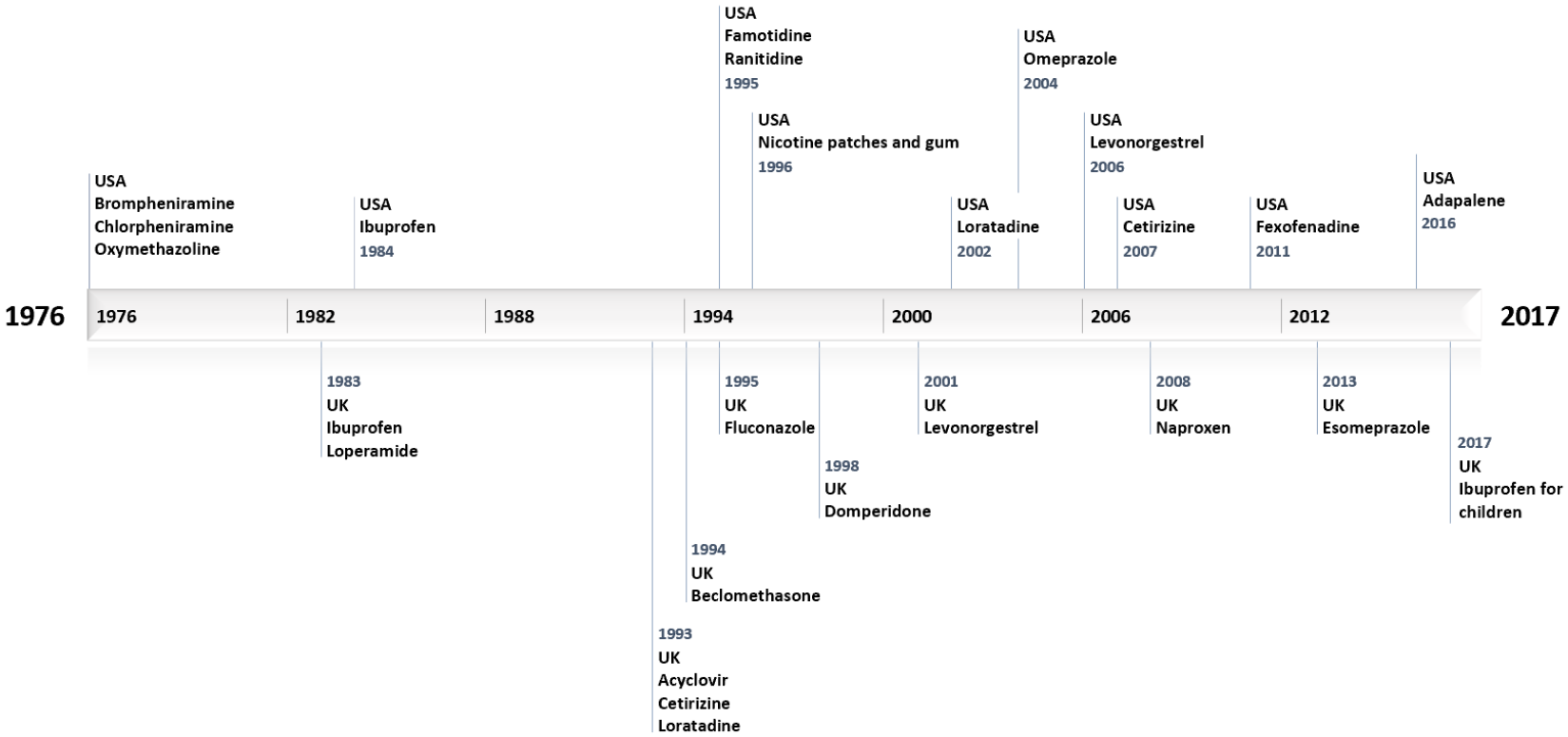
Increased potential risk

In the UK, diclofenac potassium 12.5 mg were switched in 2008 from prescription to non-prescription status for mild pain relief in short-period [33]. However, it was re-classified up to prescription in 2015 due to increased serious cardiac risk, which require health assessment by physicians before using [2].

Increased drug abuse

In Thailand, pseudoephedrine was re-classified from Dangerous drugs to Controlled drugs in 2012 because many people use it as a precursor of amphetamine or methamphetamine. In the present, pseudoephedrine is the Controlled drug that must be sold only in the hospital. It is strictly not allowed be sold in the pharmacies. The Thai FDA implemented this law in order to limit the distribution, expecting that drug abuse from pseudoephedrine would decrease [34].

Figure 1: The timeline of Rx-to-OTC switch examples in the US and the UK.



References: [3, 22, 31]

3. The impacts of drug re-classification from prescription to non-prescription drugs.

In order to understand the impacts of Rx-to-OTC switch, research and literatures were reviewed. There are 4 major groups that are affected: patients, healthcare professionals, stakeholders and payers.

Patients

When a drug re-classified into an OTC drug, patients can access to that drug easier. This is because it can be sold in pharmacies or retailers which are easier to visit compared to hospitals. Moreover, direct-to-consumer advertisements are also allow in OTC drugs. This could give more information to patients to decrease misunderstanding about drug use, side effects, drug interaction, among others. The impacts of Rx-to-OTC switch to patients is described in **Table 3**.

Table 3: The impacts of Rx-to-OTC switch to patients

	Positive impacts	**Negative impacts**
Patient safety	-	Misdiagnosis, side effects, drug abuse and drug misuse increase due to lack of physician's involvement [35-37].
Drug efficacy	For some disease, timely accessibility increases drug effectiveness significantly, such as in migraine, the faster patients access to drug, the faster symptoms relieve. This also decrease the quantity of drug use [38].	Drug misuse can decrease drug efficacy due to subtherapeutic dose or drug interaction [39].
Productivity	Increase productivity because patients do not have	-

	Positive impacts	Negative impacts
	to waste time for visiting physician [40].	
Expense	The doctor fee decreases [37].	Out-of-pocket expense of drug increase [37, 41, 42].

Healthcare professionals

The impacts of Rx-to-OTC switch to patients is described in **Table 4**.

Table 4: The impacts of Rx-to-OTC switch to healthcare professionals

	Positive impacts	Negative impacts
Physicians	Decrease workload due to patients' self-medication [43, 44].	More workloads if Rx-to-OTC switch cause more potential side effects to patients [45].
Pharmacists	Extend pharmacists' role in self-care [46].	More workloads for pharmacists [46].

Pharmaceutical company

The impacts of Rx-to-OTC switch to pharmaceutical company is described in **Table 5**.

Table 5: The impacts of Rx-to-OTC switch to pharmaceutical company

	Positive impacts	Negative impacts
Profits	The pharmaceutical company generally get more profits from OTC drug due to elastic demand and direct-to-consumer advertisements [37].	Some drugs might have lower sale volume. The example is simvastatin as OTC drug in the UK that has lower profit than when it was prescription drug

	Positive impacts	Negative impacts
		[47].
Competitiveness	Rx-to-OTC switch has been used as marketing strategy in after the patent expiration in order to competitive with the generic drug company since patients can access to OTC drugs easier [37].	-

Payers

The impacts of Rx-to-OTC switch to payers is described in **Table 6**.

Table 6: The impacts of Rx-to-OTC switch to payers

	Positive impacts	Negative impacts
Costs	Cost-saving because patients has to pay instead (out-of-pocket) [43].	More costs if Rx-to-OTC switch cause more potential side effects to patients [43, 45].

It can be seen that Rx-to-OTC switch can cause both positive and negative impacts to people. Thus, not every drugs can reclassified as OTC drugs since there are some drawbacks from re-classification. To re-classify one drug in the right category, the criteria must also be suitable in order to satisfy every perspective: patients, healthcare professionals, stakeholders and payers.

4. Reimbursement policy on non-prescription drugs

Nowadays, the drug reimbursement policy is vary around the world. The criteria for selecting drug for reimbursement are also different. In some countries, the drug class is one of the criteria.

Classify one drug as prescription or non-prescription can affect the healthcare budget in each country.

The reimbursement policy of nonprescription drugs from other countries were reviewed. The selected countries are the US, the UK, Germany, Sweden, Italy, Canada and Taiwan. **Table 7** shows the details of reimbursement policy of non-prescription drugs in each country.

Table 7: The reimbursement policy of nonprescription drugs in selected countries

Countries	Drug class is one of the criteria	Details
The US	Depends on plans	Most insurance plans cover non-prescription drugs only when a prescription from a physician is obtained [48].
The UK	No	Non-prescription drugs are eligible for reimbursement. However, NHS now focuses on the reimbursement for prescription drugs only. The drug list, which is called 'black-listed' has been developed. The list contains the drugs that physicians should stop dispensing. These drugs are mild-disease treatments [49].
Germany	Yes	All non-prescription drugs are non-reimbursable, except for the drugs that are the standard of care of a severe disease [50].
Sweden	No	Non-prescription drugs are eligible for reimbursement. However, only a few non-prescription drugs is reimbursable [51, 52].
Italy	Yes	All non-prescription drugs are non-reimbursable. Patients have to pay by themselves entirely [26].
Canada	Depends on plans	Generally, all drug products are eligible for reimbursement. However, some plans may not reimburse for non-prescription drugs [53].

Countries	Drug class is one of the criteria	Details
Taiwan	No	Most drugs can be reimbursed, regardless of legal status. However, National Health Insurance delisted more than 200 behind-the-counter drugs in 2004-2005 to decrease the expenditures [54, 55].

From the selected countries, non-prescription drugs are not eligible for reimbursement in the US, Germany and Italy [26, 48, 50]. There are some exceptions for non-prescription drug reimbursement if necessary. In the rest selected countries, although non-prescription drugs are eligible for reimbursement, the drug groups that are not reimbursed mostly are mild-disease treatments or non-prescription drugs. This is especially true in the UK. Due to a financial burden, NHS England identified 33 conditions that should stopped reimbursement in 2017. These symptoms are mild disease that can be self-medicated from non-prescription drugs [5]. The example is loratadine for allergic rhinitis. Loratadine is currently not eligible for reimbursement for both adults and children in the UK [56]. Other mild-disease treatments are cough and cold, indigestion, heartburn and mild acne [5]. Therefore, Rx-to-OTC switch can save the healthcare fund since the payers of non-prescription drugs are the patients, not the insurance. It is one of healthcare strategy in order to decrease financial burden or to properly allocate resources to real needed people.

In Thailand, we still do not have drug class as a criteria for reimbursement policy. Thus, Rx-to-OTC switch tend to not save much money when compared to other countries. In order to decrease financial burden and allocate fund to the patients that really need, stopping reimbursement some group of non-prescription drugs might lead to sufficient cost-saving.

5. Healthcare system in Thailand

Thailand has been the leader of healthcare system in Southeast Asia. Nowadays, approximately 99% of Thai population is covered by Universal healthcare, which has been introduced since 2002. the National List of Essential Medicines (NLEM), which is the reimbursable drug list, is the major tool for patients to access to necessary treatments and health problem

preventions in Thailand. In the present, all Thai citizens are covered by one of the three schemes: Civil Servants Medical Benefits Scheme (CSMBS), Social Security Scheme (SSS) and Universal Coverage Scheme (UCS) [7, 57].

Civil Servants Medical Benefits scheme (CSMBS) is the scheme that provide healthcare for government employees, including their family and retired civil servants [7]. CSMBS was established in 1980. In 2019, approximately 12% of Thai citizens are covered by this scheme [7, 57]. The Ministry of Finance, the Comptroller General's Department is the responsible agency of this scheme. The budget is from the general taxation. The CSMBS get the most benefits compared with other two schemes since it covers inpatient and outpatient service; emergency service; and drugs, that are both listed and unlisted in the NLEM with approval from physicians. People covered by this scheme get the benefits in all public hospitals. However, the patients have to pay by themselves (known as full out-of-pocket) if they visit private hospitals [7].

Social Security Scheme (SSS) is the scheme for employees that work in private sectors. This scheme covers just the employees themselves.[7] SSS was established in 1990. In 2019, approximately 16% of Thai citizens is covered by this scheme [7, 57]. The Ministry of Labour, Social Security Office is the responsible agency. The budget for this scheme is from 3 sections: government, employers and employees. Each section pays 1.5% of the salary, which lead to the 4.5% payroll. SSS get the coverage of inpatient and outpatient service from limited private and public hospitals depending on the contract. Only drugs listed in NLEM are reimbursable. The patients have to pay by themselves (known as full out-of-pocket) if they visit hospitals outside the contract [7].

Universal Coverage scheme (UCS) is the scheme that covers left Thai citizens from CSMBS and SSS [7]. UCS was established in 2002. In 2019, approximately 72% of Thai citizens is covered by this scheme [7, 57]. National Health Security Office is the responsible agency. The budget of this scheme is from the general taxation. UCS covers both inpatient and outpatients services in public hospitals that patients has registered. Only drugs listed in NLEM are reimbursable. The patients have to pay by themselves (known as full out-of-pocket) if they visit private hospitals or public hospitals that they do not register with [7].

Although all Thai citizens get the healthcare insurance coverage from the three schemes, they still have difficulty to access to most of expensive drugs [58, 59]. The examples are docetaxel

and leuprorelin, the cancer treatments. In order to support these drugs, an optimal policy should be implemented. Stop reimburse some Non-dangerous drugs and Household remedies to allocate the fund to severe disease treatments might be the effective solution.

6. Relevant studies

After searching for previous studies regarding the economic impact of Rx-to-OTC switch or delisting OTC drugs from drug reimbursement list , twelve studies were found.[38, 45, 60-69] 11 studies were obtain from the systematic review conducted by *cohen et al* [45, 60-70]. This study covers economic impact of Rx-to-OTC switch studies conducted between 2000-2010 [70]. One study was further found from the google scholar using the same search term from *Cohen et al.* study but range between 2010-2019 [38, 70]. Characteristics, methodologies and results from 12 studies were extracted.

The characteristics of 12 studies has some variations. 10 out of 12 studies were conducted in the US [45, 60, 62-69]. Other 2 studies conducted in Europe [38, 61]. The models covered various therapeutic area: allergy, dyslipidemia, gastro-enterology, contraceptive, smoking cessation, virology and migraine disorder. A majority of research conducted by using societal and payer perspectives [38, 45, 60-69]. Only one research use patient perspective [61]. Budget impact analysis was most frequently used, followed by cost-utility analysis and cost-effectiveness analysis.

After extraction, the variations of methodologies were found. Decision tree analysis was used in eight studies [38, 45, 60, 64-66, 68, 69]. One study used Markov model [61]. One was micro-simulation [67]. Two studies did not report a model type [62, 63]. Decision tree with 1-year timeframe was reasonably used in the research that scope in acute disease, while Markov model was used in chronic disease. Only one research conducted in 2013 referred to the guideline that used to develop the method [38]. This guideline was obtained from the systemic review research by *Cohen et al* [70].

A majority of research have found positive results. 9 out of 12 studies report cost-saving from Rx-to-OTC switch [38, 45, 60, 62, 65-69]. However, it was believed that the cost-saving was overestimated since some costs were not included, such as physician visit fee due to side-effects from switched OTC drugs and misuse costs [70]. Allergy was the only therapeutic area that all covered research report in the same direction, cost-saving [45, 60, 69]. Gastro-enterology and

hypercholesterolemia covered research report in different directions [61-65]. Whereas, the comparison from other therapeutic area cannot be done due to no compared research (Each therapeutic area was conducted by only one research) [38, 66-68].

It can be seen that a few economic impact analysis of Rx-to-OTC switch research has been conducted. The quality of research seems lack of accuracy. However, after the published guideline from *Cohen et al.* has released [70]. The quality of the research using this guideline was improved when compare with the previous studies. More research in economic impact analysis of Rx-to-OTC switch need to be done in order to effectively support the policy-makers.

7. Information using to shape the decision tree model in the context of Thailand

In order to shape a decision tree model in the context of Thailand, the information about allergic rhinitis must be reviewed. The Thai allergic rhinitis guidelines 2011, National List of Essential Medicines and legal classification of allergic rhinitis treatments in Thailand were described below.

7.1. The Thai allergic rhinitis guidelines 2011

Classification of allergic rhinitis

According to the Thai allergic rhinitis guidelines, there are two types of allergic rhinitis: that with intermittent symptoms and that with persistent symptoms. The difference between these two types relates to the length of the symptoms. Intermittent allergic rhinitis symptoms last for no more than four days in a single week and no more than one day per week for four consecutive weeks. If the symptoms persist for more than four days in a single week or one day per week for more than four consecutive weeks, then the allergic rhinitis is classed as persistent. Both the intermittent and persistent types of allergic rhinitis have two levels of severity: 'mild' and 'moderate to severe'. If the symptoms do not disturb a patient's quality of life, they are classified as mild. If the symptoms disturb quality of life, they are classified as moderate to severe [71] .

Allergic rhinitis treatments

The treatments of each allergic rhinitis types are presented in **Table 8** below. It can be seen that there are three treatments covered in this guideline: antihistamines, antileukotrienes, and intranasal corticosteroids. For mild intermittent symptoms, antihistamines are the first-line drugs for

general patients, while antileukotrienes are the second-line drugs unless patients have other comorbidities, such as asthma. Moderate to severe intermittent symptoms and mild persistent symptoms have the same recommended treatments. Antihistamines, antileukotrienes or intranasal corticosteroids can be used as the first-line drugs for both levels of symptoms. Whereas, for moderate to severe and persistent symptoms, only intranasal corticosteroids are recommended as first-line drugs [71].

Table 8: Allergic rhinitis treatments from the Thai allergic rhinitis guidelines 2011.

Types	Severity	Treatments
Intermittent symptoms	Mild	Antihistamines or antileukotrienes*
	Moderate to severe	Choose one of these: antihistamines, intranasal corticosteroids or antileukotrienes*
Persistent symptoms	Mild	
	Moderate to severe	Use intranasal corticosteroids first, if the symptoms persist, switch to antihistamines. If symptoms still persist, change to antileukotrienes.*

References: [71]

Side effects of allergic rhinitis treatments

H1 Antihistamines

H1 Antihistamines are drugs that inhibit histamine receptors in the body to reduce inflammation or immune response from histamines. Their common side effects are sedation; impaired cognitive function and psychomotor performance; and anticholinergic effects, including dry month, dry eye, urinary retention, and dizziness. The severity of the side effects depend on the their blood brain barrier penetration ability. H1 antihistamines are divided by this ability into two major categories: first generation antihistamines and second generation antihistamines. First generation antihistamines can cause much stronger side effect than second generation antihistamines because

more blood brain barrier penetration ability. Second generation antihistamines cause very mild side effect that previously mention since the blood brain barrier penetration ability is low. However, this ability also related to individual person so that some patients taking second generation antihistamines still experience sedation. Due to sedation, impaired cognitive function and psychomotor performance; it strongly advised that patients taking antihistamines should not drive or use machinery since it can lead to motor vehicle or occupational accidents [72, 73].

Intranasal corticosteroids

Intranasal corticosteroids diminish allergy symptoms by effectively reduce inflammation of the nasal mucosa and improve mucosal pathology by anti-inflammatory mechanism of action. They has been proved by many research as the most effective treatments for allergic rhinitis. Examples of the side effect of intranasal corticosteroids are burning sensation in a nose, dryness nose, swelling in the nose, and irritated throat. The side effects are not significantly noticed when used correctly at a normal therapeutic dose, but used at too high dose may cause general steroid side effect, such as increased appetite, mood changes, and insomnia [74, 75].

7.2. National List of Essential Medicines and legal classification of allergic rhinitis treatments in Thailand.

The NLEM was reviewed to learn which allergic rhinitis treatments are currently eligible for reimbursement. The legal classes of the reimbursable drugs were also found on the Thai FDA website. It can be seen that all allergic rhinitis treatments: antihistamines, antileukotrienes, and intranasal corticosteroids, are eligible for reimbursement. However, only some from each group were selected. The reimbursable allergic rhinitis treatments are presented in **Tables 9, Table 10 and Table 11.**

Table 9: Antihistamines listed in National List of Essential Medicines

Generation	Drugs	Dosage forms	NLEM category	Legal class
Sedating antihistamines	Brompheniramine maleate	Tablets, Syrups	A	Dangerous drugs

Generation	Drugs	Dosage forms	NLEM category	Legal class
	Chlorpheniramine maleate	Capsules, Tablets, Syrups, Sterile solutions	A	Non-dangerous drugs (2mg in 10-tablet packages) Dangerous drugs (4mg)
	Diphenhydramine hydrochloride	Capsule, Sterile solutions	A	Dangerous drugs
	Hydroxyzine hydrochloride	Tablets, Syrups	A	Dangerous drugs
Non-sedating antihistamines	Cetirizine hydrochloride	Tablets, Syrups	A	Dangerous drugs
	Loratadine	Tablets, Syrups	A	Non-dangerous drugs (10 mg in 10-tablet, 2 strip packages) Dangerous drugs

References: [21, 71, 76]

Table 10: Intranasal corticosteroids listed in National List of Essential Medicines

Drugs	Dosage forms	NLEM category	Legal status
Budesonide*	Nasal spray	B	Dangerous drugs
Fluticasone furoate**	Nasal spray	D	Controlled drugs

* For patients aged at least 6 years old

** For patients aged at least 2 years with indication for intermittent or persistent allergic rhinitis and allergic conjunctivitis

References: [22, 71, 76]

.

Table 11: Antileukotrienes listed in National List of Essential Medicines

Drugs	Dosage forms	NLEM category	Legal status
Montelukast sodium	5 mg chewable tablets 10 mg film coated tablets 4 mg oral granules*	C	Dangerous drugs

* Oral granules is for children aged 6 months to 5 years old

References: [21, 71, 76]

CHAPTER 3

Methodology

This study was divided into two parts: the review of drug classification scheme and the economic impact of delisting non-prescription drugs from National List of Essential Medicines using non-sedating antihistamines as a case study.

1. The review of drug classification scheme

1.1. Select compared countries.

The countries were selected by the targeted review. There were two groups of countries that were selected: countries with stringent regulatory agencies, and countries that are the member of Association of Southeast Asian Nations (ASEAN).

Countries with stringent regulatory agencies

World Health Organization (WHO) has defined the stringent regulatory agencies as

(a) The member or founder of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH),

(b) The ICH observer, and

(c) A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement.

Four countries with stringent regulatory agencies were selected to compared; they are the US, the UK, Japan and Canada [77, 78].

The member of ASEAN

Three out of ten ASEAN members were chosen to compare; they are Malaysia, the Philippines and Singapore were selected to compare with Thailand.

In conclusion, the study compared drug regulatory in eight countries: the US, the UK, Japan, Singapore, Malaysia, the Philippines, Canada, and Thailand.

1.2. Searching for drug classification scheme and criteria in selected eight countries.

To explore drug classification scheme and criteria, the study first used literature review. Targeted review was then performed using respective countries' drug regulatory agency website, and available published research. Expert interviews were also performed to explore more information from Malaysia, the Philippines, and Thailand since data from the websites was insufficient.

1.3. Actual drug classification by different drug regulatory agencies

In order to compare the drug classification category of the selected drugs by different drug regulatory agencies. The indications of drugs or diseases were selected by two categories: chronic, and acute diseases; and systemic and topical uses. As a results, 11 indications were selected. They are insomnia, dyslipidemia, diabetes, hypertension, bacterial infection, fungal infection, pain, allergy, nausea and vomiting, smoking cessation, and vaccines.

In each indication, drugs were selected to compare. The drug classes of 53 selected drugs in each countries were searched from the government or credible database. Targeted review was conducted through government websites and other credible sources shown in **Table 12**.

Table 12: Sources of the drug classification scheme across different drug regulatory agencies

Country	Source	Link
The US	Drugs@FDA	https://www.accessdata.fda.gov/scripts/cder/daf/
The UK	The electronic medicines compendium (emc)	https://www.medicines.org.uk/emc/search?q=drug&t=advanced&st=true&sc=true&l=4
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	http://www.pmda.go.jp/english/search_index.html
	Ministry of Health Labour and Welfare	https://www.mhlw.go.jp/bunya/iyakuhin/ippanyou/newyoushidou.html
	OTC	http://search.jsm-db.info/sp_en/
Singapore	Singapore Drugs Database	https://pharmfair.com/
Malaysia	Official portal of	https://www.pharmacy.gov.my/v2/sites/default/files/d

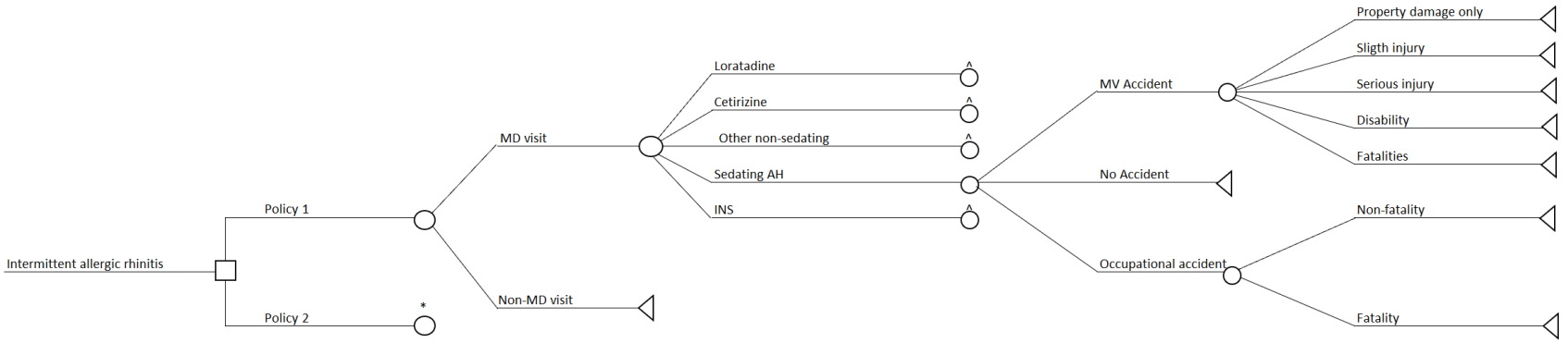
Country	Source	Link
	pharmaceutical services program	ocument-upload/poisons-list-25.07.2019_1.pdf
	Industry & QUEST3+ System	https://quest3plus.bpfk.gov.my/pmo2/index.php
The Philippines	Center for Drug Database 2019	Center for Drug Database 2019
Canada	National Drug Schedules	https://napra.ca/national-drug-schedules?keywords=sulindac&schedule=
	Drug Product Database online query	https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
Thailand	Drug registration database	http://pertento.fda.moph.go.th/FDA_SEARCH_DRUG/SEARCH_DRUG/FRM_SEARCH_DRUG.aspx

2. The economic impact of delisting non-prescription drugs from National List of Essential Medicines using non-sedating antihistamines as a case study.

2.1. Study design

A decision tree was used for budget impact analysis to compare between abandoning and continuing reimbursement of non-sedating antihistamines listed in NLEM (loratadine and cetirizine) from healthcare system perspective (**Figure 2**). The outcome of the model was net benefit between two policies. The time frame of the model was limited to one year. All figures were expressed in the Thai Baht and USD (1 USD = 31.0470 Thai baht), according to its value in the year 2019 (using the consumer price index) [79]. The targeted populations were new patients older than 12 who suffered from intermittent allergic rhinitis in both mild and moderate severity. Intermittent allergic rhinitis patients were excluded if they had asthma as a comorbidity since allergic rhinitis symptoms could make asthma symptoms worse.

Figure 2: The decision tree model of policy options in the context of Thailand



* Same as policy 1
^ Sam as sedating AH
Abbreviation: MD , medical doctor; AH , antihistamines ; INS, intranasal corticosteroids; MV accident, motor-vehicle accident.

2.2. Policies

The new proposed policy was compared with the present policy by calculating the reimbursed costs of the healthcare system. Policy 1 was the present policy in Thailand. All non-sedating antihistamines were eligible for reimbursement in intermittent allergic rhinitis. Whereas, policy 2 was the new proposed policy that the reimbursement of loratadine and cetirizine were abandoned in non-asthma intermittent allergic rhinitis patients aged more than 12 (**Table 13**).

Table 13: Drugs that are eligible for reimbursement in patients suffering from allergic rhinitis of each proposed policies

Policy	Loratadine		Cetirizine		Other allergic rhinitis treatments in NLEM	
	Intermittent	Persistent	Intermittent	Persistent	Intermittent	Persistent
1	Yes	Yes	Yes	Yes	Yes	Yes
2	No	Yes	Yes	Yes	Yes	Yes

Notes: yes, reimbursable drugs; no, non-reimbursable drugs.

2.3. Model development

The decision tree from the published research was adopted and modified to be used in the context of Thailand [45]. Used to shape the effective model were the review of treatment choices, effect of each treatment choice and physicians' prescribing behavior.

(i) Treatment choices

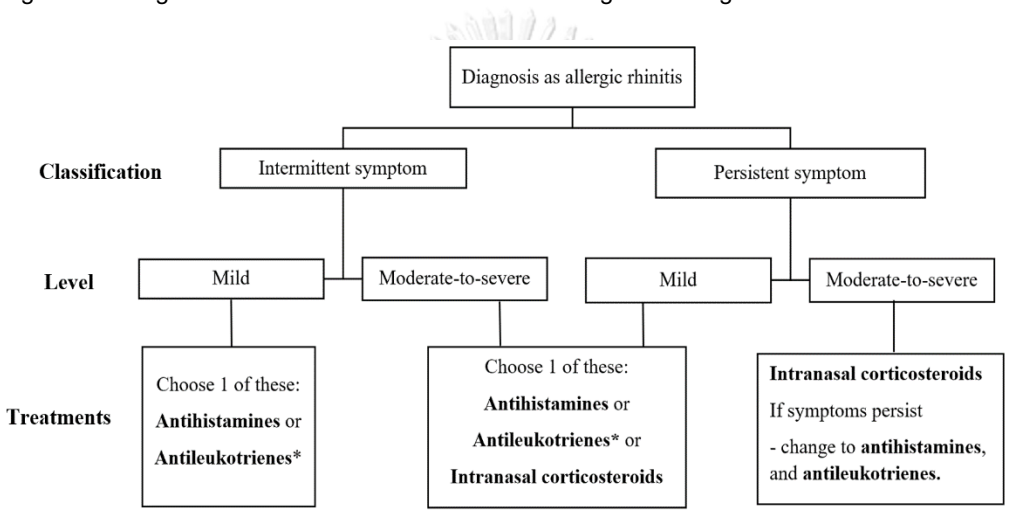
The symptoms of allergic rhinitis were easy for self-diagnosis. The examples of them were an itchy nose, a runny nose, sneezing or watery eyes. Therefore, some patients may choose not to visit a hospital, but self-medicate from pharmacies.

Patients visiting a hospitals would receive treatments according to the Thai allergic rhinitis guidelines of 2011 (**Figure 3**) [71]. There were three drug pharmacology classes for intermittent allergic rhinitis listed in the guidelines: antihistamines, antileukotrienes and intranasal corticosteroid. However, antileukotrienes were excluded from the model because they were recommended to use only when the patients also suffered from asthma. Whereas, this study excluded allergic rhinitis

patients who have asthma as comorbidities because allergy can aggravate asthma symptoms. Therefore, asthma patients should visit a doctor frequently and deserve drug reimbursement.

All drugs from guideline listed in NLEM were then included in the model (**Table 14**) [76]. Other non-sedating antihistamines, such as levocetirizine and desloratadine, were also accepted as a choice for patients who covered by CSMBS, although they were not listed in NLEM. Five drug groups; which were loratadine, cetirizine, other non-sedating antihistamines, sedating antihistamines and internasal corticosteroids; eventually included in the model.

Figure 3: Allergic rhinitis treatments from the Thai allergic rhinitis guideline 2011



* Use antihistamines before antileukotrienes, except patients with asthma or other comorbidities

Table 14: The allergic rhinitis treatments that listed in National list of essential medicines

Group	Drug	Legal status
Sedating antihistamine	Brompheniramine maleate	Dangerous drugs
	Chlorpheniramine maleate	Non-dangerous drugs
	Diphenhydramine hydrochloride	Dangerous drugs
	Hydroxyzine hydrochloride	Dangerous drugs
Non-sedating antihistamine	Cetirizine hydrochloride	Dangerous drugs
	Loratadine	Non-dangerous drugs
Antileukotriene	Montelukast	Dangerous drugs

Group	Drug	Legal status
Intranasal corticosteroids	Budesonide	Dangerous drugs
	Fluticasone furoate	Controlled drugs

References: [21, 76]

(ii) Effects of each treatment choice

Antihistamines and intranasal corticosteroids had various adverse drug reactions. However, the most concern was the side effects of antihistamines, such as drowsiness, blurred vision, and dizziness. These side effects potentially impaired the driving and working performance, leading to accident, which were the great amount of reimbursed costs. This model thus included motor-vehicle accident and occupational accident as the consequence of using allergic rhinitis treatments. The results from both types of accident were obtained from the published research conducted in Thailand. Accordingly, results from motor-vehicle accident were categorized into 4 groups: property damage only, slight injury, serious injury, disabilities and fatalities; while results from occupational accident were non-fatalities and fatalities [80, 81].

Some patients who decided not to visit a doctor and also not self-medicate can consequently became untreated patients, which could lead to other complications, such as asthma or conjunctivitis. However, the consequence of untreated allergic rhinitis seemed to be significant only in persistent allergic rhinitis, not intermittent category. This model consequently did not include untreated patients arms.[82, 83]

(iii) Physicians' prescribing behavior

When the new proposed policy was implemented, physicians' prescribing behavior tend to change. Generous physicians would likely shift to prescribe other allergic rhinitis treatments listed in NLEM. The drug probability in scenario that policy 2 was implemented mainly obtained from the published research and if not available, the assumption.

2.4. Input parameter

All input data were obtained from government sources, published research, expert interview and assumption. Although some parameters might be found in different value, the most credible value was used in a base case. The sensitivity analysis would then performed to analyze the uncertainty.

(i) Populations

The methodology used to estimate a number of patients in the model was described in this section and presented in **Table 15**. First, the number of Thai populations were searched and finally obtained from Official Statistics Registration System. These populations were the number of Thai citizens with registered house particulars and aged more than 12 in 2019. [84] The prevalence rate then was used to calculate the number of allergic rhinitis patients. A percentage of allergic rhinitis patients suffering from asthma was utilized to exclude asthma patients from the model. Lastly, a proportion of intermittent allergic rhinitis patients was used to calculate the number of non-asthma intermittent AR patients aged more than 12, which were targeted populations of this study.

Table 15: Epidemiological inputs in the model

Variables	Base value	References
Thai citizens aged more than 12	61,421,149.00	[84]
% AR patients	26%	[85]
Number of AR patients	16,153,762.19	
% AR patients suffering from asthma	28%	[83]
Number of AR patients without asthma	11,630,708.77	
% Intermittent AR patients	49%	[86]
Number of non-asthma intermittent AR patients aged more than 12	5,699,047.30	

Abbreviation: AR, allergic rhinitis

(ii) Probability

The probability value in this model are shown in **Table 16**. Many probability values were gained from published research and articles, however, only the most credible value was selected as a base value of the model.

MD visit probability

Having introduced universal healthcare coverage scheme by the government in Thailand, the market distribution between hospitals and pharmacies were found to be 70% and 30%, respectively [87]. Although these values were not specific to allergic rhinitis patients, the researcher decided to use them as the base value of MD visit in policy 1. After the new proposed reimbursement policy had introduced, it was believed that some patients would switch to self-medicate since the treatments were not free for them anymore. It was assumed that the proportion of MD visit would decrease from 70% to 30%. This assumption was based on published research [45, 88].

Drug probability

Drug probability of policy 1 of receiving loratadine, cetirizine, sedating antihistamines and intranasal corticosteroids were calculated from market share data in hospital setting in Thailand obtained from expert interview. For other non-sedating antihistamines, only Thai citizens covered by CSMBS were eligible to be reimbursed for this drug group since they were not listed in NLEM. To obtain the probability of receiving other non-sedating antihistamines, it was begun with searching for the number of Thai citizens covered by CSMBS. Although this proportion was found to vary between 5-12% [7, 23, 57]. the researcher used 12% since it was the most updated data [57]. The researcher then calculated the proportion of allergic rhinitis patients covered by CSMBS that receive other non-sedating antihistamines based on the hospital database obtained from the interview.

For policy 2, drug probability was based on published research and assumption. From the research conducted in the US. It was found that physicians' prescribing behavior was change after loratadine reimbursement was cancelled from Medicaid Program. Most loratadine users switch to use desloratadine instead [88]. Thus, all patients covered by CSBMS would likely to receive desloratadine, levocetirizine and other non-sedating AH. While, the rest patients were assumed to receive sedating antihistamines or intranasal corticosteroids.

Accident probability

It was found that sedating antihistamines were the only drug that can cause side effect, which significantly increase accident risk [89, 90]. Cetirizine was found to be controversy. Some research reported the significant drowsiness risk, while others reported not significant [45, 91-93].

The researcher decided to use accident probability for cetirizine as zero since the amount of risk was very small.

Both motor-vehicle and occupational accident probability from taking sedating antihistamines were calculated based on research conducted in France and the US [45, 89]. Probability of each result from motor-vehicle accident and occupational accident was gained from cost of illness research conducted in Thailand [80, 81].

Table 16: Probability inputs in the model

Variables	Base value (%)		References
	Policy 1	Policy 2	
MD visit	70%	30%	[87], assumption
Drugs			
- Loratadine	27	0	Interview
- Cetirizine	33	0	Interview
- Other non-sedating AH	5	12	[57, 88]
- Sedating AH	27	55	Interview, assumption
- INS	8	33	Interview, assumption
Accident from sedating AH			
- MV accident	31		[89]
Property damage only	49		[81]
Slight injury	39		[81]
Serious injury	11		[81]
Disabilities	0.5		[81]
Fatalities	1		[81]
- Occupational accident	41		[90]
Non-fatalities	99		[80]
Fatalities	0.4		[80]

Abbreviation: MD, medical doctor; AH, antihistamines; MV, motor-vehicle

(iii) Costs

Input cost in this model are reported in **Table 17**. All costs were gained from the research conducted in Thailand or Thai standard sources. All costs were presented in year 2019 value, using consumer price index method for inflation adjusting. The consumer price index were obtained from the Economic and Trade Indices database, Trad Policy and Strategy Office, Ministry of Commerce [79].

MD visit costs

MD visit cost was obtained from standard cost list for health technology assessment (HTA) arranged by Health Intervention and Technology Assessment Program (HITAP) [94]. The number of MD visit of allergic rhinitis patients was assumed to be twice per year.

Drug costs

According to HTA guideline for Thailand, each drug price was the median price gained from Drug And Medical Supply Information Center, Ministry of Public Health [95]. From the research, it was found that the period of symptoms of Thai people suffering from intermittent allergic rhinitis were approximately 30 days per year [85]. Using these data, drug costs per year were then calculated.

Accident costs

Both cost of each result from motor-vehicle accident and occupational accident from taking sedating antihistamines were obtained from the same research that probability value were found. As said previously, these research were cost-of-illness gained from primary sources research conducted in Thailand [80, 81].

Table 17: Cost inputs in the model

Cost per patient	Base value		Range (+/- 25% of base value)		References
	Thai baht	USD	Thai baht	USD	
MD visit					
MD visit cost per time	449.80	14.49	337.35-562.25	10.87-18.12	[94]
MD visit costs per year (2 times per year)	899.61	28.99	674.71-1,124.51	21.74-36.24	Assumption
Drug cost per day					
Loratadine	0.44	0.01	0.33-0.55	0.01-0.02	[95]
Cetirizine	0.21	0.01	0.16-0.26	0.01-0.01	[95]
Other non-sedating AH	7.48	0.24	5.61-9.34	0.18-0.30	[95]
Sedating AH	0.34	0.01	0.25-0.42	0.01-0.01	[95]
INS	9.23	0.30	6.92-11.54	0.22-0.37	[95]
Drug cost per year (AR symptoms persist 30 days)					[85]
Loratadine	13.19	0.43	9.89-16.49	0.32-0.53	Calculation
Cetirizine	6.30	0.20	4.73-7.88	0.15-0.25	Calculation
Other non-sedating AH	224.25	7.23	168.19-280.31	5.42-9.03	Calculation
Sedating AH	10.13	0.33	7.59-12.66	0.24-0.41	Calculation
INS	276.90	8.92	207.68-346.13	6.69-11.15	Calculation
MV accident					
Property damage only cost per year	0	0	0	0	[81]
Slight injury cost per year	652.49	21.03	489.37-815.61	15.77-26.28	[81]

Cost per patient	Base value		Range (+/- 25% of base value)		References
	Thai baht	USD	Thai baht	USD	
Serious injury cost per year	22,262.70	717.41	16,697.02-27,828.37	538.06-896.76	[81]
Disability cost per year	415,401.04	13,386.22	311,550.78-519,251.30	10,039.66-16,732.77	[81]
Fatality cost per year	14,779.11	476.25	11,084.33-18,473.89	357.19-595.32	[81]
Occupational accident					
Non-fatality cost per year	533.71	17.20	400.28-667.14	12.90-21.50	[80]
Fatality cost per year	17,131.60	552.06	12,848.70-21,414.50	414.05-690.08	[80]

All costs present in year 2019 value, exchange rate: 1 USD = 31.0470 baht

2.5. Sensitivity analysis

Lacking of several input data, this model contained some assumption and estimation. Sensitivity analyses were performed to see the uncertainty and conditions that lead the policy 2 implementation to achieve cost saving. A scenario analysis, a univariate sensitivity analysis and a multivariate sensitivity analysis were performed.

Scenario analysis

Scenario analysis was also performed to examine the extreme different situations after policy 2 implementation. These situations were related to physicians' prescribing behavior. There were two situations selected to perform the analysis:

(i) When physicians switch to prescribe sedating antihistamines for all patients, except who covered by CSMBS.

(ii) When physicians switch to prescribe intranasal corticosteroids for all patients, except who covered by CSMBS.

Due to uncertainty physicians' prescribing behavior, the two different extreme situations were used as inputs of the model. Cost-saving of different situations would be reported compared with the base case.

Univariate sensitivity analysis

To examine the parameters that affect the model, univariate sensitivity analysis was performed by changing different parameters of policy 2 in the model by ±25%. These parameters were allergic rhinitis prevalence in Thailand, MD visit probability, MD visit costs, all of each drug costs and all of accident costs. The ranges are reported in **Table 16 and 17**.

Multivariate sensitivity analysis

Having found significantly impacted parameters from the univariate sensitivity analysis, multivariate sensitivity analysis were further performed to find the best conditions for policy 2 implementation. Parameters using for multivariate sensitivity analysis would be high impact parameters, analyzed from the univariate sensitivity analysis.

CHAPTER 4

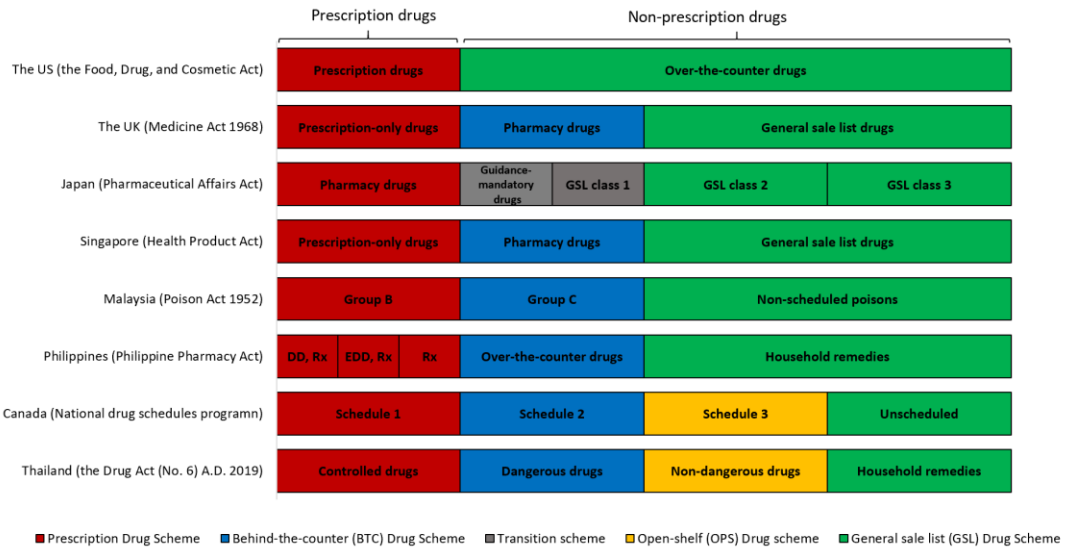
Results

The results of this study are divided in two parts: the review of drug classification scheme and the economic impact of delisting non-prescription drugs from National list of essential medicines using non-sedating antihistamines as a case study.

1. The review of drug classification system among countries.

    1.1. Drug classification schemes

Figure 4: Drug classification schemes among selected eight countries



Note: this figure does not represent quantity.

Abbreviation: DD, dangerous drugs; EDD, exempted dangerous drugs; Rx, prescription; GSL, general sale list.

References: [12, 96-102]

Table 18: The differences among each drug scheme

Regulations	**Scheme**				
	Prescription	**BTC**	**OPS**	**GSL**	**Transition**
Gate keeper	Physician	Pharmacist	None	None	Pharmacist
Document required for purchase	Prescription	None	None	None	None
Distribution channel					
Hospital	Yes	Yes	Yes	Yes	Yes
Retailed pharmacy	Yes	Yes	Yes	Yes	Yes
Online pharmacy	Yes, except JP, MY, TH	Yes, except JP, MY, TH	Yes, except TH	Yes	Yes[1]
Retailer	No	No	No	Yes	No
Countries that direct-to-consumer advertisement is permitted	US, CA[2]	UK, SG, CA	CA, TH	All countries	JP

Abbreviation: BTC, behind-the-counter drugs; OPS, open-shelf drugs

1: The advertisement in Canada cannot mention the benefits or risks of drugs.

2: Only GSL class 1 can be sold over the internet

References: [12, 96-108] [109-117]

It was found that drug classification scheme among eight studied countries are operated under Drug Acts and other relevant Acts, such as Narcotics Acts, Controlled Substances Acts or Psychotropic Substances Acts. In Canada, Japan, Malaysia, Singapore, UK and US, one drug is simultaneously regulated under several Acts. In Thailand and the Philippines, on the other hand, one drug is regulated under one Act. All psychotropic substances in Thailand are under the Psychotropic Substance Act A.D. 2016. To access to these psychotropic substances, prescriptions are required [118]. Narcotic drugs are controlled under the Narcotic Act A.D. 2019. Some narcotic drugs, such as codeine, require prescriptions and are available only at hospitals. However, combination drugs contained narcotic drugs can be sold in pharmacies without prescription requirement, but patient names and citizen identification are requested to prevent drug abuse. Community pharmacies must strictly report this information to the Thai FDA [119, 120]. In the Philippines, narcotic and psychotropic drugs are regulated under the Comprehensive Dangerous Drugs Act 2002. These drugs require special prescriptions called yellow prescriptions to be dispensed.[121]

Among eight countries, drugs are universally classified into two major schemes: prescription drugs and non-prescription drugs. Prescription drugs are homogeneously regulated across eight studied countries. To access to prescription drugs, physicians must diagnose patients before prescribing drugs to patients. However, some regulations vary across countries. Among eight studied countries, excluding the US and Canada, prescription drugs cannot be directly advertised to consumers [109-117]. Moreover, prescription drugs are mainly distributed through community pharmacies and hospitals. Online pharmacies are permitted to sell prescription drugs in the US, the UK, Singapore, the Philippines, and Canada [12, 96-108].

Non-prescription drugs, on the other hands, are diversely regulated across countries. The numbers of sub-schemes are ranged from one sub-scheme in the US to four sub-schemes in Japan. Detailed drug classification schemes across eight countries can be seen in **Figure 4**. Although regulations of non-prescription schemes vary, they could be grouped into the following four sub-schemes (**Table 18**).

i. Behind-the-Counter (BTC) Drug Scheme

Drugs under the BTC drug scheme do not require prescriptions but required pharmacists' involvement. These drugs are kept behind the pharmacist's counters. Patients must ask their pharmacists in order to access to these drugs. Pharmacists must provide recommendation whether BTC drugs are appropriate for patient's conditions. Counseling is also required to ensure patient's rational drug use. There are six countries that have the BTC scheme: the UK, Singapore, Malaysia, the Philippines, Canada and Thailand. These drugs are permitted to be sold over the internet in the UK, Singapore, the Philippines, and Canada [12, 97, 99-102, 104-108]. Direct-to-consumer advertisements of BTC drugs were permitted only in the UK and Canada, but not allowed in Singapore, Malaysia, the Philippines and Thailand.

ii. Open-Shelf (OPS) Drug Scheme

Drugs under OPS drug scheme are evaluated safe enough for consumer to practice self-medication. These drugs could be sold without pharmacist supervision; however, drugs are still confined to be distributed only from healthcare settings, and not yet allowed to distribute in retailers. It implied that patients could seek pharmacist advise if needed. The countries that had the OPS drug scheme were Canada and Thailand. In Thailand, these drugs can be sold in type 2 community pharmacies. OPS drugs are permitted to be sold over the internet only in Canada; while direct-to-consumer advertisements are permitted in both countries [12, 102, 106, 111, 112].

iii. General Sale List (GSL) Drug Scheme

Drugs under the GSL scheme are also evaluated safe enough for self-medication practice. All studied countries have this scheme. GSL drugs can be sold in retailers and over the internet [12, 96-108]. Direct-to-consumer advertisements of GSL drugs are also permitted in all studied countries [109-117].

iv. Transition Drug Scheme

The transition drug scheme is observed only in Japan when drugs are re-classified from prescription status to GSL drug class 2 and 3. This new scheme was implemented in 2014 [122]. Potential prescription drugs were re-classified into the guidance-mandatory drug scheme for at least three years for safety monitoring purpose. Drugs in the guidance-mandatory scheme required face-to-face pharmacist dispensing. Once safety evidence was established and confirmed, guidance-mandatory drugs were re-classified as GSL drug class 1 for at least one year for more safety monitoring purpose over the internet. Distribution of GSL drug class 1 is more relaxed as they could be sold via internet. Pharmacists' involvement, however, is still required. Pharmacists are required to assess the necessity of drug use and to instruct patients to appropriately use drugs. Methods other than face-to-face, such as email or telephone, can be utilized to ensure rational use of drugs. Having established drug safety confirmation, GSL drug class 1 could be reclassified into GSL drug class 2 or 3 for self-medication [27, 98].

Although the commonality among drug classification schemes from eight studied countries are summarized, there were some unique points worth mentioning about.

The US is the only country with a two-classification scheme: prescription drugs and over-the-counter (OTC) drugs [32]. The BTC scheme is not implemented in this country. However, some GSL drugs (OTC drugs), such as insulin and pseudoephedrine, need to be strictly kept behind the pharmacist's counter and dispensed by pharmacists [123]. This management process mimics the BTC scheme which is not currently existed in the US [124].

In Japan, not only the transition scheme that is uniquely implemented to ensure safety of downward re-classification, stricter self-medication handling mechanism is also observed. GSL drug class 2 and 3 although considered as self-medicated drugs, they require certified sale personnel to assist the consumers [27, 98].

In Canada, Health Canada and the National Association of Pharmacy Regulatory Authorities (NAPRA) are responsible for drug classification for Canadian provinces and territories. However,

centralized drug classification decision is not country-wide adopted. British Columbia, Newfoundland & Labrador, and Quebec have their own drug regulatory agencies. Inconsistency of drug classification can be observed in Canada [125].

In Malaysia, drugs are regulated along with other poison substances under the Poison Act 1952. The Poison Act classified substances into four categories; Group A, Group B, Group C, and Group D. Group A poisons are high toxicity substances that are not allowed for sell, while group D poisons are chemical substances used in a laboratory. Only Group B (equivalent to prescription drugs) and Group C (equivalent to BTC drugs) are considered as drugs. Other drugs exempted from the Poison Act are considered as non-scheduled poisons or GSL drugs [100].

In the Philippines, drugs that required prescriptions can be further divided into three categories. The first category contains narcotic and psychotropic drugs listed in the Comprehensive Dangerous Drugs Act of 2002. The second category, called exempted dangerous drugs, contains dangerous drugs that are exempted if it meets all criteria. These drugs need to be dispensed by doctors who has the S2 license. The last category is prescription only medicines, which are the general drugs that require prescriptions to be dispensed [101, 121].

Among the studied countries, drug re-classification is identified at active ingredient, strength, indication and dosage form level. However, re-classification by brand is found in the US, the UK, Japan, and Singapore. This is because of market exclusivity issue, which delays other competitive re-classification applicants [126, 127]. Under the market exclusivity period, a initiated company needs to undertake a post-marketing surveillance or conducts an additional research for the re-classification. It also offers the initiated company to receive their payback from the re-classification. The period ranges from 1 year in the UK and Singapore to 3 years in the US and Japan [126-131]. An example is sildenafil in the UK. In 2017, only brand Viagra was reclassified from prescription drugs to BTC drugs (known as pharmacy drugs in the UK), while other brands remained the prescription status. A year following, other brands were, then, reclassified as BTC drugs [132].

1.2. Drug classification criteria

Drug classification criteria from eight countries were obtained from drug regulatory agency websites, conferences and publish research. Half of the studied countries (US, JP, MY, PHL) provided principle of drug classification criteria without detail, while the other half (UK, SG, CA, TH) provided detailed criteria. **Table 4** summarized drug classification criteria. It indicated “Yes” only

when criteria were explicitly mentioned. Thus, blank cell referred to criteria not mentioned, but did not mean do not have those criteria.

Table 19: The comparison of drug classification criteria among countries

	US	UK	JP	SG	MY	PHL	CA	TH
Disease characteristic								
1. Require disease diagnosis from healthcare professional	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Require subsequence disease monitoring	Yes	Yes		Yes		Yes	Yes	
3. Demand timely access to drugs		Yes	Yes				Yes	
4. Nature of disease: acute, chronic or recurring		Yes[1]	Yes				Yes[2]	
Drug safety profile								
1. Drugs require healthcare profession evaluation or management	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.1 Severe side affect		Yes	Yes	Yes		Yes	Yes	Yes
1.2 Narrow safety margin (e.g. narrow therapeutic index)	Yes	Yes	Yes			Yes	Yes	Yes
1.3 Drug interaction		Yes				Yes	Yes	Yes
1.4 High risk in vulnerable population [3]			Yes			Yes		
2. Drug resulted in potentially negative consequences	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.1 Habit forming	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.2 Misuse	Yes	Yes	Yes				Yes	Yes
2.3 Masking serious diseases' symptoms		Yes		Yes			Yes	
2.4 Micro-organism resistant							Yes	
2.5 Have negative impact on reproductive system or genetic, or was a mutagenic agent			Yes					Yes
2.6 Pack size		Yes						Yes
3. Other safety issues/More information needed			Yes		Yes	Yes		Yes
3.1 Comparative risk with other same indication drugs								Yes
3.2 Time since market authorization					Yes	Yes		
3.3 Assured effectiveness			Yes			Yes		
Other drug characteristics								

	US	UK	JP	SG	MY	PHL	CA	TH
1. Must be administered at health care facilities		Yes		Yes			Yes	
2. Injection dosage form		Yes[4]		Yes[4]			Yes[5]	Yes[5]
3. Need special storage and handling				Yes[6]				

Notes:
1: Drugs for recurring symptoms or chronic diseases were classified as prescription or BTC in the UK.
2: Drugs for recurring symptoms or chronic diseases were classified as prescription, BTC or OPS in Canada.
3: Vulnerable people refers to children, pregnant woman, breastfeeding and patients suffering from liver and renal dysfunction.
4: Injection drugs were classified as prescription drugs in the UK and Singapore.
5: Injection drugs were classified as prescription or BTC drugs in Canada and Thailand.
6: Drugs require special storage or management were classified as prescription or BTC in Singapore.
References: [11, 22, 97, 133-142]

Content analysis found that drug classification criteria composed of three themes: i) disease characteristic, ii) drug safety profile, and iii) other drug characteristic. The details of drug classification criteria across eight countries were illustrated in **Table 19**.

Common drug classification criteria explicitly mentioned across eight countries were i) "Require disease diagnosis from healthcare professional", ii) "Drugs require healthcare profession evaluation/management", and iii) "Drugs creating potentially negative consequences, especially habit-forming drugs". Among these three criteria, "Require disease diagnosis from healthcare professional" was the first discriminating criteria to differentiate prescription from non-prescription drugs. If a lay person cannot accurately identify their illness, drugs indicated for those illness cannot be classified non-prescription. However, if a lay person can identify their illness, but indicated drugs required healthcare profession evaluation/management", then drugs must be classified prescription. If a lay person can identify their illness and drugs did not require health professional to evaluate/manage, but drugs creating potentially negative consequences", then drugs must be considered prescription.

Other common criteria explicitly mentioned in at least half of studied countries were "Require subsequence disease monitoring" (US, UK, SG, PHL, CA), "Misuse" (US, UK, JP, CA, TH), and "Injection dosage form"(UK,SG, CA, TH). The UK and Singapore classified injection drug as prescription status, while Canada and Thailand classified injection drug as either prescription or BTC drugs [11, 22, 97, 133-142].

Other less common explicit criteria worth mentioning about were "micro-organism resistant" (CA), "masking serious diseases' symptom" (UK,SG, CA) ,"Pack size" (UK, TH), "need special

storage and handling" (SG), and "Time since market authorization" (MY, PHL). Micro-organism resistant was obviously a global problem, however only one country list it as an explicit criteria. Malaysia and Philippines required that drug product listed as GSL must be in the market for at least 10 years to ascertain safety profile [11, 22, 97, 133-142].

Each drug scheme among countries seem to share a lot of principles. Nevertheless, the most distinguish criteria, found in this study, is the OPS drug scheme between Canada and Thailand. In Canada, OPS drugs are drugs that still need a supervision from healthcare professionals, but at the least level compared to prescription and BTC drugs. Whereas, OPS drugs are basically GSL drugs that have larger pack sizes. OPS drugs in Thailand clearly is stated that a supervision from healthcare professionals is not required [11, 137]. The details of differences are shown in **Table 20**.

Table 20: OPS drug scheme criteria in Canada and Thailand

OPS drug scheme criteria	CA	TH
Disease characteristics		
Recurring symptoms or long term conditions	Yes	
Safety profiles		
Pharmacist supervision is needed in several cases	Yes	
Pharmacist supervision is not required		Yes
Chronic use of drugs may mask symptoms of serious diseases	Yes	
Drug may be abused	Yes	
Low risk for vulnerable people (i.e. Children, pregnant women, breastfeeding, and people suffering from renal and liver dysfunction)		Yes
Other drug characteristic		
New drug for GSL drugs	Yes	
Not an injection	Yes	Yes
Easy to use by following labels		Yes

Abbreviations: CA, Canada; TH, Thailand; GSL drugs, general sale list drugs.

Reference: [11, 137]

1.3. Actual drug classification from drug regulatory agencies' decision among countries.

The classification category of 53 drugs from 11 indications are shown in **Table 21**. It can be seen that there are variations among countries.

A few prescription drugs are classified as the same category in all countries. These drugs are alprazolam, lorazepam, and diazepam, which are insomnia treatments that are psychotropic substances. Ondansetron and granisetron, which are used for a prevention of nausea and vomiting associated with highly emetogenic chemotherapy in cancers, are also other examples.

Nonetheless, it can be seen that most selected drugs in Thailand are classified as BTC drugs. Antibiotics, lipid-lowering drugs and antihypertensives in Thailand are differently classified from other countries, while some diabetes drugs in Thailand and Malaysia are similar, but still different when compare with the rest countries. Most countries classify them as prescription drugs, while Thailand and some drugs in Malaysia are BTC drugs.

Other drugs that treat minor ailments: fungal infection, pain, allergy and smoking cessation vary among countries. The result shows that minor ailment treatments that have low risk are likely classified in the US, the UK, Japan, Singapore and Canada as less stringent controlled categories than in Thailand, Malaysia and the Philippines. The examples are ibuprofen 200 mg and cetirizine 10 mg. In Thailand, most of these minor ailment drugs are BTC drugs, with only few low risk drugs classified as OPS drugs. The examples are loratadine tablets, nicotine gums and nicotine patches. Malaysia classified some minor ailment drugs similar to Thailand. It also can be seen that some minor ailment drugs that have serious side effect, such as, diclofenac sodium (Increase serious cardiovascular effects) and ketoconazole tablets (liver damage) likely to classified as prescription drugs in all countries, except Thailand and Malaysia.

The classification of vaccines is another interesting point. All vaccines are classified as prescription drugs in every country, except Canada and Thailand. Vaccine regulations in the US vary among states, depending on the states' law; while, in Canada, the law states that all vaccines required a prescription, except those that are parts of a routine immunization program are classified as BTC vaccines. In Thailand, some vaccines are classified as BTC drugs either. However, all vaccines, not strict to only those that are parts of a routine immunization program, can be BTC vaccines. The examples of them are rabies and influenza vaccines.

Table 21: Actual drug classification from drug regulatory agencies' decision across countries (Updated February 2020)

Indication	Drug	Strength and dosage form	US	UK	JP	SG	MY	PH	CA	TH
Insomnia	Alprazolam	0.4 mg tablets	-	-	P	-	-	-	-	-
	Alprazolam	0.5 mg tablets	P	P	-	P	P	P [1]	P	P [2]
	Lorazepam	1 mg tablets	P	P	P	P	P	P [1]	P	P [2]
	Diazepam	5 mg tablets	P	P	P	P	P	P [1]	P	P [2]
Nausea and vomiting	Ondansetron	4 mg tablets	P	P	P	P	P	P	P	P
	Ondansetron	8 mg tablets	P	P	-	P	P	P	P	P
	Granisetron	1 mg tablets	P	P	P	P	P	-	P	P
	Domperidone	10 mg tablets	-	P	P	P / BTC [3]	P	BTC [4]	P	BTC
Dyslipidemia	Simvastatin	10 mg tablets	P	P	P	P	P	P	P	BTC
	Atorvastatin	20 mg tablets	P	P	P	P	P	P	P	BTC
	Gemfibrozil	600 mg tablets	P	P	-	P	P	P	P	BTC
	Fenofibrate	200 mg tablets	P	P	-	P	P	P	P	BTC
Hypertension	HCTZ	50 mg tablets	P	-	P	P	P	P	P	BTC / OPS [5]
	Propranolol	10 mg tablets	P	P	P	P	P	P	P	BTC
	Enalapril	5 mg tablets	P	P	P	P	P	P	P	BTC
	Enalapril	10 mg tablets	P	P	P	P	P	P	P	BTC
	Losartan	50 mg tablets	P	P	P	P	P	P	P	BTC

Indication	Drug	Strength and dosage form	US	UK	JP	SG	MY	PH	CA	TH
Diabetes	Metformin	500 mg tablets	P	P	P	P	BTC	P	P	BTC
	Glipizide	5 mg tablets	P	P	-	P	BTC	P	P	BTC
	Glimepiride	1 mg tablets	P	P	P	P	BTC	P	P	BTC
	Sitagliptin	100 mg tablets	P	P	P	P	P	P	P	BTC
	Linagliptin	5 mg tablets	P	P	P	P	P	P	P	BTC
Bacterial infection	Amoxicillin	250 mg capsules	P	P	P	P	P	P	P	BTC
	Levofloxacin	250 mg tablets	P	P	P	P	P	P	P	BTC
	Azithromycin	250 mg capsules	P	P	P	P	P	P	P	BTC
	Azithromycin	200 mg/5 mL[6]	P	P	-	P	P	P	P	BTC
	Doxycycline	100 mg capsules	P	P	P	P	P	P	P	BTC
	Clindamycin	150 mg capsules	P	P	P	P	P	P	P	BTC
Fungal infection	Clotrimazole	1% cream	P / GSL[4]	BTC / GSL [4]	P / T [4]	GSL	GSL	P	GSL	OPS
	Ketoconazole	2% cream	P	P / BTC / GSL [4]	P	BTC / GSL [4]	BTC	GSL	P	BTC
	Ketoconazole	200 mg tabs	P	P	-	P	P	-	P	BTC
Pain	Ibuprofen	200 mg capsules	GSL	BTC / GSL [4]	P / GSL [4]	P/BTC /GSL[3,4]	BTC	BTC	GSL	BTC
	Ibuprofen	400 mg tablets	P	P / BTC / GSL [4]	-	P / BTC	BTC	BTC	GSL	BTC
	Celecoxib	200 mg capsules	P	P / BTC [4]	P	P	P	P	P	BTC
	Diclofenac Na	25 mg tables	P	P	P	P	BTC	P	P	BTC
	Diclofenac K	25 mg tablets	P	P	-	P	-	BTC	P	BTC

Indication	Drug	Strength and dosage form	US	UK	JP	SG	MY	PH	CA	TH
	Piroxicam	20 mg tablets	P	P	P	P	BTC	P	P	BTC
Allergy	Hydroxyzine	10 mg tablets	P	P	P	P	BTC	P	P	BTC
	Cetirizine	10 mg tablets	GSL	P / BTC/ GSL [4]	P / GSL [4]	P / GSL [4]	BTC	BTC	GSL	BTC
	Cetirizine	1 mg/ml syrup	P / GSL [4]	BTC / GSL [4]	-	BTC / GSL [4]	BTC	BTC	OPS	BTC
	Loratadine	10 mg tablets	GSL	P / BTC/ GSL [4]	P / T [4,7]	BTC / GSL [4]	BTC	BTC	GSL	BTC / OPS [8]
	Levocetirizine	5 mg tablets	P	P	P	P / BTC [3]	BTC	P	-	BTC
	Desloratadine	5 mg tablets	P	P	P	P / BTC [3]	BTC	P	GSL	BTC
Smoking cessation	Nicotine	2 mg gums	GSL	GSL	GSL	BTC	BTC	BTC	GSL	OPS
	Nicotine	4 mg gums	GSL	GSL	-	BTC	BTC	-	GSL	OPS
	Nicotine	2 mg lozenges	GSL	GSL	-	BTC	BTC	BTC	-	BTC
	Nicotine	4 mg lozenges	GSL	GSL	-	-	BTC	BTC	-	BTC
	Nicotine	patches	GSL	GSL	P / T [4]	BTC	BTC	-	GSL	OPS
Preventive vaccines	BCG	Injections	P [9]	P	P	P	P	P	P [10]	BTC
	IPV	Injections	P [9]	P	P	P	P	P	BTC [10]	P
	Influenza	Injections	P [9]	P	P	P	P	P	BTC [10]	BTC
	MMR	Injections	P [9]	P	-	P	P	P	BTC [10]	BTC
	Rabies	Injections	P [9]	P	P	P	P	P	P [10]	BTC

Abbreviations: US, the United States; UK, the United Kingdom; JP, Japan; SG, Singapore; MY, Malaysia; PH, the Philippines; CA, Canada; TH, Thailand; P, prescription drugs, BTC, Behind-the-counter drugs; T, transition drugs; OPS, Open-shelf drugs, GSL, General sale list drugs

1. These drugs are exempted dangerous drugs (EDD, Rx).

2. These drugs are classified by the Psychotropic Substances Act B.E. 2559 as psychotropic substances schedule 2. A seller must be granted for a license to sell psychotropic substances in schedule 2 and must dispense only when prescriptions are available.

3. These drugs are granted the exemptions for supply without a prescription as BTC drugs if certain criteria are met.

4. Each brand of these drugs classified into different schemes.

5. This drug is classified as OPS drugs if they are contained in four or ten tablet-packaging with designated warning. Otherwise, it is classified as BTC drugs.

6. Powder for oral solutions or suspensions.

7. This drug is reclassified from prescription to BTC drugs on 17 January 2017. The post-marketing survey on safety was planned to be three years.

8. This drug is classified as BTC drugs unless it met certain criteria, which are in divided solid dosage forms for oral use containing 10 milligrams or less per dose form with label "only for a season allergic rhinitis, not for runny nose from the common cold" when sold in the manufacturer's original pack containing not more than 10 tablets per strip, 2 strips per carton.

9. In the US, the regulations of vaccines vary among states. The same vaccines in some states may require prescription, while other states might not require [143].

10. All vaccines in Canada are classified into S1 except which are part of a routine immunization program in most/all provinces and territories [144].

Reference: concluded in table 12

1.4. The contexts of each country

The contexts of each country that may associate were collected. These are healthcare context, citizen education levels and socioeconomic status. The results are shown in Table 22.

Table 22: The associated context of each country

Country	Healthcare context		Citizen education levels	Socioeconomic status
	Pharmacists can response to patients' symptoms.	Pharmacists can vaccinate.	Learning-Adjusted Years of Schooling (LAYs) [145]	Human Development Index (World ranking) [146, 147]
The US	No [148]	Yes [149]	11.1	Very High (15)
The UK	Yes [150]	Yes [149]	11.5	Very High (15)
Japan	No [151]	No [149]	12.3	Very High (19)
Singapore	Yes [152]	No [153]	12.9	Very High (9)
Malaysia	Yes [100]	No [154]	9.1	High (61)
Philippines	Yes [101]	Yes [143]	8.4	Medium (106)
Canada	Yes [155]	Yes [149]	11.7	Very High (13)
Thailand	Yes [156]	No [156]	8.6	High (77)

2. the economic impact of delisted non-prescription drugs from NLEM in Thailand using non-sedating antihistamines as a case study.

2.1. Net benefits

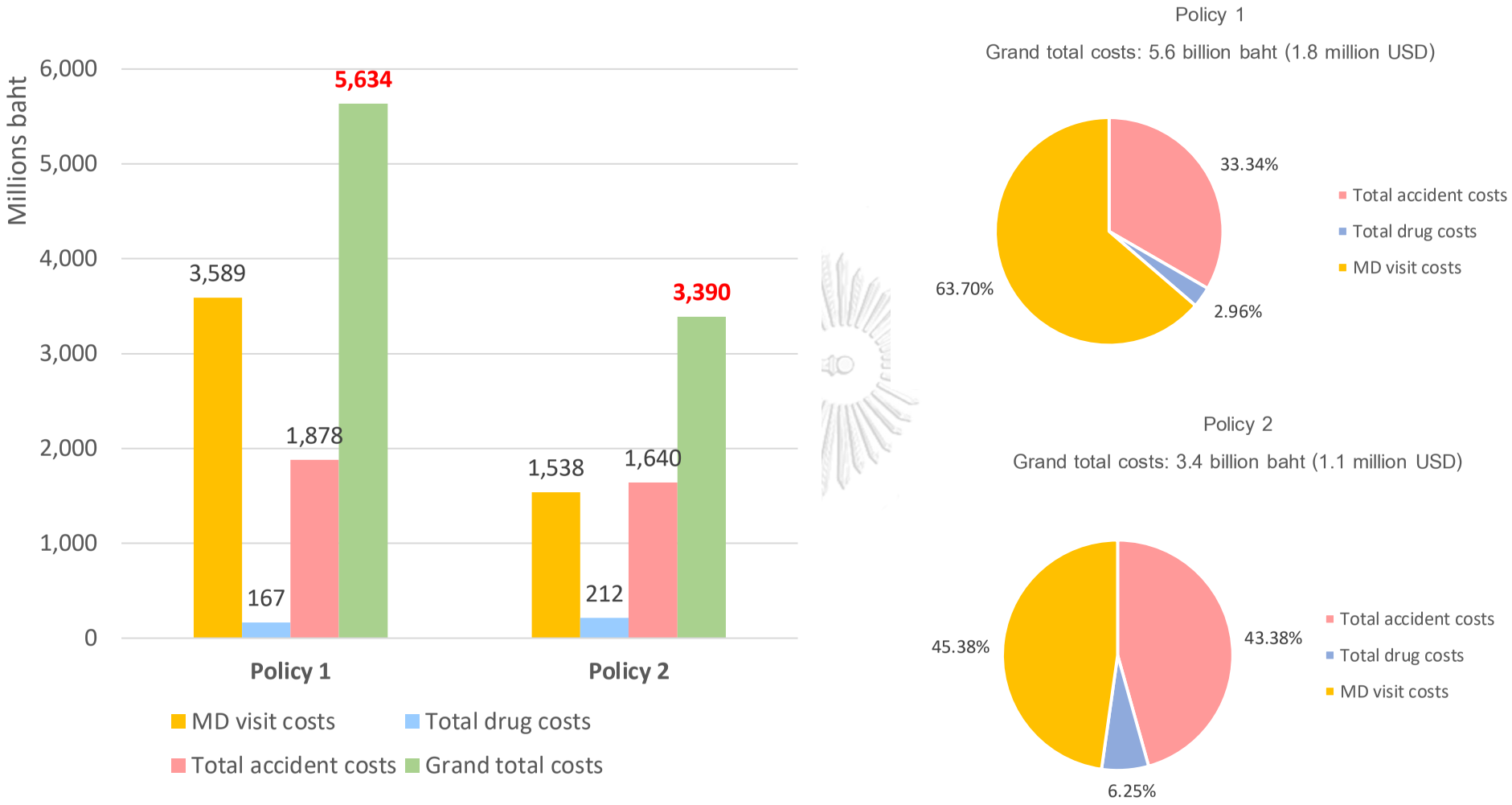
From the healthcare system perspective, the model estimates that the present policy (policy 1) implementation results in 5.63 million baht (181.46 million USD) annual expenses. Whereas, the implementation of policy 2, assuming loratadine and cetirizine were no longer reimbursed and MD visits were decreased from 70% to 30% or 40% decrease, results in 3.39 million baht (109.18 million USD) annual expenses. Therefore, the annual total net benefit from policy 2 implementation would be 2.24 billion baht (72.39 million USD). Patients who self-medicate have to annually pay 13.19 baht (0.42 USD) and 6.30 baht (0.20 USD) for loratadine and cetirizine, respectively.

Table 23: Cost components of policy 1 and policy 2.

Components	Policy 1			Policy 2		
	Thai baht	USD	% (from grand total costs)	Thai baht	USD	% (from grand total costs)
MD visit costs	3,588,834,925	115,593,613.70	63.70%	1,538,072,111	49,540,120.16	45.38%
Total drug costs	166,508,118	5,363,098.46	2.96%	211,757,933	6,820,560.22	6.25%
Loratadine	14,206,350	457,575.62	0.25%	0	0.00	0.00%
Cetirizine	8,293,824	267,137.68	0.15%	0	0.00	0.00%
Sedating AH	10,905,839	351,268.70	0.19%	9,520,971	306,663.15	0.28%
Other non-sedating AH	44,730,397	1,440,731.71	0.79%	46,008,409	1,481,895.48	1.36%
INS	88,371,707	2,846,384.74	1.57%	156,228,554	5,032,001.60	4.61%
Total accident costs	1,878,311,301	60,498,962.89	33.34%	1,639,795,580	52,816,554.90	48.38%
MV accident costs	1,614,297,603	51,995,284.65	28.65%	1,409,307,431	45,392,708.83	41.58%
Occupational accident costs	264,013,698	8,503,678.24	4.69%	230,488,149	7,423,846.08	6.80%
Grand total costs	5,633,654,343	181,455,675.05	100.00%	3,389,625,624	109,177,235.29	100.00%

Abbreviations: MD, medical doctor; Exchange rate: 1 USD = 31.0470 Baht

Figure 5: Bar chart and pie charts demonstrating cost components of policy 1 and policy 2



The grand total costs of both policies show in the bar chart and pie charts **(Figure 5)**. The grand total costs can be distributed into three major parts: MD visit costs, total drug costs, and total accident costs. The majority of healthcare system expenses of policy 1 are MD visits costs (63.70%), following by total accident costs (33.34%) and total drug costs (2.96%). Whereas, the expenses in policy 2 consist of both MD visits costs (45.38%) and total accident costs (48.38%) as the major parts, and a small portion from total drug costs (6.25%). For net benefit from policy 2 implementation, majority of the expenses clearly from huge decreased MD visit costs. However, the healthcare system pay more drug costs, compared to policy 1. The further details of cost components are shown in **Table 23**. It can be seen that total drug costs increase from the increasing costs of other non-sedating antihistamines and intranasal corticosteroids. Although cetirizine and loratadine costs are abandoned in Policy 2, the remaining patients visiting hospitals would receive non-sedating antihistamines and intranasal corticosteroids instead. Since both of these drugs are more expensive than loratadine and cetirizine, total drug costs increase in policy 2.

2.2 Sensitivity analysis

Scenario analysis

The results from two different scenarios are presented in **Table 24**. When all patients, except who covered by CSMBS, switched to receive sedating antihistamines; the net benefit would decrease from the base case approximately 834 million baht (27 million USD). In the contrary, if the patients switched to use intranasal corticosteroids instead, the net benefit would increase from the base case 1.4 billion baht (25 million USD). In conclusion, patients switching to receive intranasal corticosteroids would save cost more than switching to sedating antihistamines. However, cost saving is still demonstrated.

Table 24: Scenarios around the switch rates in policy 2

Scenario	Probability		Net benefits	
	Sedating AH	INS	Thai baht	USD
Base case	55%	33%	2,244,028,719	72,278,440
Scenario 1	88%	0%	1,410,667,342	45,436,511
Scenario 2	0	88%	3,632,964,348	117,014,988

Abbreviations: AH, antihistamines; INS, intranasal corticosteroids.

Univariate sensitivity analysis

To examine the parameters that affect the model, a univariate sensitivity analysis was performed by changing different parameters of policy 2 in the model by ±25%. These parameters were allergic rhinitis prevalence in Thailand, MD visit probability, MD visit costs, all of each drug costs and all of accident costs. The results from this sensitivity analysis are presented as a tornado diagram in **Figure 7**. The parameters are listed in descending order, according to their impact level to cost saving. It can be seen that MD visit probability has the greatest impact to the model, following by AR prevalence and MD visit costs. Whereas, the rest parameters affect the model at small levels.

Multivariate sensitivity analysis

Having found that MD visit probability was the greatest impact on the model, multivariate sensitivity analysis was further performed due to uncertainty of MD visit probability in both policy 1 and policy 2. The results of this analysis would show the decreased MD visit probability in policy 2 that still results in cost saving from various MD visit probability, ranging from 0-100%, in policy 1. The results are demonstrated in **Figure 6**. It can be seen that all MD visit probability in policy 1 can achieve cost saving in particular point when policy 2 is implemented. At base case scenario –MD visit probability of policy 1 is 70 %– the probability of MD visit from policy 2 implementation should decrease to 49.86% in order to achieve cost saving.

Figure 6: Multivariate (two-way) sensitivity analysis graph demonstrating MD visit probability, resulting in cost saving, after policy 2 implementation at each MD visit probability in policy 1

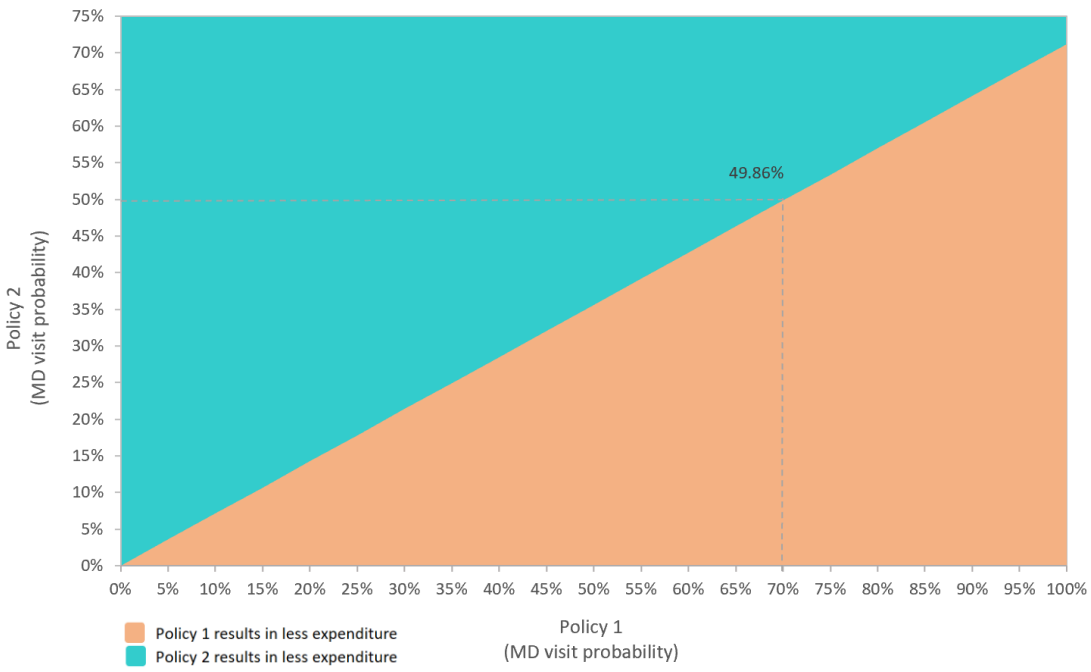
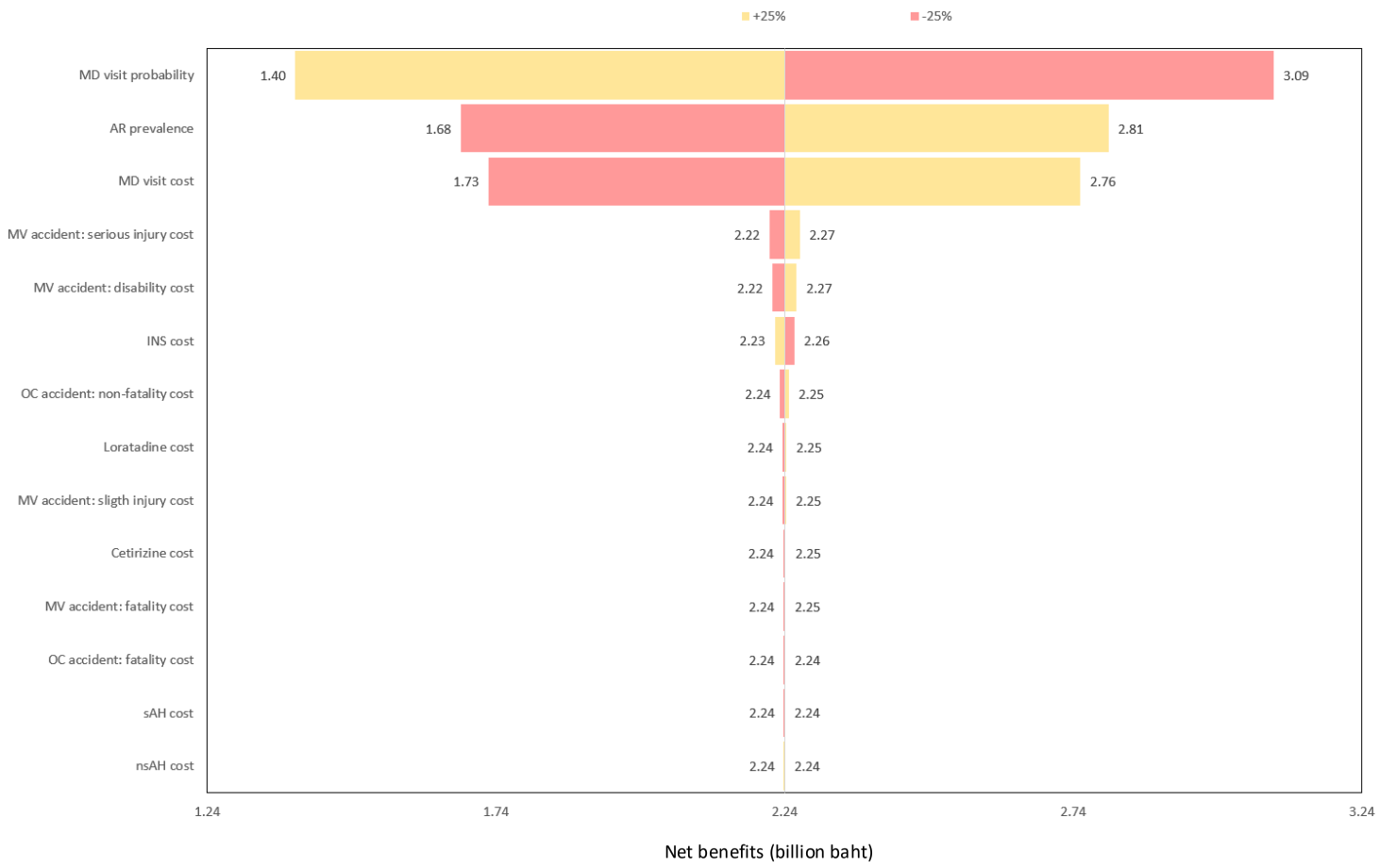


Figure 7: Tornado diagram of the impact on net benefits from varying each parameter in policy 2 by ±25%



Abbreviations: AR, allergic rhinitis; MD, medical doctor; MV, motor-vehicle; INS, intranasal corticosteroids; OC, occupational; sAH, sedating antihistamines; nsAH, other non-sedating antihistamines, apart from loratadine and cetirizine

CHAPTER 5

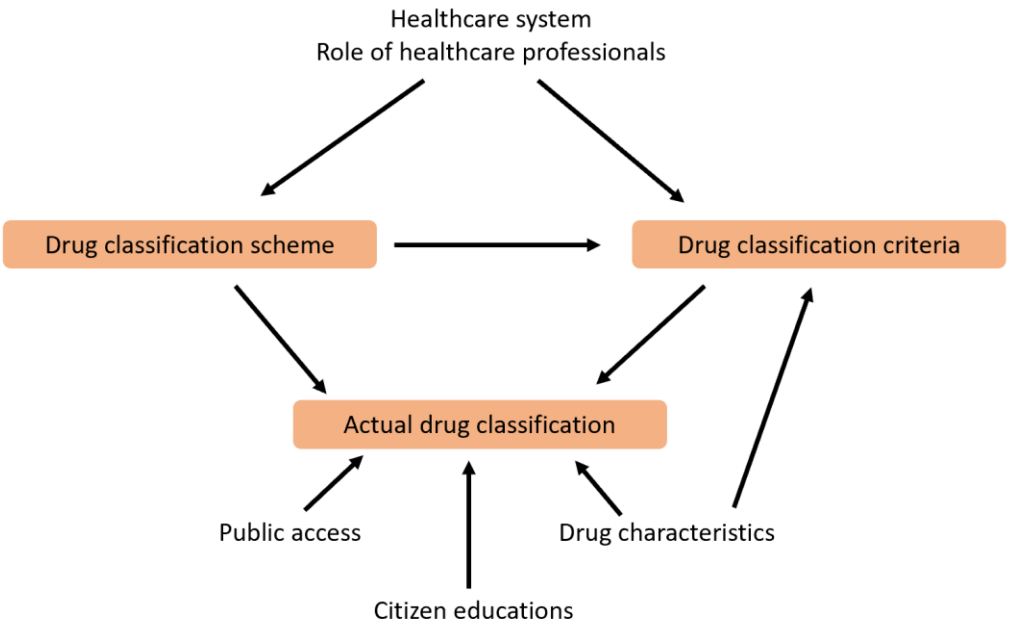
Discussion

This is the first study that comprehensive review drug classification scheme and examine the economic impact when use it as the criteria for listing drug reimbursement list in Thailand. Good drug classification scheme should maintain patient safety, increase timely access, and decrease healthcare system expenditure as possible.

1. Principles

From the drug classification system review, the results show that most countries share the same principle of drug classification system; however, each country has their own enforcement details. Drug classification schemes of each country are not related to how stringent the drug regulatory agencies are, but mainly related to healthcare system and role of healthcare professionals. Drug classification criteria in each country affected by healthcare system, role of healthcare professionals and drug classification scheme. While classifying drugs into one scheme is affected by drug classification scheme and criteria, drug characteristics, public access, citizen educations of each country **(Figure 8)**.

Figure 8: Factors that associate with drug classification scheme.



Each drug scheme has their own implementation purpose, related to healthcare system and roles of healthcare professionals. If a purpose of a scheme is repealed, that scheme should be discontinued. One example of the relation between the drug scheme and healthcare system and roles of healthcare professionals can be seen in the BTC drug scheme. This scheme is implemented for the purpose as framing drugs that pharmacists are allowed to dispense without prescriptions. Thus, BTC drugs are responsible by pharmacists to make a decision whether to dispense a drug to a patient. BTC drug scheme can be found in countries that pharmacists have one of the roles as response to patients' symptoms. Whereas, countries (the US and Japan) that pharmacists are not allowed to do so does not implement this scheme.

Apart from the scheme, the criteria of drug classification are another important part in drug classification system since it directly affects the actual drug classification from drug regulatory agencies' decisions. The good criteria of drug classification should be established in order to classify drugs that meet a scheme purpose into that scheme. Moreover, after classification, balance between patient safety and timely access of drugs should be observed.

To establish the good criteria of a drug scheme, we need to know the responsibility of that scheme first. Then, we need to consider the roles of the schemes' responsibility across three themes

of drug characteristics: disease characteristics, drug safety profile, and other drug characteristic. If a drug need physicians to do any job in one of these three themes of drug characteristics, that drug should be classified as the scheme that responsible by physicians: prescription drug scheme. If a drug do not need physicians to do any job in these three themes of drug characteristics, but need pharmacists; that drug should be classified as the scheme that responsible by pharmacists: behind-the-counter drugs scheme. However, if a drug do not need any healthcare professionals to do their jobs, it can be classified as the general sale list drug scheme, which is responsible by patients (**Table 25**).

Table 25: Principles of drug classification criteria.

Drug scheme	**Whose responsibility**	**Drug characteristics**		
		Disease characteristics	**Drug safety profile**	**Other drug characteristic**
Prescription drugs	Physicians	Diagnosis that require special tools	Need monitoring from physicians	Administration by physicians
BTC drugs/ transition drugs	Pharmacists	Diagnosis without special tools	Need advice or enforcement from pharmacists	Administration by pharmacists or drug use need instruction.
OPS drugs	Pharmacists (CA) Certified sellers (TH)	Self-diagnosis by patients	Need enforcement from pharmacists/ certified sellers	Drug use need instruction or enforcement from pharmacists/ certified sellers
GSL drugs	Patients	Self-diagnosis and self-selection	Self-management	Self-administer

Abbreviations: BTC drugs, behind-the-counter drugs; OPS drugs, open-shelf drugs; GSL drugs, general-sale list drugs; CA, Canada; TH, Thailand.

Nonetheless, although all selected countries share the similar criteria principles, the actual drug classification vary in minor ailment drug groups, such as fungal infection, pain, and allergy. This is because the cut of point that patients can responsible or manage drugs by their selves of each countries are different. This depends on education level of citizens. More educated citizens would be able to understand standardize patient information leaflets and follow them to use drugs properly. This can be seen from the results of actual drug classification caparison of 200 mg ibuprofen tablets and 10 mg cetirizine tablets. The countries that have very high level of HDI or LAYs scores classify these drugs as GSL drugs, while the countries that have lower level classify these drugs as BTC drugs.

From the review, it was found that actual drug classification are not only affected by the scheme and criteria, but also public access. Thus, after considering the drug classification criteria, we need to further contemplate weight between public access and risk level. Some drugs need to limit distribution, although they do no need healthcare professionals' responsibility. An example of them is antibiotics that leading to microorganism resistant crisis. Most countries classify them as prescription drugs although pharmacists can diagnose some types of bacterial infection. In contrast, some drugs need high public access although they need some responsibility from healthcare professionals. An example of them is nicotine gums and patches. They need pharmacists' instruction to use them correctly, however, some countries classify them as GSL drugs. This is because the governments want their citizens to easily access to smoking cessation aids. However, more management plans are required to ensure patient safety using these treatments.

Many countries in Europe maximize drug classification system by using it as a healthcare strategy. They delisted nonprescription drugs from drug reimbursement list to decrease healthcare system's expenditure; and many research report the success. Would it still significantly decrease the expenditure if Thailand adopt this new principle to drug reimbursement policy? The second part of this study was conducted to find the answer using non-sedating antihistamines for intermittent allergic rhinitis as a case study.

The second part of this study shows that whether delisting non-sedating antihistamines from NLEM in adult patients suffering from intermittent allergic rhinitis can reduce annual healthcare

system expenditure or not depends mainly on the number of MD visits per year. Cost saving can be achieved when the number of MD visits decrease to the particular point. For example, at the base case –MD visit before the new policy implementation is 70%– the MD visit must decrease to 49.86% to achieve cost saving. If the number of MD visits were not decrease to this point, there would be no cost saving, but more expenditures instead. This is because the delisting may affect generous physicians to shift from prescribing the delisted drugs to other listed drugs. in this case study; shifted prescribing drugs are (i) intranasal corticosteroids that are more expensive than non-sedating antihistamines, and (ii) sedating antihistamines that can lead to more accidents, which increase healthcare system expenditure due to more hospitalization.

There are two reasons why decreasing MD visit of the new policy –delisting non-sedating histamines in adult patients who suffering from intermittent allergic rhinitis from NLEM— lead to cost saving.

First, allergic rhinitis is a mild ailment that a large number of people suffer from. It is easily to be recognized, and treatments of this disease do not have serious side effect from misuse. Patients can safely self-diagnose, self-manage, and self-medicate.

Second, untreated intermittent allergic rhinitis patients do not have a tendency to suffer from other comorbidities. Although allergic rhinitis can lead to another comorbid: asthma. They significantly affect only to patients who suffer from persistent allergic rhinitis. Moreover, data reporting that untreated allergic rhinitis patients would likely to have asthma more than treatment group has not been found.

How big of the net benefit depends on the percentage between sedating antihistamines and intranasal corticosteroids that the remaining MD visit population receive. From the scenario analysis, patients should switch to use intranasal corticosteroids instead due to more total cost saving. Patients also get benefits from intranasal corticosteroids more than sedating antihistamines since it has more effectiveness and less side effects. However, the healthcare system have to pay more in total drug cost part because intranasal corticosteroids are the most expensive treatments among others. Thus, hospital would prefer to prescribe sedating antihistamines, which is the cheapest treatments. Sedating antihistamines would be the better choice than intranasal corticosteroids only if patients strictly follow the pharmacists advice –not drive or use machinery after taking sedating

antihistamines. This would decrease accident probability and results in decreasing expenditure from hospitalization.

Nonetheless, this economic impact study cannot be generalized to other drugs because each drug has different side effects and different impact of physicians' prescribing behavior. Further research in different mild ailments in Thailand scenario should be conducted in different model.

Comparing to other research conducting about the economic impact of drug classification scheme, research that report cost saving often conduct in mild ailment area; while others that report more healthcare system's expenditure often conduct in disease that actually need prescriptions to be dispensed. An example is dyslipidemia [38, 45, 60-69]. This reflects that before introducing the new drug reimbursement policy, all drugs should be classified into their most proper schemes. if drugs that should be classified as prescription drugs are classified by the drug regulatory agency to BTC or GSL drugs, risks would outweigh benefits and result in more expenditures for healthcare system, especially if the new reimbursement policy is implemented.

2. Limitation

For the drug classification scheme review part; although the results of the study may change overtime, the analysis principles from this study are robust enough for adoption. Most results were obtained mainly from high credible sources, such as government documents, however, it may not reflect the real practice, which sometimes different from documents. In contrary, data from Malaysia, the Philippines, and Thailand may reflect the real practice more as the expert interview was done since some documents were not written in English or difficult to access. Further research should explore in more countries to obtain more beneficial drug classification principles.

Several limitations can also be observed in the economic impact analysis part. First, This study contains several assumptions, for example the number of MD visit per patient per year. Therefore, the cost-saving might be varied from the base case. Second, it was assumed that all MD visits from a hospital database are intended for intermittent allergic rhinitis; although in the real practice, patients might visit a hospital for other symptoms, but coincidently suffer from intermittent allergic rhinitis either. Unfortunately, there is no way to know the real patients' intention. Third, the researcher did not include non-md visit scenario in the study due to lacking of market share data, and data regarding patient behaviors' change in pharmacy setting when the new reimbursement

policy is implemented. Nonetheless, accident cost is the only cost from non-md visit scenario that healthcare system need to pay. These costs were already varied in univariate sensitivity analysis in the study; and the results show only small impact. Forth, from patient perspective, although drug costs shifted from healthcare system to patients are the small amount, indirect cost, such as productivity loss, has not yet been analyzed. Further research may conduct by using societal perspective or patient perspective. Lastly, this study assumes that all patients receive one drug to simplify the model, but in real practice, most patients receive the combination drugs, such as non-sedating antihistamines and sedating antihistamines.

3. Policy recommendations

In Thailand, all four drug schemes have their own purpose and well related to the healthcare context. Whether the OPS (non-dangerous) drug scheme in Thailand should be discontinued or not, depending on the present of type 2 community pharmacies since it is the main purpose of the OPS drug scheme implementation. If four-classification scheme were maintain, the OPS drug scheme and type 2 community pharmacies should be continued. Since type 2 community pharmacies establish in order to increase public access in rural area, policy makers should review all OPS drugs to ensure that they are suitable to be classified into this scheme. OPS drugs should be drugs that actually meet the safety criteria of BTC drugs, but really need timely access. However, if the scheme were changed to three-classification scheme, both OPS drug scheme and type 2 community pharmacies should be repealed. Each OPS Drug should then be re-classified into other proper schemes.

Considering relation between the criteria and the roles of healthcare professionals, Thailand need to review several BTC drugs and OPS drugs since they need physicians' involvement.

This is especially true for chronic disease drugs, such as lipid-lowering drugs, antihypertensives and diabetes drugs. They should be re-classified from BTC drugs upward to prescription drugs because physician involvement is needed since blood test and monitoring from a hospital are required. This unsuitable drug status can be confirm from a case study in the UK. Simvastatin 10 mg was reclassified from prescription drugs to BTC drugs once, however, they reclassified upward as prescription drugs a few years later.[47] Re-classification of statins was also

proposed in the US and New Zealand, but both drug regulatory agencies rejected these applications [28, 157].

Another point is vaccines. In some countries, pharmacists not only response to patients' symptoms, advice or instruct how to use drugs to patients; but also vaccinate if they achieve the certification. Pharmacists in these countries can vaccinate patients with or without prescriptions, depending on vaccine legal status decided by drug regulatory agencies. Nonetheless, in Thailand, the criteria of BTC drugs described that injection can be classified as BTC drugs. Some vaccines also classified into the BTC scheme, while pharmacists are not permitted to vaccinate. Only physicians or nurses are allowed to do this role. It can be seen that this criteria is not relate with the pharmacists' role; besides it's not reasonable to classify any vaccines as products responsible by pharmacists in Thailand. To improve the drug classification scheme, vaccines in Thailand should be re-classified as prescription drugs. Otherwise, pharmacists should allow to vaccinate patients. The interesting policy was found in Canada that vaccines that are parts of immunization program are classified into the BTC scheme [144]. This policy properly extend the role of pharmacists, maintain patient safety and increase vaccine accessibility to community. Although it is difficult to be implemented due to the conflict between healthcare professionals, Thailand should consider this policy option with effective pharmacovigilance plan establish.

For currently OPS drugs in Thailand, some selected drugs are mis-classified. The criteria state that OPS drugs are GSL drugs that have bigger pack size, however, the actual classification is not the same as criteria. HCTZ is not suitable to be OPS drugs at all, because it needs physicians to diagnose and monitor drug use. OPS Loratadine is currently a small pack size of BTC loratadine, but according to the criteria, the small pack should be GSL drugs, while the big pack should be OPS drugs.

When considering the public access, several BTC drugs in Thailand need to be re-classified. Currently, the Thai FDA is trying to re-classified all antibiotics as prescription drugs due to antibiotic resistance issue, which is believed that will be success in a next few years. This should be the right decision since risk levels seems to outweigh public access in this case. The rest countries also classify all antibiotics as prescription drugs, although Canada is the only country that clearly include drugs that contribute to microbial resistance as one of the criteria of prescription drugs. Other BTC drugs that have potential life-threatening risk to patients, such as ketoconazole (liver

damage), celecoxib (heart disease) and diclofenac (heart disease) are also need reconsideration because its risks seem to outweigh public access; moreover, there are other pain killers more safe available for self-medication. In contrary, some BTC drugs might have the potential to be GSL drugs if effective patient information leaflets and labels are established. Examples of them are cetirizine and loratadine tablets. These drugs are for allergy, which is the self-diagnosed disease. They also have mild side effects, subsequently they can be self-medicated and self-managed.

From the finding, in Thailand, both four and three-classification scheme is acceptable if it still relates with role of healthcare professionals and other factors. However, whether the number of schemes would change or not, BTC drugs in Thailand need to be reclassified since several of them classified into improper scheme. This reflects that the criteria using for drug classification also need to be re-established.

To adopt the new reimbursement policy by delisted non-prescription drugs in Thailand, drugs should be classified into the most proper class first. Delisting nonprescription drugs that actually should be prescription drugs would results in disadvantage in every aspects: Patients can be easily harm from self-medication, governments need to pay for that harm and results in more expenditure, Healthcare professionals also have more burden from that harm.

It can be seen that good drug classification scheme not only maintains safety and drug accessibility for patients; but also decrease healthcare expenditures and burdens to healthcare system. It is very important to find out which drugs need healthcare professionals to look after and which one can be self-medicated by patients. Putting wrong drugs in the non-prescription scheme can lead patients to danger, while putting wrong drug in the prescription scheme limits drug timely access and also increases burden to healthcare system. However, the good system will be nothing if the enforcement is not strongly adopted by healthcare professionals. Physicians should prescribe drugs that most suitable for patients and provides them at proper amounts. Pharmacists should be available during operation hours at pharmacies, and dispense drugs that they are allowed to do. The governments should strongly enforce healthcare professionals to strict to the law by establishing more strategies.

Nonetheless, to help decrease burden of healthcare professionals, a campaign need to be established to reduce unimportant hospital visits. Only delisting non-prescription drug

reimbursement may not strong enough to decrease unnecessary hospital visits. Thai citizens also need to be empowered by being educated that they have to responsible for their own health and understand which situations that they really need to visit hospitals. If their symptoms are minor ailments, they should self-medicate from pharmacies or retailers first; and avoid unimportant hospital visit. Patients also get benefits from this principle since they do not have to waste their time to visit hospitals and wait for a long queue. Patient information leaflets, labels, advertisements and other developed digital media may be the good options to educate this matters to the citizens. Patients should also learn to prevent themselves from diseases if they can. For example, in allergic rhinitis, the best way to reduce the symptoms is away from allergens. This prevention does not need any investment from healthcare system and patients. This cost saving from self-care of minor ailments would be allocated to healthcare system and physicians to support patients who are in more need, such as patients who suffer from cancers, kidney failure, liver dysfunction, and other catastrophic diseases. Nonetheless, the government should also concern regarding what patients would face from delisting OTC drugs from the benefit scheme before implementation. Plans might be needed to compensate for patients.

The new drug classification scheme and criteria in Thailand proposal

From all finding, I propose the new drug classification scheme and criteria in Thailand (**Table 25 and Figure 9**). The context of Thailand using for this model is described in **Table 26**. In this model, type 2 community pharmacies are repealed since they have a tendency to be cancelled in the future.

This proposed model should then be developed further by expert consultation and public hearing.

Table 26: Thai healthcare context using in the proposed criteria of drug classification

Context	Data
Drug regulatory agency	Thai Food and Drug Administration (TH FDA)
Universal healthcare coverage implementation	Yes
Physician's main job	Diagnosis, operation, invasive drug administration.
Pharmacists' main job	Self-diagnosis confirmation, minor illness and drug consultation, lifestyle change advice, drug

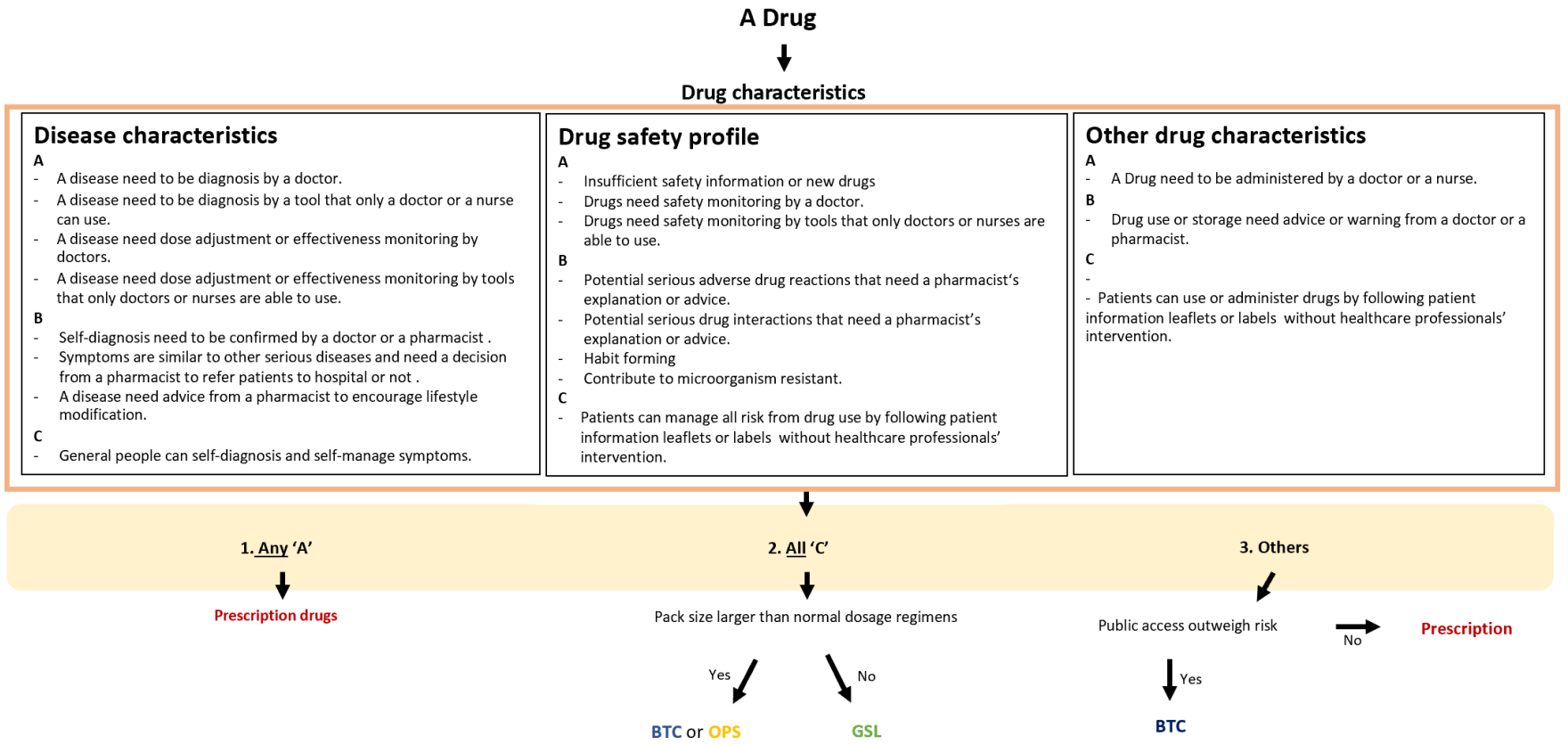
Context	Data
	use instruction, medication conciliation.
- Response to patients' symptoms	Yes
- Vaccination	No
Retailed pharmacy	
- Pharmacy schedule	No, only type 1 community pharmacy
- Non-pharmacist pharmacy	No

Table 27: The new drug classification scheme and regulation proposal in Thailand

Drug scheme	Description	Drug reimbursement eligibility
Controlled drugs (Prescription drugs)	The physicians' responsible scheme or need prescriptions from physicians to be dispensed.	Yes
Dangerous drugs (BTC drugs)	The pharmacists' responsible scheme or need to be dispensed by pharmacists with or without prescriptions, must kept behind the counter.	No or conduct economic impact analysis to help making decisions
Non-dangerous drugs (OPS drugs)	The lower stringent pharmacists' responsible scheme or need to be sold in pharmacies, but can be displayed at public section.	No or conduct economic impact analysis to help making decisions
Household remedies (GSL drugs)	No gate keeper or can be sold in retailers	No or conduct economic impact analysis to help making decision

Abbreviations: BTC, behind-the-counter; GSL, general sale list

Figure 9: Proposed criteria of drug classification in Thailand



Abbreviations: BTC drugs, behind-the-counter drugs, GSL drugs, general sale list drugs

CHAPTER 6

Conclusion

All eight selected countries classify drugs into two major categories: prescription and non-prescription drugs. Some countries may further subclassify non-prescription drugs. Drug classification scheme in each country affected by many factors, including healthcare system, the roles of healthcare professionals, citizen education levels and socioeconomic status. In Thailand, policymakers should review drug classification scheme because several drugs are classified into unappropriated schemes. The new reimbursement policy of non-prescription drug is worth considering policy since the case study, delisting non-sedating antihistamines from NLEM, results in huge cost-saving. However, drugs that classified into non-prescription drug scheme should be the suitable drugs for this scheme first.

All learning from this study provides the new drug classification scheme, drug classification criteria and new reimbursement policy in Thailand. The model proposal should be further developed by expert consultations and public hearing before implementation in the future.

REFERENCES

1. Sukrod N. Principle of Thailand Medicine Reclassification Guidelines 2015 [cited 2020 23 April]. Available from: http://www.tsmia.or.th/RTD2015/5-THAILAND%20(Sept%2017)%20Drug%20reclassification%20guideline%20(final).pdf.
2. GOV.UK. Oral diclofenac presentations with legal status 'P' – reclassified to POM 2015 [cited 2019 23 Oct]. Available from: https://www.gov.uk/drug-device-alerts/drug-alert-oral-diclofenac-presentations-with-legal-status-p-reclassified-to-pom.
3. Consumer Healthcare Product Association. Rx-to-OTC Switch: switch list 2018 [cited 2019 26 Oct]. Available from: https://www.chpa.org/Switch.aspx.
4. Nguyen-Kim L, Or Z, Paris V, Sermet C. The politics of drug reimbursement in England, France and Germany. Health economics letter. 2005;99:1-6.
5. Ewbank L, Omojomolo D, Sullivan K, McKenna H. The rising cost of medicines to the NHS: What's the story? 2019 [cited 2019 26 Oct]. Available from: https://www.kingsfund.org.uk/sites/default/files/2018-04/Rising-cost-of-medicines.pdf.
6. World Health Organization. Measuring Overall Health System Performace for 191 Countries 2010 [cited 2020 23 April]. Available from: https://www.who.int/healthinfo/paper30.pdf.
7. Sakulbumrunsul R, Taychakhoonavudh S. Pricing and Patient Access Framework to Support Universal Coverage in Thailand [Available from: http://www.pharm.chula.ac.th/dept5/source/images/data/files/NHSO_PPA_Report_240317(2).pdf.
8. Strategy and Planning division OotPSfMoPH. Number of hospitals by category in Thailand 2014 [cited 2020 12 April]. Available from: http://203.157.10.8/hcode_2014/query_02.php?p=3%20/.
9. Thai Food and Drug Administration. Number of Pharmacies 2017 [cited 2020 23 April]. Available from: http://www.fda.moph.go.th/sites/drug/Shared%20Documents/Statistic/establishment.pdf.
10. Thai Food and Drug Administration. Designation of Number of Type 2 Community Pharmacies 2005 [cited 2020 23 April]. Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2548/00155157.PDF?fbclid=IwAR2Qksp4wyeb5ZnkhGZXUNyigAjknzu92GMReDzdSdIfZGWjd6E32VwRwwE.
11. Thai Food and Drug Administration. Guideline of drug reclassification 2019 [cited 2019 23 Oct]. Available from: http://www.fda.moph.go.th/sites/drug/Shared%20Documents/reclass/%E0%B8%A0%E0%B8%B2%E0%B8%84%E0%B8%9C%E0%B8%99%E0%B8%A7%E0%B8%81%20%E0%B8%84.pdf.
12. Office of the Council of State. The Thai Drug Act, B.E. 1967 2019 [cited 2019 18 December]. Available from: http://www.fda.moph.go.th/sites/drug/LawDrug/drug2510-krisdika-v2019.pdf.
13. World Health Organization. Thailand Pharmaceutical Profile 2017 [cited 2020 23 April]. Available from: https://apps.who.int/iris/bitstream/handle/10665/274873/2017-Thailand-pharm-profile.pdf?sequence=1&isAllowed=y.
14. mClinica. New data: Thai pharmacists fear loratadine sales OTC will harm patients 2019 [cited 2019 25 Oct]. Available from: https://mclinica.com/2019/06/thailand-loratadine-convenience-stores/.
15. Thai Tribune. Thai FDA has reclassified loratadine from Dangerous drugs to Non-dangerous drug, while the council of pharmacy do not agree. 2018 [cited 2019 25 Oct].

Available from: http://thaitribune.org/contents/detail/307?content_id=33919&rand=1543412605.
16. MGR Online. The propose of new drug classification scheme: 2018 [cited 2019 25 Oct]. Available from: https://mgronline.com/qol/detail/9610000088655.
17. Sumpradit N, Chongtrakul P, Anuwong K, Pumtong S, Kongsomboon K, Butdeemee P, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. Bulletin of the World Health Organization. 2012;90:905-13.
18. Bamgkok Post. Teens taking 'taxi' ride to drug addiction 2018 [cited 2020 23 April]. Available from: https://www.bangkokpost.com/thailand/special-reports/1529006/teens-taking-taxi-ride-to-drug-addiction.
19. Thai Food and Drug Administration. Counterfeit drug manufacturing was found 2018 [cited 2020 23 April]. Available from: http://pca.fda.moph.go.th/public_media_detail.php?id=2&cat=50&content_id=1671.
20. Thai Food and Drug Administration. Risks of 4x100 (Pro drug) 2020 [cited 2020 23 April]. Available from: https://oryor.com/oryor_miniweb/knowledge_detail.php?cat=2&id=7.
21. Thai Food and Drug Administration. Drug database 2019 [cited 2019 4 Nov]. Available from: http://pertento.fda.moph.go.th/FDA_SEARCH_DRUG/SEARCH_DRUG/FRM_SEARCH_DRUG.aspx.
22. GOV.UK. Medicines: reclassify your product 2019 [cited 2019 23 Oct]. Available from: https://www.gov.uk/guidance/medicines-reclassify-your-product#classifications-of-medicines.
23. Patikorn C, Taychakhoonavudh S, Thathong T, Anantachoti P. Patient access to anti-cancer medicines under public health insurance schemes in Thailand: A mixed methods study. TJPS. 2019;43(3):168-78.
24. Sruamsiri R, Wagner AK, Ross-Degnan D, Lu CY, Dhippayom T, Ngorsuraches S, et al. Expanding access to high-cost medicines through the E2 access program in Thailand: effects on utilisation, health outcomes and cost using an interrupted time-series analysis. BMJ open. 2016;6(3):e008671.
25. Chuengsaman P, Kasemsup V. PD First Policy: Thailand's Response to the Challenge of Meeting the Needs of Patients With End-Stage Renal Disease. Semin Nephrol. 2017;37(3):287-95.
26. Selletti S, Putignano M. Pricing & Reimbursement 2019, Italy 2019 [cited 2019 25 Oct]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/italy#chaptercontent3.
27. Nomura K, Kitagawa Y, Yuda Y, Takano-Ohmuro H. Medicine reclassification processes and regulations for proper use of over-the-counter self-care medicines in Japan. Risk management and healthcare policy. 2016;9:173.
28. Gauld NJ, Kelly FS, Emmerton LM, Buetow SA. Widening consumer access to medicines: A comparison of prescription to non-prescription medicine switch in Australia and New Zealand. PloS one. 2015;10(3):e0119011.
29. Gauld NJ, Kelly FS, Kurosawa N, Bryant LJ, Emmerton LM, Buetow SA. Widening consumer access to medicines through switching medicines to non-prescription: a six country comparison. PLoS One. 2014;9(9):e107726.
30. Organization WH. The Role of the pharmacist in self-care and self-medication: report of the 4th WHO Consultative Group on the Role of the Pharmacist, The Hague, The Netherlands, 26-28 August 1998. Geneva: World Health Organization; 1998.
31. Self-care Federation. THE STORY OF SELF-CARE AND SELF-MEDICATION: 40 years of progress, 1970-2010 2010 [cited 2019 23 Oct]. Available from: https://www.selfcarefederation.org/sites/default/files/media/documents/2019-

07/Story%20of%20Self-Care-pdf.pdf.
32. Consumer Healthcare Product Association. FAQs About Drug Distribution in the United States 2019 [cited 2019 23 Oct]. Available from: https://www.chpa.org/FAQDrugDistribution.aspx.
33. The Pharmaceutical Journal. Diclofenac tablets switch from POM to P 2008 [cited 2019 23 Oct]. Available from: https://www.pharmaceutical-journal.com/news-and-analysis/diclofenac-tablets-switch-from-pom-to-p/10015538.article?firstPass=false.
34. Chuapun W. Pseudoephredrine 2012 [cited 2019 26 Oct]. Available from: http://kmfda.fda.moph.go.th/Journal/Chapter/1/16_163_A1_2.55.pdf.
35. Oster G, Huse DM, Delea TE, Colditz GA, Richter JM. The risks and benefits of an Rx-to-OTC switch. The case of over-the-counter H2-blockers. 1990.
36. Rapaport L. Many people take dangerously high amounts of ibuprofen 2018 [cited 2019 26 Oct]. Available from: https://www.reuters.com/article/us-health-nsaids-overdosing/many-people-take-dangerously-high-amounts-of-ibuprofen-idUSKBN1FS336.
37. Shih Y-CT, Prasad M, Luce BR. The effect on social welfare of a switch of second-generation antihistamines from prescription to over-the-counter status: a microeconomic analysis. Clinical therapeutics. 2002;24(4):701-16.
38. Millier A, Cohen J, Toumi M. Economic impact of a triptan Rx-to-OTC switch in six EU countries. PloS one. 2013;8(12):e84088.
39. Daughton CG, Ruhoy IS. Lower-dose prescribing: minimizing “side effects” of pharmaceuticals on society and the environment. Science of the Total Environment. 2013;443:324-37.
40. Pellisé L, Serra M. The economic impact of an hypothetical Rx-To-OTC switch in Spain. Value Health. 2015;18(November (7)):A341.
41. Gianfrancesco F, Manniing B, Wang R-h. Effects of prescription-to-OTC switches on out-of-pocket health care costs and utilization. Drug Benefit Trends. 2002;14(3):13-.
42. Thorndike AN, Biener L, Rigotti NA. Effect on smoking cessation of switching nicotine replacement therapy to over-the-counter status. American Journal of Public Health. 2002;92(3):437-42.
43. Gurwitz JH, McLaughlin TJ, Fish LS. The effect of an Rx-to-OTC switch on medication prescribing patterns and utilization of physician services: the case of vaginal antifungal products. Health services research. 1995;30(5):672.
44. Ryan M, Yule B. Switching drugs from prescription-only to over-the-counter availability: economic benefits in the United Kingdom. Health Policy. 1990;16(3):233-9.
45. Sullivan PW, Nichol MB. The economic impact of payer policies after the Rx-to-OTC switch of second-generation antihistamines. Value in health. 2004;7(4):402-12.
46. Sansgiry SS, Bhansali AH, Bapat SS, Xu Q. Abuse of over-the-counter medicines: a pharmacist's perspective. Integrated pharmacy research & practice. 2016;6:1-6.
47. Kline. Flipping the Switch: Disparity between the United States and Rest of World 2015 [cited 2019 26 Oct]. Available from: https://www.iriworldwide.com/iri/media/IRI%20Kline%20-%20Flipping%20the%20Switch%20-%20Disparity%20between%20the%20US%20and%20Rest%20of%20World.pdf.
48. Bank of America. What expenses are covered? 2019 [cited 2019 25 Oct]. Available from: https://healthaccounts.bankofamerica.com/what-expenses-are-covered-by-an-hsa-fsa-hra.shtml.
49. Castle G, Kelly B. Pricing & Reimbursement 2019, United Kingdom 2019 [cited 2019 26 Oct]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/united-kingdom#chaptercontent3.
50. Vogler S, Haasis M, Dedet G, Lam J, Bak PH. Medicines reimbursement policiies in

Europe. Copenhagen: World Health Organization. 2018.
51. Swarting C, Appelgren C. Pricing & Reimbursement 2019, Sweden 2019 [cited 2019 26 Oct]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/sweden#chaptercontent3.
52. Moïse P, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Sweden 2007 [cited 2019 26 Oct]. Available from: https://www.oecd.org/sweden/40699881.pdf.
53. Fullbright NR, Guerreiro C. Pricing & Reimbursement 2019, Canada 2019 [cited 2019 26 Oct]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/canada.
54. Taiwan Health Industries. An Introductory market overview 2018 [cited 2019 26 Oct]. Available from: https://www.pwc.tw/en/publications/assets/taiwan-health-industries.pdf.
55. Hsu JC, Lu CY. The evolution of Taiwan's National Health Insurance drug reimbursement scheme. DARU Journal of Pharmaceutical Sciences. 2015;23(1):15.
56. National Health Service. Amendments to the drug tariff 2019 [cited 2019 5 Nov]. Available from: https://www.nhsbsa.nhs.uk/sites/default/files/2019-09/Drug%20Tariff%20October%202019.pdf.
57. Thailand Development Research Institute. The Central Meachanism for the integration of health insurances in Thailand. 2019 [cited 2019 26 Oct]. Available from: https://tdri.or.th/wp-content/uploads/2019/03/wb148.pdf.
58. Health Intervention and Technology Assessment Program. HITAP meeting for accessibility of National List of Essential Medicine. 2019 [cited 2019 26 Oct]. Available from: http://www.hitap.net/news/174286.
59. Hfocus. National Health Security office announced to help patients access to expensive drugs by providing the reimbursement of cancer treatments. 2016 [cited 2019 26 Oct]. Available from: https://www.hfocus.org/content/2016/06/12262.
60. Sullivan PW, Follin SL, Nichol MB. Transitioning the second-generation antihistamines to over-the-counter status: a cost-effectiveness analysis. Medical care. 2003:1382-95.
61. Amirsadri-Naeini M, Jackson P. PCV41 COMPARISON OF COST-EFFECTIVENESS OF POM (PRESCRIPTION ONLY) STATINS; OTC (OVERTHE COUNTER) STATIN AND PLANT STEROL/STANOL PRODUCTS FOR PRIMARY CVD (CARDIOVASCULAR DISEASE) PREVENTION IN THE UNITED KINGDOM FROM THE PATIENT'S PERSPECTIVE. Value in Health. 2008;11(3):A198.
62. Gandhi P, McGhan W, Peterson A. PCV49 COST-UTILITY ANALYSIS USING A MARKOV MODEL TO COMPARE PRESCRIPTION STATINS VERSUS POTENTIAL OVER THE COUNTER STATINS IN USA. Value in Health. 2006;9(6):A352.
63. Gandhi P, McGhan W, Peterson A. Decision analysis to compare the cost-effectiveness of the statins available by prescription versus over the counter based from a societal perspective. Value in Health. 2006;9(3).
64. Kalish SC, Bohn RL, Avorn J. Policy analysis of the conversion of histamine2 antagonists to over-the-counter use. Medical care. 1997;35(1):32-48.
65. Kunz K, Arundell E, Cisternas M, Heaton A. Economic Implications of Self-treatment of Heartburn/Nonulcur Dyspepsia with Nonprescription Famotidine in a Managed Care Setting. Journal of Managed Care Pharmacy. 1996;2(3):263-71.
66. Zhu M, Wertheimer A, Field R. The financial impact of over-the-counter availability of oral contraceptive pills. Journal of Research in Pharmaceutical Economics. 2001;11(3-4):125-42.
67. Keeler TE, Hu Tw, Keith A, Manning R, Marciniak MD, Ong M, et al. The benefits of switching smoking cessation drugs to over-the-counter status. Health Economics. 2002;11(5):389-402.
68. Chang J, Nichol M. PIN8 THE ECONOMIC IMPACT OF TRANSITIONING VALACYCLOVIR

TO OVER THE COUNTER STATUS FOR THE TREATMENT OF GENITAL HERPES. Value in Health. 2009;12(3):A111.
69. Cohen J, DiMasi J. Modeling a switch of loratadine from prescription to over-the-counter status. J Res Pharm Econ. 2001;11:43-54.
70. Cohen J, Millier A, Karray S, Toumi M. Assessing the economic impact of Rx-to-OTC switches: systematic review and guidelines for future development. Journal of Medical Economics. 2013;16(6):835-44.
71. Thai Rhinologic Society. Practice and Guidance in Allergic Rhinitis Management in Thailand 2011 2011 [cited 2019 4 Nov]. Available from: http://www.rcot.org/datafile/_file/_doctor/d7e0cb0b21c47bcf747da6d863f8a7ce.pdf.
72. Amboss. Antihistamines 2020 [cited 2020 24 April]. Available from: https://www.amboss.com/us/knowledge/Antihistamines.
73. MedlinePlus. Antihistamines for allergies 2018 [cited 2020 24 April]. Available from: https://medlineplus.gov/ency/patientinstructions/000549.htm.
74. U.S. Pharmacist. Allergic rhinitis and intranasal corticosteroid spray 2020 [cited 2020 24 April]. Available from: https://www.uspharmacist.com/article/allergic-rhinitis-and-intranasal-corticosteroid-spray.
75. National Health Service. Steroid nasal sprays 2020 [cited 2020 24 April]. Available from: https://www.nhs.uk/conditions/steroid-nasal-sprays/.
76. Thai Food and Drug Administration. National listed essensial medicines notification 2018 [cited 2019 4 Nov]. Available from: http://www.fda.moph.go.th/sites/drug/Shared%20Documents/New/nlem2561.PDF.
77. World Health Organization. Proposal for Updating the Definition of Stringent Regulatory Authority 2017 [cited 2019 26 Oct]. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/SRA_QAS17-728Rev1_31082017.pdf?ua=1.
78. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Members & Observers 2019 [cited 2019 26 Oct]. Available from: https://www.ich.org/page/members-observers.
79. Economic and Trade Indices Database. Consumer price index 2020 [cited 2020 24 April]. Available from: http://www.price.moc.go.th/price/cpi/index_new_all.asp.
80. Thepaksorn P, Pongpanich S. Occupational injuries and illnesses and associated costs in Thailand. Safety and health at work. 2014;5(2):66-72.
81. Thongchim P, Taneerananon P, Luathep P, Prapongsena P, editors. Traffic accident costing for Thailand. Proceedings of the Eastern Asia Society for Transportation Studies Vol 6 (The 7th International Conference of Eastern Asia Society for Transportation Studies, 2007); 2007: Eastern Asia Society for Transportation Studies.
82. Scadding G, Durham S, Mirakian R, Jones N, Leech S, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clinical & Experimental Allergy. 2008;38(1):19-42.
83. Bunnag C, Jareoncharsri P, Tantilipikorn P, Vichyanond P, Pawankar R. Epidemiology and current status of allergic rhinitis and asthma in Thailand -- ARIA Asia-Pacific Workshop report. Asian Pac J Allergy Immunol. 2009;27(1):79-86.
84. Official Statistics Registration System. Population and house statistics - Population by age 2019 [cited 2020 24 April]. Available from: http://stat.dopa.go.th/stat/statnew/upstat_age.php.
85. Kulthanan K, Chusakul S, Recto MT, Gabriel M, Aw DC-W, Prepageran N, et al. Economic burden of the inadequate management of allergic rhinitis and urticaria in Asian countries based on the GA2LEN model. Allergy, asthma & immunology research.

2018;10(4):370-8.
86. Tantilipikorn P, Juntabenjapat J, Thongngarm T, Assanasen P, Bunnag C, Thinkhamrop B. Prevalence of impaired lower airway function in Thai patients with allergic rhinitis. Asian Biomedicine. 2017;10(1):67-74.
87. The Board of Investment of Thailand. Thai Market is Large and Growing Fast 2015 [cited 2020 24 April]. Available from: https://www.boi.go.th/tir/issue/201507_25_7/42.htm.
88. Trygstad TK, Hansen RA, Wegner SE. Evaluation of product switching after a state Medicaid program began covering loratadine OTC 1 year after market availability. Journal of Managed Care Pharmacy. 2006;12(2):108-20.
89. Orriols L, Luxcey A, Contrand B, Bénard-Laribière A, Pariente A, Gadegbeku B, et al. Road traffic crash risk associated with prescription of hydroxyzine and other sedating H1-antihistamines: A responsibility and case-crossover study. Accident Analysis & Prevention. 2017;106:115-21.
90. Administration NHTS. Antihistamines and driving-related behavior: A review of the evidence for impairment. Annals of emergency medicine. 2000;36(4):388-9.
91. Jauregui I, Mullol J, Bartra J, Del Cuvillo A, Davila I, Montoro J, et al. antihistamines: psychomotor performance and driving. J Investig Allergol Clin Immunol. 2006;16(1):37-44.
92. Doms M, Vanhulle G, Baelde Y, Coulie P, Dupont P, Rihoux J-P. Lack of potentiation by cetirizine of alcohol—Induced psychomotor disturbances. European journal of clinical pharmacology. 1988;34(6):619-23.
93. Gawit KG, Sathe GM, Tiwari SA, Deshpande PK, Ghongane BB. Effect of Single Dose 10 mg Cetirizine on Visual Processing Speed for low and high intensity stimuli in Healthy Human Volunteers.
94. Health Intervention and Technology Assessment. Standard Cost List for Health Technology Assessment 2011 [cited 2020 24 April]. Available from: http://costingmenu.hitap.net/.
95. Drug and Medical Supple Information Center MoPH. Normal purchasing reference price (medicine) 2019 [Available from: http://dmsic.moph.go.th/index/drugsearch/1.
96. The Food, Drug, and Cosmetic Act, (2019).
97. Medicines Act 1968, (2020).
98. Japan Pharmaceutical Manufacturers Association. Pharmaceutical Administration and Regulations in Japan 2019 [cited 2020 12 Jan]. Available from: http://www.jpma.or.jp/english/parj/pdf/2019.pdf.
99. Health Products Act 2016 [cited 2020 12 Jan]. Available from: https://sso.agc.gov.sg/SL/HPA2007-S329-2016.
100. Poisons Act 1952 and Regulations 2019 [cited 2020 12 Jan]. Available from: http://www.agc.gov.my/agcportal/uploads/files/Publications/LOM/EN/Act%20366%20online.pdf.
101. Philippine Pharmacy Act 2015 [cited 2020 12 Jan]. Available from: https://www.lawphil.net/statutes/repacts/ra2016/ra_10918_2016.html.
102. National Association of Pharmacy Regulatory Authorities. Drug Scheduling in Canada - General Overview 2019 [Available from: https://napra.ca/drug-scheduling-canada-general-overview.
103. U.S. Food and Drug Administration. How to Buy Medicines Safely From an Online Pharmacy 2018 [cited 2020 25 April]. Available from: https://www.fda.gov/consumers/consumer-updates/how-buy-medicines-safely-online-pharmacy.
104. GOV.UK. Register for the Distance Selling logo 2017 [cited 2020 25 April]. Available from: https://www.gov.uk/guidance/register-for-the-distance-selling-logo.

105. Ministry of Health Malaysia. Tips on how to buy medicines online 2020 [cited 2020 25 April]. Available from: https://www.pharmacy.gov.my/v2/en/content/tips-how-buy-medicines-online.html.
106. Government of Canada. Choosing a safe online pharmacy 2020 [cited 2020 25 April]. Available from: https://www.canada.ca/en/health-canada/topics/buying-using-drug-health-products-safely/safe-use-online-pharmacies.html.
107. Faculty of Medicine Ramathibodi Hospital. Online drug sale 2018 [Available from: https://med.mahidol.ac.th/ramapharmacy/th/knowledge/general/05192016-1800-th.
108. Health Sciences Authority. Explanation note for application of a pharmacy licence 2016 [cited 2020 25 April]. Available from: https://www.hsa.gov.sg/docs/default-source/hprg-ald/phl_explanation-noteb201f748dd3a4a8ca9bd36f432a3fded.pdf.
109. U.S. Food and Drug Administration. Prescription Drug Advertising 2019 [cited 2020 25 April]. Available from: https://www.fda.gov/drugs/drug-information-consumers/prescription-drug-advertising.
110. GOV.UK. Advertise your medicines 2020 [cited 2020 25 April]. Available from: https://www.gov.uk/guidance/advertise-your-medicines#advertise-to-the-public.
111. Graham JS, Swanson R. Distribution and marketing of drugs in Canada: overview 2018 [cited 2020 25 April]. Available from: https://ca.practicallaw.thomsonreuters.com/0-618-6695?transitionType=Default&contextData=(sc.Default)&firstPage=true&bhcp=1.
112. Government of Canada. Health Products Advertising on Physician Web Sites - Questions and Answers 2011 [cited 2020 25 April]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/regulatory-requirements-advertising/policies-guidance-documents/health-products-advertising-physician-questions-answers.html.
113. Health Sciences Authority. Advertisements and promotions of therapeutic products 2019 [cited 2020 25 April]. Available from: https://www.hsa.gov.sg/therapeutic-products/advertisements.
114. The International Comparative Legal Guide to: Pharmaceurical Advertising 2016 2016 [cited 2020 25 April]. Available from: https://www.jurists.co.jp/sites/default/files/tractate_pdf/en/PA16_Japan.pdf.
115. Thai Food and Drug Administration. Things to know for drug advertisements 2020 [cited 2020 25 April]. Available from: http://www.fda.moph.go.th/sites/drug/SitePages/advertisement03.aspx.
116. Baker McKenzie. Promoting Medical Products Globally 2018 [cited 2020 25 April]. Available from: https://www.bakermckenzie.com/-/media/files/insight/publications/2018/03/healthcare/ap/promoting-medical-products-globally_malaysia.pdf?la=en.
117. The Ministry of Health in collaboration with the World Health Organization. Philippines Pharmaceutical Country Profile 2011 [cited 2020 25 April]. Available from: https://www.who.int/medicines/areas/coordination/Philippines_PSCPBNarrativeQuestionnaireEndorsement_13062012.pdf?ua=1.
118. The Psychotropic Substances Act B.E. 2559 (2016) 2016 [cited 2020 12 Jan]. Available from: http://www.fda.moph.go.th/sites/Narcotics/en/Shared%20Documents/Psychotropic-Substances-Act-B.E.2559.pdf.
119. NARCOTICS ACT B.E. 2562 (2018) 2018 [updated 18 Febuary 2018; cited 2020 12 Jan]. Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2562/A/019/T_0001.PDF.
120. NARCOTICS ACT B.E. 2522 (1979) 1979 [cited 2020 12 Jan]. Available from: http://www.fda.moph.go.th/sites/Narcotics/en/Shared%20Documents/Narcotics-Act-B.E.2522.pdf.

121. Comprehensive Dangerous Drugs Act of 2002 [cited 2020 12 Jan]. Available from: https://www.ddb.gov.ph/images/Board_Regulation/2014/BD.REG1.14.pdf.
122. Japan Pharmaceutical Manufacturers Association. Pharmaceutical Administration and Regulations in Japan 2017 [cited 2019 23 Oct]. Available from: http://www.jpma.or.jp/english/parj/pdf/2017.pdf.
123. U.S. Food and Drug Administration. Legal Requirements for the Sale and Purchase of Drug Products Containing Pseudoephedrine, Ephedrine, and Phenylpropanolamine 2017 [cited 2020 12 Jan]. Available from: https://www.fda.gov/drugs/information-drug-class/legal-requirements-sale-and-purchase-drug-products-containing-pseudoephedrine-ephedrine-and.
124. Consumer Healthcare Product Association. Rx-to-OTC Switch 2019 [cited 2019 23 Oct]. Available from: https://www.chpa.org/switch.aspx.
125. National Association of Pharmacy Regulatory Authorities. Implementation of the National Drug Schedules 2019 [cited 2020 12 Jan]. Available from: https://napra.ca/implementation-national-drug-schedules.
126. Gauld N, Bryant L, Emmerton L, Kelly F, Kurosawa N, Buetow S. Why does increasing public access to medicines differ between countries? Qualitative comparison of nine countries. Journal of health services research & policy. 2015;20(4):231-9.
127. Hennebry S. When a 20 year patent term just isn't enough: Market and data exclusivity 2018 [cited 2020 25 April]. Available from: https://fpapatents.com/resource?id=483.
128. Medicines and Healthcare products Regulatory Agency. How to change the legal classification of a medicine in the UK 2006 [cited 2020 25 April]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/277307/Legal_classification_changes.pdf.
129. Agency for care effectiveness. Drug evaluation methods and process guide 2018 [cited 2020 25 April]. Available from: http://www.ace-hta.gov.sg/public-data/our-process-and-methods/ACE%20methods%20and%20process%20guide%20for%20drug%20evaluation%20(5%20Feb%202018).pdf.
130. Gauld NJ. How and why do developed countries vary in reclassifying medicines from prescription to non-prescription? : University of Auckland; 2013.
131. Camargo. Rx-to-OTC switch: expanding to the US over-the-counter market 2017 [cited 2020 25 April]. Available from: https://camargopharma.com/resources/blog/rx-to-otc-switch-expanding-to-the-us-over-the-counter-market.
132. Medicines and Healthcare products Regulatory Agency. MHRA reclassifies Viagra Connect tablets to a Pharmacy medicine 2017 [cited 2020 25 April]. Available from: https://www.gov.uk/government/news/mhra-reclassifies-viagra-connect-tablets-to-a-pharmacy-medicine.
133. Mithun Raja. B, Raghavendra Rao. K. Regulatory and Clinical Requirements for Prescription to OTC Switches in USA and India 2013 [cited 2020 12 Jan]. Available from: https://www.complianceonline.com/articlefiles/Regulatory_Requirements_Prescription_to_OTC_Switches_USA_India.pdf.
134. U.S. Food and Drug Administration. Bringing an Over-the-Counter (OTC) drugs to market 2020 [cited 2020 25 April]. Available from: https://www.accessdata.fda.gov/scripts/cder/training/OTC/topic2/topic2/da_01_02_0080.htm

135. Health Sciences Authority. Therapeutic products guidedance 2019 [cited 2020 25 April]. Available from: https://www.hsa.gov.sg/docs/default-source/hprg/therapeutic-products/guidance-documents/guidance-on-therapeutic-product-registration-in-

singapore_jan2019.pdf.
136. Tago S, Ueda A, Kudo R, Guesdon L. Distribution and marketing of drugs in Japan: overview 2019 [cited 2020 25 April]. Available from: https://uk.practicallaw.thomsonreuters.com/5-618-3562?transitionType=Default&contextData=(sc.Default)&firstPage=true&comp=pluk&bhcp=1.
137. National Association of Pharmacy Regulatory Authorities. National Drug Scheduling Factors 2017 [cited 2020 12 Jan]. Available from: https://napra.ca/sites/default/files/documents/NDSAC_Scheduling_Factors_website_September2017.pdf.
138. Hidemi Katsura. The Approval Standards for OTC Drugs in Japan. Self-carer Conference; 17 Sep; Bangkok2015.
139. Bakah SA. Regulation of OTC medicines in Malaysia. International OTC Medicine Regulator Forum 2017 20 Oct; Novotel Hotel, Sydney2017.
140. Official Portal of Pharmaceutical Services Programme, Ministry of Health Malaysia. Application for poisons classification guideline under the Poisons Act 1952 2013 [cited 2020 12 Jan]. Available from: https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/garispanduan.pdf.
141. Policies and Guidelines on Over-the-counter (OTC) drug Products 2000 [cited 2020 12 Jan]. Available from: https://ww2.fda.gov.ph/attachments/article/16557/ao%2023c%202000.pdf.
142. Republic of the Philippines DoH, Food and Drug Administration,. Application process and requirements for post-approval changes of pharmaceutical products 2014 [cited 2020 25 April]. Available from: https://ww2.fda.gov.ph/attachments/article/148395/FC2014-008%20-%20Application%20Process%20and%20Requirments%20for%20Post-Approval%20Changes%20of%20Pharmaceutical%20Products.pdf.
143. International Pharmaceutical Federation. An overview of current pharmacy impact on immunisation 2016 [cited 2020 12 Jan]. Available from: https://www.fip.org/www/streamfile.php?filename=fip/publications/FIP_report_on_Immunisation.pdf.
144. National Association of Pharmacy Regulatory Authorities. National Drug Schedules 2020 [cited 2020 4 July]. Available from: https://napra.ca/national-drug-schedules?keywords=vaccine&schedule=.
145. The World Bank. Education statistics 2019 [cited 2020 12 Jab]. Available from: https://databank.worldbank.org/indicator/UIS.SAP.CE?id=c755d342&report_name=EdStats_Indicators_Report&popularttype=series.
146. Human Development Index (HDI) by country 2019 [cited 2020 12 Jan]. Available from: http://worldpopulationreview.com/countries/hdi-by-country/.
147. United Nations Development Programme. Global Human Development Indicators 2020 [cited 2020 25 April]. Available from: http://hdr.undp.org/en/countries/profiles/.
148. Albanese NP, Rouse MJ, Schlaifer M, Pharmacy CoCi. Scope of contemporary pharmacy practice: roles, responsibilities, and functions of pharmacists and pharmacy technicians. Journal of the American Pharmacists Association. 2010;50(2):e35-e69.
149. Deloitte Access Economics. Remuneration and regulation of community pharmacy 2016 [cited 2020 12 Jan]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/4E0B6EEE19F56A40CA2581470016D688/$File/deloitte-community-pharmacy-literature-review-2016.pdf.
150. General Pharmaceutical Council. What does a pharmacist do? 2019 [cited 2020 12 Jan]. Available from: https://www.pharmacyregulation.org/raising-concerns/raising-concerns-about-pharmacy-professional/what-expect-your-pharmacy/what-does-0.

151. Nakagawa S, Kume N. Pharmacy Practice in Japan. The Canadian Journal of Hospital Pharmacy. 2017;70(3):232.
152. Competency Standards for Singapore Pharmacists 2010 [cited 2020 12 Jan]. Available from: https://www.healthprofessionals.gov.sg/docs/librariesprovider3/forms-publications/competency-standards-for-singapore-pharmacists-(march-2010).pdf.
153. An Chau. Are pharmacists' roles as primary health professionals underutilised in Singapore? 2016 [cited 2020 12 Jan]. Available from: https://today.mims.com/are-pharmacists--roles-as-primary-health-professionals-underutilised-in-singapore-?channel=GN-Local-News-SG.
154. Annuar A. Counter-productive' for pharmacists to administer vaccines, doctors' body says 2019 [cited 2020 12 Jan]. Available from: https://www.malaymail.com/news/malaysia/2019/02/25/counter-productive-for-pharmacists-to-administer-vaccines-doctors-body-says/1726723.
155. Sonya Collins. A tale of two countries: The path to pharmacist prescribing in the United Kingdom and Canada 2014 [cited 2020 12 Jan]. Available from: https://www.pharmacist.com/article/tale-two-countries-path-pharmacist-prescribing-united-kingdom-and-canada.
156. Pharmacists Act 2015 [cited 2020 12 Jan]. Available from: https://library2.parliament.go.th/giventake/content_nla2557/law21-260358-69.pdf.
157. Choudhry NK, Avorn J. Over-the-counter statins. Annals of internal medicine. 2005;142(11):910-3.
158. U.S. Government Services and Information. Health insurance 2020 [Available from: https://www.usa.gov/health-insurance.
159. The World Bank. Population 2020 [cited 2020 25 April]. Available from: https://data.worldbank.org/indicator/sp.pop.totl.
160. U.S. Food and Drug Administration. Drugs 2020 [cited 2020 25 April]. Available from: https://www.fda.gov/drugs.
161. World Population Review. Countries with Universal Healthcare 2020 [cited 2020 26 Arpil]. Available from: https://worldpopulationreview.com/countries/countries-with-universal-healthcare/.
162. World Health Organization. Density of physicians [cited 2020 25 April]. Available from: https://www.who.int/gho/health_workforce/physicians_density/en/.
163. World Health Organization. Pharmacists (per 10,000 populations) [cited 2020 25 April]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/pharmacists-(per-10-000-population).
164. United States Drug Enforcement Administration. The Controlled Substances Act 2020 [cited 2020 25 April]. Available from: https://www.dea.gov/controlled-substances-act.
165. Raja BM, Rao KR. Regulatory and clinical requirements for prescription to OTC switches in USA and India 2020 [cited 2020 25 April]. Available from: https://www.complianceonline.com/articlefiles/Regulatory_Requirements_Prescription_to_OTC_Switches_USA_India.pdf.
166. U.S. Food and Drug Administration. Bringing an over-the-counter (OTC) drug to market: Regulatory overview 2020 [cited 2020 25 April]. Available from: https://www.accessdata.fda.gov/scripts/cder/training/OTC/topic3/topic3/da_01_03_0170.htm.
167. Consumer Healthcare Products Association. FAQs about the regulation of OTC medicines 2020 [cited 2020 25 April]. Available from: https://www.chpa.org/FAQsRegOTCs.aspx.

168. U.S. Food and Drug Administration. Bringing an over-the-counter (OTC) drug to market: OTC vs prescription 2020 [cited 2020 25 April]. Available from: https://www.accessdata.fda.gov/scripts/cder/training/OTC/topic2/topic2/da_01_02_0080.htm.
169. Chang J, Peysakhovich F, Wang W, Zhu J. The UK health care system. The United Kingdom. 2011;30:2019.
170. The UK in a changing Europe. When did Britain decide to join the European Union? 2020 [cited 2020 26 April]. Available from: https://ukandeu.ac.uk/fact-figures/when-did-britain-decide-to-join-the-european-union/#.
171. GOV.UK. Medicines and Healthcare products Regulatory Agency, 2020 [cited 2020 26 April]. Available from: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.
172. Royal Pharmaceutical Society. Classifications of medicines. Medicines, Ethics and Practice Classification of medicines. 42 ed. London: Pharmaceutical Press; 2018. p. 35-7.
173. Nomura H, Nakayama T. The Japanese healthcare system. British Medical Journal Publishing Group; 2005.
174. Pharmaceuticals and Medical Devices Agency 2020 [cited 2020 26 April]. Available from: https://www.pmda.go.jp/.
175. Japan Pharmaceutical Manufacturers Association. Pharmaceutical laws and regulations, 2017 [cited 2020 25 April]. Available from: http://www.jpma.or.jp/english/parj/pdf/2017_ch02.pdf.
176. Health Products Act,, (2016).
177. Poison Act 1952 and Regulations 2020 [cited 2020 25 April]. Available from: https://www.pharmacy.gov.my/v2/en/documents/poisons-act-1952-and-regulations.html.
178. Food and Drug Administration Phillippines, 2020 [cited 2020 26 April]. Available from: https://www.fda.gov.ph/category/drugs-announcements/.
179. World Health Organization. UHC Act in the Philippines: a new dawn for health care 2019 [cited 2020 26 April]. Available from: https://www.who.int/philippines/news/feature-stories/detail/uhc-act-in-the-philippines-a-new-dawn-for-health-care.
180. Government of Canada. Canada's health care system 2020 [cited 2020 26 April]. Available from: https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-system/canada.html.

APPENDIX

The United States of America

The United states of America, generally known as the United States (the US), has been recognized as one of the most highly developed country from its economy in the world. It is a federal public consisting of 50 sates, one federal district, five major self-governing territories, and various possessions. The US is one of the founding regulatory members of ICH[1], which designated by WHO[2] as stringent regulatory agencies.[78] Healthcare coverage in the US is not universal, but from the combinations of private and public insurances. There are two public insurance program: Medicaid, covering people with low income; and Medicare, covering people aged more than 65 [158].

Table A: Country context of the United states of America

Context	Data
States	Federal states
Populations	327 million people [159]
Life expectancy of birth	78.9 years[147]
Human development index (world ranking)	0.920 [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	11.1[145]
Gross domestic product (GDP) per capita	55,681 (2011 PPP$[3]) [147]
Current health expenditure	17.1% of GDP [147]
Regulatory agency	U.S. Food and Drug Administration [160]
Healthcare system world ranking by WHO[2]	37 [6]
Universal healthcare coverage implementation	No [161]
Physician density (per 10,000 populations)	25.948 [162]
Pharmacist density (per 10,000 populations)	9.25 [163]
Pharmacy practice	
- Response to patients' symptoms	No [148]
- Vaccination	Yes, with a certification [149]
Pharmacy	
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

[1] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

[2] World Health Organization

[3] Purchasing Power Parity

Drug classification scheme

In the US, a particular drug is simultaneously regulated under several Acts, such as the Federal Food, Drug and Cosmetic Act and the Controlled Substance Act [96, 164]. If the regulations are conflict between two drug acts, the one that are stronger would be utilized. The US FDA is a decision maker of classifying each drug into the scheme [160]. Drugs in the US will be reclassified by brands to provide three year-market exclusivity for the originate company [126]. This affect that drugs containing same active ingredient are possible to be classified into different schemes. According to the Federal Food, Drug and Cosmetic Act, drugs in the US has been classified into two schemes: prescription and over-the-counter drugs [96].

1. Prescription drug scheme

Drugs that are classified as prescription drugs require prescriptions to be dispensed. Physicians are a gate keeper, or make a decision whether patients need to use these drugs or not. Pharmacists are responsible for drug dispensing by reviewing and interpreting physician orders and detecting therapeutic incompatibilities. Prescription drugs can be distributed through hospitals, both retail and online pharmacies, but not in retailers [165]. In the US, it's permitted to advertise prescription drugs to public, with brand names, generic names, indications and risks. Patient information leaflets of these drugs are also compulsory [109].

Criteria of prescription drugs in the US are described widely in the Durham-Humphrey amendments to the FD&C act [165]. Drugs must be classified as prescription drugs if they can lead to habit forming, unsafe unless healthcare professionals are involved, and approved by New Drug Application as a prescription status.

2. Over-the-counter (OTC) drug scheme

Drugs that are classified as OTC drugs can be sold in retailers and over the internet without any healthcare professional involvement [165]. Direct-to-consumer advertisements are allowed same as prescription drugs. Although patient information leaflets are not compulsory for this scheme, the regulatory strictly focus on labels instead. To ensure the effective labels, the US FDA sometimes require sponsors to conduct label comprehension studies, self-selection studies, and actual use studies before placing drugs on the market [166].

OTC drugs in the US can be registered through two ways.

(i) OTC drug monograph system - OTC drug monograph is like a recipe book; containing list of drugs and their characteristics, which are dose, formulations, labelling and testing, that are

generally recognized as safe and effective for self-medication by the US FDA. Any drugs that meet all criteria stated in the monograph can be marketed without pre-approval from the US FDA [167].

(ii) New Drug Application (NDA) process – Other drugs that do not meet criteria in OTC drug monograph have to register via Investigational New Drug Application (IND) or New Drug Application (NDA). Products must be approved from the US FDA before marketing. These drugs can be directly register as OTC drugs or switched from prescription to OTC status (Rx-to-OTC process).

The criteria of OTC drugs in the US are found in the US FDA websites. OTC drugs must have a wide range of safety margin, low rate of misuse and abuse, not require healthcare professional involvement, and the label should be suitably described on the products. Moreover, the symptoms that OTC drugs treat must be self-diagnosed, self-medicated, self-treated, and self-managed by consumers [168].

The United Kingdom

The United Kingdom of Great Britain and Northern Ireland, generally known as Britain or the United Kingdom (the UK), is one of the high power nations in the world. Located in Northern Europe, the UK made up of four parts: England, Scotland, Northern Ireland, and Wales. The UK was once a member of European Union until formally leave the union in January 2020. This affect their regulatory, including healthcare policy, to gradually change after the leaving. Healthcare system in the UK provides universal coverage for all citizens, funding from general taxation. The public health sector has been responsible by government-sponsor organization called National Health Service (NHS). It includes 4 different parts, which are National Health Service (England), NHS Scotland, NHS Wales and Health and Social Care in Northern Ireland. This results in some variation of healthcare system among these four nations [169, 170].

Table B: Country context of the United Kingdom

Context	Data
States	Unitary state
Populations	66 million people[159]
Life expectancy of birth	81.2 years[147]
Human development index (world ranking)	0.920 (15) [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	11.5 [145]
Gross domestic product (GDP) per capita	40,158 (2011 PPP$[3]) [147]
Current health expenditure	9.8% of GDP [147]
Regulatory agency	Medicines & Healthcare products Regulatory Agency (MHRA) [171]
Healthcare system world ranking by WHO[2]	18 [6]
Universal healthcare coverage implementation	Yes, responsible by National Health Service [161]
Physician density (per 10,000 populations)	28.058 [162]
Pharmacist density (per 10,000 populations)	8.89 [163]
Pharmacy practice	
- Response to patients' symptoms	Yes[150]
- Vaccination	Yes, with a certification [149]
Pharmacy	

Context	Data
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

Drug classification scheme

A particular drug in the UK can simultaneously regulated under several Acts. If the regulations are conflict between two drug acts, the one that are stronger would be utilized. It is the responsibility of Medicines & Healthcare products Regulatory Agency (MHRA) to make a decision of drug classification [97]. Drugs in the UK will be reclassified by brands to provide one year-market exclusivity for the originate company [126]. This affect that drugs containing same active ingredient are possible to be classified into different schemes. According to The Human Medicines (Amendment) Regulations 2019, drugs in the UK has been classified into three legal categories: prescription-only medicines (POM), pharmacy-only medicines (P) , and general sale list medicines (GSL) [97].

1. Prescription-only medicines (POM)

Drugs that are classified as POM require prescriptions from authorized health professionals to be dispensed. To receive POM, patients must take a prescription, prescribed by physicians, to retailed or online pharmacies and only obtain them under pharmacist supervision. POM are not allowed to be sold by non-healthcare professional or in retailers. Direct-to-consumer advertisements of POM are strictly prohibited. Patient information leaflets are also compulsory for a registration [22].

The criteria of POM are stated in the Human Medicines Regulations 2012, and the UK government website repeat describe them. Drugs must be POM status if (i) their danger can direct or indirect affect to human health, although it is used correctly, (ii) they are usually misused and lead to direct or indirect danger, (iii) monitoring of effectiveness or side-effect are required, (iv) they are injection [22].

2. Pharmacy only medicines (P)

Pharmacy only medicines do not require prescriptions to be dispensed, however, it needs to be dispensed under pharmacist supervision at both retailed and online pharmacies. This legal status is equivalent to OTC drug category in the US. Self-selection of pharmacy only medicines without pharmacist supervision are prohibited according to The General Pharmaceutical Council meeting in September 2012. This means that pharmacy only medicines cannot be sold in retailers or

pharmacies without the present of pharmacists. Pharmacy only medicines are allowed to advertise directly to public. Patients information leaflets are also compulsory [22, 97, 110, 172].

The criteria of pharmacy only medicines are actually any drugs that do not meet POM criteria and not safe or effective enough for GSL status. However, the UK government website describes some important characteristics of pharmacy only medicines. This includes the drugs for both short-term or not likely to persist conditions, and sometimes long-term diseases; drugs that need special advice form pharmacists during use, and GSL drugs in larger pack size [22, 97].

3. General sale list medicines (GSL)

GSL drugs in the UK can be sold not only in hospitals and pharmacies, but also retailers and over the internet; without any healthcare professional involvement. The manufacturer who wishes to sell GSL drugs only in the pharmacies are allowed to do so. Unlike, pharmacy only drugs, GSL drugs in pharmacies can be sold when pharmacists are physically absent. Direct-to-consumer advertisements are allowed, while Patient information leaflets are compulsory [22, 97, 110, 172].

The criteria of GSL drugs can be concluded from the UK government website s as drugs that treat easily recognize and minor ailments, has few side effect from normal use, and contained in small pack size for a few days treatment to prevent patients from incorrect use of drugs, and force them to go back for pharmacists or physicians' advice if the symptoms do not improve [22, 97].

Japan

Japan has been recognized as one of the most prosperous, technology leader and urbanized countries in the world. Their regulatory agency also one of the founding regulatory members of ICH[4], which designated by WHO[5] as stringent regulatory agencies [78]. Japanese pharmaceutical industry also invents many original drugs. Healthcare system in Japan is in high standard and provide universal healthcare coverage to the citizens through National Health Insurance System (NHI). All citizens under NHI must pay tax for the system based on their income. Japanese citizens have to pay for their drug costs for 30%, while the remaining is responsible by the government. However, low birth rate and significantly increase of the elderly in Japan results in financial difficulty for the national insurance recently [173].

Table C: Country context of Japan

Context	Data
States	Unitary state
Populations	127 million people[159]
Life expectancy of birth	84.5 years [147]
Human development index (world ranking)	0.915 [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	12.3[145]
Gross domestic product (GDP) per capita	39,294 (2011 PPP$[3]) [147]
Current health expenditure	10.9% of GDP[147]
Drug regulatory agency	Pharmaceuticals and Medical devices agency (PMDA) [174]
Healthcare system world ranking by WHO[2]	10 [6]
Universal healthcare coverage implementation	Yes [161]
Physician density (per 10,000 populations)	24.118 [162]
Pharmacist density (per 10,000 populations)	18.02 [163]
Pharmacy practice	
- Response to patients' symptoms	No [151]
- Vaccination	No [151]
Pharmacy	

[4] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

[5] World Health Organization

Context	Data
- Pharmacy schedule	Yes, health insurance pharmacy and non-health insurance pharmacy [151]
- Non-pharmacist pharmacy	No, but licensed person in retailers are required for drug selling. [27]

Drug classification scheme

In Japan, a particular drug can simultaneously regulated under several Acts. Regulated by Pharmaceuticals and Medical devices agency (PMDA), drugs classification in Japan is based on Pharmaceutical Affair acts [98]. The system was re-structured in 2014 once [175]. In the present, there are three major drug scheme: pharmacy drugs, guidance-mandatory drugs and general sale list drugs [98].

1. Pharmacy drugs

Pharmacy drugs in Japan are drugs that required prescriptions to be dispensed. These drugs need physician or dentists to instruct before use. Patients can obtain pharmacy drugs under pharmacist supervision only from health insurance pharmacies. Other pharmacies (non-health insurance and online pharmacies) and retailers are not allowed to sell these drugs. Direct-to-consumer advertisements are also strictly prohibited [98, 136].

The criteria of pharmacy drugs generally prescribed by the Minister of the Ministry of Health, Labour, and Welfare as: drugs that need to be selected by physicians to ensure effectiveness and safety, drugs that need monitoring or medical checks to prevent serious adverse drug reactions, and drug that are able to be abused [136].

2. Guidance-mandatory drugs

Guidance-mandatory drugs are the new drug scheme enacted in June 2014. It is designated by Ministry of Health, Labor, and Welfare as drugs that do not require prescriptions to be dispensed. They are allowed to be sold in non-health insurance pharmacies, but still need to be under face-to-face supervision of pharmacists. Sale over the internet is prohibited for these scheme, but DTC advertisements are allowed. Drug classified as guidance-mandatory drugs are actually GSL drug candidates. Drugs are designated in this scheme at least three year for pharmacovigilance. During this period, other brands are not allowed to be re-classified. This affects that drugs containing the same active ingredient are possible to be classified into different schemes. After the safety for self-medication established, guidance-mandatory drugs may be reclassified downward to GSL drugs

further. Thus, it is like a trial period for GSL drug candidates and also similar to market exclusivity period of drug re-classification in the US or the UK [27, 98, 136].

The criteria of guidance-mandatory drug scheme was not clearly described, but shortly written in the governments' documents as drugs that do not have clinical effects as significant as prescription drugs, and also intend to be for self-medication, however, pharmacist supervision is still required to ensure patient safety [98].

3. General sale list (GSL) drugs / non-prescription drugs

GSL drugs are drugs that do not need prescriptions same as guidance-mandatory drugs. It can be further sub-classified into three categories, depending on their risk.

3.1. GSL drug class 1

GSL drug class 1 still need supervision from pharmacists, however, they can be sold over the internet. Pharmacists can advise patients not only face-to-face, but also through media, such as e-mail or other programs. GSL class 1 are the next switch class after guidance-mandatory drug shows adequate safety for self-medication. Pharmacovigilance data over the internet sale is required while drugs classified into the scheme at least 1 year. Having established safety data, drugs may further classified into GSL drug class 2 and 3.

3.2. GSL drug class 2

GSL drug class 2 are drugs that already show safety for self-medication, but the risk of drugs is in moderate level. Supervision from pharmacists are not compulsory.

3.3 GSL drug class 3

Similar to GSL class 2, they are drugs that safe for patients to self-medicate, but the risk of drugs is in low level. Supervision from pharmacists are also not compulsory [27, 98, 136].

GSL drug class 1 can be distributed only in non-health insurance pharmacies, while GSL drug class 2 and 3 can be distributed through retailers. However, these retailers must have non-pharmacist licensed sellers available during operation. All GSL drug class can be sold over the internet and allowed to DTC advertise [27, 98, 136, 151].

The criteria of GSL drug class are not detailly described, but can be obtain from the conference presented by PMDA. OTC drugs should have the guaranteed safety, quality and safety; their labels and other information should be available for consumers to self-medicate. They also might be lifestyle medicines that consumers need. They must comply with the latest standard knowledge in pharmacy, such as public health and nutrition [138].

Singapore

Singapore, officially name as the republic of Singapore, is most successful country located in Southeast Asia. Although it is a small island country, Singapore is placed in high ranking in many aspects, such as educations, quality of life, and healthcare. Healthcare system in Singapore is responsible by the Ministry of Health of Singapore. Accepted in globally, healthcare system in Singapore has been noticed as one of the most efficient system in the world from maintain financing, while achieve good health outcomes.

Table D: Country context of Singapore

Context	Data
States	Unitary state
Populations	5.63 million people[159]
Life expectancy of birth	83.5 years [147]
Human development index (world ranking)	0.935 (9) [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	12.9 [145]
Gross domestic product (GDP) per capita	90,091 (2011 PPP$[3]) [147]
Current health expenditure	4.5% of GDP [147]
Regulatory agency	Health Sciences Authority (HSA) [135]
Healthcare system world ranking by WHO[2]	6 [6]
Universal healthcare coverage implementation	Yes [161]
Physician density (per 10,000 populations)	23.063 [162]
Pharmacist density (per 10,000 populations)	5.09 [163]
Pharmacy practice	
- Response to patients' symptoms	Yes [152]
- Vaccination	No[153]
Pharmacy	
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

Drug classification scheme

In Singapore, a particular drug can simultaneously regulated under several acts, such as Poison acts. However, all drugs are regulated under Health Product acts. The final decision of drug classification is responsible by Health Science Authority (HSA) [99]. Drugs in Singapore will be reclassified by brands to provide one year-market exclusivity for the originate company [129]. This affect that drugs containing same active ingredient are possible to be classified into different schemes.

Based on quality, safety and efficacy characteristics, drugs are classified into three forensic classifications: prescription-only medicines, pharmacy-only medicines, and general sale list medicines [135].

1. Prescription-only medicines (POM)

POM are drugs that designated to require prescriptions to be dispensed. Patients can obtain them from physicians or dentists, or have to take prescriptions to retailed or online pharmacies and receive drugs under pharmacist supervisions [108, 135]. POM in Singapore are not allowed to directly advertise to public. Their patient information leaflets are not compulsory [113].

The criteria of POM are thoroughly described in HSA government website.

Drugs must be POM if they meet these criteria:

(i) The drug use can affect to human health directly or indirectly, although they are correctly used,

(ii) Drugs usually incorrectly used and result in direct or indirect danger to health,

(iii) Drug monitoring is required to ensure effectiveness and safety from side-effects,

(iv) Drugs are injections.

HSA also provides more criteria that need to take into consideration when deciding to classify drugs as POM. These criteria are:

(i) whether active ingredients are listed in the Narcotic Drug Convention or the Psychotropic Substances Convention,

(ii) whether drugs can be abused or used for recreation purpose,

(iii) whether drugs must be administered only in the hospitals,

(iv) whether the symptoms need special facilities that available in the hospitals or other specific institutions to diagnose, and

(v) whether products require medical supervision throughout the treatment course to ensure safety from side-effects, although the products are intended for outpatients [135].

2. Pharmacy-only medicines (P)

Pharmacy-only medicines do not require prescriptions to be dispensed, however, they still need pharmacist involvement. In retailed pharmacies, they need to be kept behind the pharmacists' counter. Online pharmacies are also allowed to sell this drug scheme only under pharmacist supervision [108, 135]. DTC advertisements are permitted for these drugs, while patient information leaflets are not compulsory [108].

Pharmacy-only medicines in Singapore can be further sub-classified into two categories: the first schedule and the second schedule [176].

2.1 The first schedule contains pharmacy-only medicines that can be sold under pharmacist supervision in all case [176].

2.2 The second schedule contains drugs that their actual status is POM, however, in some conditions, they are exempted to be sold as pharmacy-only medicines in limited sale and supply. Each drug exemption has their own criteria. The exemption criteria consists of the drugs' indications, and labels, which must describe maximum daily dose, maximum supply, and minimum age of patients allow to use drugs [176].

The criteria of pharmacy-only medicines described in details in HAS website.

Drugs must be classified as pharmacy-only medicines if they meet these criteria:

(i) pharmacist supervision and consultation are required to ensure the suitable choices of treatments,

(ii) drug interaction, contraindications, precautions, or warnings are not easy to recognized by consumers and thus require the enforcement from pharmacists, and

(iii) products need special precautions for storage and/or handling [108].

3. General sale list medicines (GSL)

In Singapore, GSL drugs can be sold in any retailers and over the internet without supervision from healthcare professionals. Designation of GSL drugs intended for patients to be self-medicated and therefore should be safe without any healthcare professional advice [108, 135]. DTC advertisements are allowed, but patients information leaflets are compulsory [108] .

The criteria of pharmacy-only medicines described in details in HSA website. These criteria are:

(i) drugs are rationally safe to be self-medicated without healthcare professionals' supervision,

(ii) drug interaction, contraindications, precautions, or warnings are easy to recognized by consumers,

(iii) drugs have only small risk of hazard, misuse, and misdiagnosis, and

(iv) special precautions of product storage and handling are not necessary [108].

Malaysia

Malaysia is the Islamic country located in Southeast Asia. It contains the multi-ethic including Malays, Chinese, Indian and others. Malaysia is the federal state consists of thirteen states and three territories. Their healthcare system contains both Universal Healthcare Coverage and private health insurance. Ministry of Health is the responsible organization, while National Pharmaceutical Regulatory Agency (NPRA) is a drug regulatory agency.

Table E: Country context of Malaysia

Context	Data
States	Federal state
Populations	32 million people[159]
Life expectancy of birth	76.0 years[147]
Human development index (world ranking)	0.804 (61)[146, 147]
Learning-Adjusted Years of Schooling (LAYS)	9.1[145]
Gross domestic product (GDP) per capita	28,176 (2011 PPP$[3])[147]
Current health expenditure	3.8% of GDP[147]
Drug Regulatory agency	National Pharmaceutical Regulatory Agency (NPRA)[177]
Healthcare system world ranking by WHO[2]	49[6]
Universal healthcare coverage implementation	Yes[161]
Physician density (per 10,000 populations)	15.132[162]
Pharmacist density (per 10,000 populations)	3.47[163]
Pharmacy practice	
- Response to patients' symptoms	Yes[100]
- Vaccination	No[154]
Pharmacy	
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

Drug classification scheme

In Malaysia, a particular drug can simultaneously regulated under several acts. However, all drugs are regulated under the Poison Act. This act classifies all chemical substances; only certain groups from classification are human drugs. Drugs are classified by their active ingredients. There are five classes of poisons: group A, group B, group C, group D and non-scheduled poisons [177].

1. Group A poison

Group A poison contains chemical substances that are highly toxicity. They are not allowed to be sold to public, or general retailers in Malaysia. Only wholesalers can sell group A poisons to licensed pharmacists in Malaysia or export to client abroad. Examples of group A poisons are alclofenac or amidopyrine [177].

2. Group B poison

Chemical substances under this class are the treatments required prescriptions from physicians to be dispensed. They are similar to prescription-only medicines in other countries. Patients can obtain group B poisons directly from physicians or taking prescriptions to pharmacies and receive them under pharmacist supervision [177]. In Malaysia, DTC advertisement of group B poisons are prohibited [116].

The criteria of group B poison is broadly stated in the government website. However, the expert reports some characteristics of group B poisons as (i) need be used for treat any symptoms that need diagnosis from physician, (ii) physician supervisions are required to ensure patient safety, and (iii) new drugs [139].

3. Group C poison

Group C poison can be sold to patients without prescriptions as treatments, but only under pharmacist supervision in pharmacies. These drugs also need to be kept behind the pharmacists' counter [177]. Although they can be sold in pharmacies, sale in retailers are still prohibited. These drugs are not permitted to be directly advertised to public [116].

The criteria of group C poison are also broadly stated in the government website. However, the expert reports some characteristics of group C poisons as treatments for disease that do not need physician supervision due to less complex, but still need pharmacists to confirm the right self-diagnosis [139].

4. Group D poison

Group D poison is the chemical substances used only in laboratories and therefore not a treatments used in humans. Examples of Group D poisons are acetone and methyl bromide [177].

5. Unscheduled poison

Any poisons not included in any group previously described are considered as not regulated under the poison act. This drug scheme is the only group that can be sold widely in retailers and over the internet without healthcare professional involvement. Therefore, it is similar to general sale list drugs in other countries [177]. DTC advertisements are allowed for these drugs. The comprehensive labels are also compulsory for this drug group [116].

Drugs exempted from the poison list are any chemical substances that do not meet criteria of other poison group. The expert also said that the characteristics of them must be self-diagnosis, self-selection and self-management [139].

The Philippines

The Philippines has the official name as the Republic of the Philippines. It locates on Southeast Asia and consist of approximately 7,600 islands. The Philippines are the member of many organizations, such as United Nations, World Trade Organization, and Association of Southeast Asian Nations. The healthcare system in the Philippines was ranked by WHO as 60 [6]. The governments recently implement the Universal Healthcare Coverage in 2019 for all Filipino citizens [161]. This is the great reform of the healthcare system since it supports health service and drug accessibility while patients do not have to endure the financial problems.

Table F: Country context of the Philippines

Context	Data
States	Unitary state
Populations	107 million people [159]
Life expectancy of birth	71.1 years [147]
Human development index (world ranking)	0.712 [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	8.4[145]
Gross domestic product (GDP) per capita	7,943 (2011 PPP$[3]) [147]
Current health expenditure	4.4% of GDP [147]
Regulatory agency	Food and Drug Administration of the Philippines (FDA) [178]
Healthcare system world ranking by WHO[2]	60 [6]
Universal healthcare coverage implementation	Yes [179]
Physician density (per 10,000 populations)	12.75 [162]
Pharmacist density (per 10,000 populations)	3.31 [163]
Pharmacy practice	
- Response to patients' symptoms	Yes [179]
- Vaccination	Yes [149]
Pharmacy	
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

Drug classification scheme

The Food and Drug Administration of the Philippines regulate drugs under the Philippine Pharmacy Act. In this country, drugs are classified by their active ingredients. If one brand is reclassified, all brands, contain the same active ingredients must be reclassified too. According to the Philippine Pharmacy Act, drugs can be divided into five categories: dangerous drugs, exempted dangerous drugs, prescription drugs, over-the-counter drugs and household remedies [101].

1. Dangerous drugs (DD, Rx)

These drugs are narcotic and psychotropic drugs, which are listed in the Comprehensive Dangerous Drugs Act 2002. They require special prescriptions called yellow prescriptions, issued by physicians to be dispensed.[121] Patients must bring the yellow prescriptions to pharmacies to obtain them. Pharmacist must check that the prescriptions are not expired before dispense these drugs to patients [121].

2. Exempted Dangerous drugs (EDD, Rx)

These drugs are narcotic and psychotropic drugs that exempt from the Comprehensive Dangerous Drugs Act 2002. Although the yellow prescriptions of these drugs are not required, they need to be prescribed from physicians who have S2 license [121].

3. Prescription drugs (Rx)

Prescription drugs must be dispensed under pharmacist supervision and with common prescriptions issued by physicians. They can be distributed in both retailed and online pharmacies. This scheme similar to Prescription-only medicines in other countries [101]. DTC advertisements are strictly prohibited [117].

The criteria of prescription drugs in the Philippines are not clearly describe in the Food and Drug Administration of the Philippines' website. So, I decide to use the criteria of these drugs based on the criteria of over-the-counter drug scheme in opposite way. They are described as drugs contain active ingredients that need physician supervision or adverse drug reaction (ADR) monitoring due to unproved safety and efficacy, narrow margin of safety, and low therapeutic index [141, 142].

4. Over-the-counter drugs

These drugs are drugs that do not require prescriptions to be dispensed but still need pharmacist supervision. The governments allow these drugs to be sold in retailed and online

pharmacies, but not in retailers [141, 142]. DTC advertisements of this drug scheme are prohibited [117].

The criteria of over-the-counter drugs are found in policies and guidelines on over the counter (OTC) drug products. These criteria are:

(i) the product is time-tested under investigation and extensive clinical use,

(ii) active ingredients of products have wide safety margin and high therapeutic index; and do not require monitoring from healthcare professionals,

(iii) active ingredients of products have been proved that they are safe and effective.

(iv) active ingredients of products must not be listed in the following lists: List B (bioequivalent problem), List A (regulated by the Dangerous Drugs Board), and controlled drugs (designated by the International Narcotics Control Board) [141].

5. Household remedies (HR)

Household remedies do not require healthcare professional supervision and also can be widely sold in retailers and over the internet [101]. Among all schemes, only this scheme is allow to directly advertise to public [117].

The criteria of household remedies are found in drug re-classification guideline in the Philippines. These criteria include (i) drugs that do not have recognized adverse drug reaction history at least 20 years, (ii) drugs that recorded in household remedies as per A.O. No. 117 s. 1992 [142].

Canada

Canada is among the most political powerful countries in the world. It is a federal state, located in Northern America. Canada consists of ten provinces and three territories with decentralized politics, including the healthcare system, known as Medicare. However, Medicare is more like standard healthcare system to all provinces and territories than the national level. Medicare also provides universal healthcare coverage for Canadian citizens, funding from their tax. All basis medical services and treatments are included in these public insurance [180]. Drug regulatory agency in Canada, known as Health Canada, is also accepted by WHO as the stringent one [78].

Table G: Country context of Canada

Context	Data
States	Federal state
Populations	37 million people[159]
Life expectancy of birth	82.3 years[147]
Human development index (world ranking)	0.922 (13)[146, 147]
Learning-Adjusted Years of Schooling (LAYS)	11.7[145]
Gross domestic product (GDP) per capita	44,051 (2011 PPP$[3])[147]
Current health expenditure	10.5% of GDP[147]
Regulatory agency	Health Canada, The National Association of Pharmacy Regulatory Authorities (NAPRA)
Healthcare system world ranking by WHO[2]	30[6]
Universal healthcare coverage implementation	Yes[161]
Physician density (per 10,000 populations)	26.102 [162]
Pharmacist density (per 10,000 populations)	11.24 [163]
Pharmacy practice	
- Response to patients' symptoms	Yes [155]
- Vaccination	Yes [149]
Pharmacy	
- Pharmacy schedule	No
- Non-pharmacist pharmacy	No

Drug classification scheme

In Canada, national drug regulatory scheme, which is regulated by the National Association of Pharmacy Regulatory Authorities (NAPRA), was analyzed in this study. This pharmacy regulatory body designates drug classification after classification by Health Canada to set standards and guidelines for all Canadian provinces and territories, except Quebec. Two members, British Columbia and Newfoundland & Labrador, designate the drug classification scheme based on their own drug regulatory agencies with recommendations from NAPRA, whereas the regulation of the rest of the provinces and territories are automatically in force from NAPRA's designation [125].

Based on NAPRRA schedule, drugs in Canada are classified by their active ingredients into four schedule: schedule 1, schedule 2, schedule 3, and unscheduled drugs [102].

1. Schedule 1

Drugs designated into schedule 1 require prescriptions to be dispensed. These drugs can be distributed in the public via hospitals, retailed pharmacies and online pharmacies under pharmacist supervision [102, 106]. The government allow DTC advertisement of these drugs only if they are not listed as controlled or narcotic substances. Moreover, only reminder advertisements[6] and help-seeking advertisements [7]are allowed, but product claim advertisements [8]of these drugs are not [112].

The criteria of drug classification in Canada use the cascading system. Thus, any drugs comply to any schedule 1 criteria below are designated to schedule 1. If they do not meet these criteria, the next step should be schedule 2 criteria consideration.

(i) Only prescribing practitioner can identify the requirement of drug use.

(ii) Drug use needs evaluation and/or adjuvant care.

(iii) Despite correct use, drugs can lead to dependency.

(iv) Despite normal therapeutic dosage levels, drugs use can result in serious drug adverse events.

(v) Drugs have narrow safety margin in healthy populations and/or multiple medical problem people.

(vi) Drugs are known to have serious drug interactions.

(vii) Drug use can contribute to microorganism resistant.

[6] Only contains drug name, price, and quantity subjected to the Health Canada regulations. Drug indications are prohibited.

[7] Only specific disease are allowed to present, while any relations specified to prescription drugs are prohibited.

[8] Advertisements that allow to present drug name, indication, benefits and risks.

(viii) New drugs that are not intended to use for self-medication.

(ix) Drugs are not widely use in populations or drugs have insufficient evidences of drug use consequence [137].

2. Schedule 2

Drugs designated in Schedule 2 do not require prescriptions to be dispensed, yet pharmacist involvement is needed. These drugs must kept behind the pharmacists' counter in retailed pharmacies, and prohibit to place in public area in pharmacies for patient self-care. Online pharmacies are permitted to sell these drugs with pharmacist supervision [102, 106]. Health Canada permits all types of DTC advertisements of drugs in schedule 2 [112].

The criteria of drug classification in Canada use the cascading system. Thus, any drugs comply to any schedule 2 criteria below are designated to schedule 2. If they do not meet these criteria, the next step should be schedule 3 criteria consideration.

(i) Healthcare professionals need to identify or confirm the correct treatment choices for the symptoms.

(ii) Drug monitoring by pharmacists is required for a long-term therapy or re-treatments.

(iii) Drugs need timely access when it is emergency or in the situation that prescriptions are not practical.

(iv) Drug administration must be in healthcare setting and under healthcare professionals

(v) Drug are injections and do not meet certain criteria of schedule 1

(vi) According to their properties, drug use can lead to misuse or potential dependency.

(vii) Pharmacists' intervention of drug selection is required to ensure the correct of self-diagnosis.

(viii) Drug use may mark or delay the recognition of serious ailments.

(ix) Drugs have serious or significant side effects, adverse drug reactions, or drug interactions; that cannot adequately explained in the labels.

(x) Pharmacists' enforcement is required to support appropriate and safe drug use, which not effective enough when describe only on labels.

(xi) New drugs for self-medication by patients [137].

3. Schedule 3

Drugs that are designated in Schedule 3 are less strict than in schedule 1 and 2. These drugs do not require both prescriptions and pharmacist supervision to be obtained. However, they

still need to be sold in retailed or pharmacies. They can be displayed in the public section of retailed pharmacies [102, 106]. DTC advertisements are also allowed for these drugs [112].

The criteria of drug classification in Canada use the cascading system. Thus, NAPRA designates drugs to schedule 3 when they comply to schedule 3 criteria below, but not schedule 1 and 2. If they do not meet these criteria, they will be unscheduled drugs.

(i) Chronic use of drugs may mark or delay the recognition of serious ailments.

(ii) New drugs, which pharmacists should provide the advice if necessary, for self-selection and self-medication by patients.

(iii) Drugs are used for persistent or recurring symptoms; pharmacists are required to advice and recommend appropriate use if necessary.

(iv) According to their properties, drug use may lead to misuse or potential dependency

(v) Pharmacists' enforcement is required to support appropriate and safe drug use, which occasionally are confused when describe only on labels [137].

4. Unscheduled drugs

Unscheduled drugs are the least strict drug scheme in Canada. They can be sold in retailers for patients to self-medicate. Healthcare professional involvement is not required [102, 106]. DTC advertisements are also permitted [112].

The criteria of drug classification in Canada use the cascading system. NAPRA designates drugs as unscheduled when they do not comply to any criteria of other previous schedules [137].

Thailand

Thailand, formerly known as Siam, is Buddhism country located in Southeast Asia. Thailand consists of 77 provinces. Its healthcare system was recognized as the most successful system among upper-middle income country. Universal Healthcare Coverage was introduced in Thailand in 2001. Thai citizens covered under one of three schemes: the National Health Security Office, the Social Security Office and the Civil Services Medical Benefits Scheme. Thailand has approximately 13,405 public hospitals, 384 private hospitals, 13,510 clinics, 17,069 type 1 community pharmacies, and 2,865 type 2 community pharmacies. Type 1 community pharmacies sell any types of drugs and require a pharmacist on duty during operating hour. Type 2 community pharmacies sell limited non-prescription drugs and allow other certified non-pharmacists on duty during operating hour [8, 9]. In 2005, the Ministry of Public Health ceased licensing of new Type 2 community pharmacies, which led to the decreasing of a number of type 2 community pharmacies [10].

Table G: Country context of Thailand

Context	Data
States	Unitary state
Populations	69 million people [159]
Life expectancy of birth	76.9 years [147]
Human development index (world ranking)	0.765 (77) [146, 147]
Learning-Adjusted Years of Schooling (LAYS)	8.6 [145]
Gross domestic product (GDP) per capita	16,905 (2011 PPP$[3]) [147]
Current health expenditure	3.7% of GDP [147]
Regulatory agency	Thai Food and Drug Administration (TH FDA) [12]
Healthcare system world ranking by WHO[2]	47 [6]
Universal healthcare coverage implementation	Yes [161]
Physician density (per 10,000 populations)	8.096 [162]
Pharmacist density (per 10,000 populations)	5.53 [163]
Pharmacy practice	
- Response to patients' symptoms	Yes [156]

Context	Data
- Vaccination	No [156]
Pharmacy	
- Pharmacy schedule	Yes [9]
- Non-pharmacist pharmacy	Yes [9]

Drug classification scheme

Thai FDA is responsible for drug classification decision. Drugs in Thailand, regulated under one of three acts: the Psychotropic Substance Act A.D. 2016, the Narcotic Act A.D. 2019 and the Thai drug act, A.D. 2019 [12, 118, 119]. the Psychotropic Substance Act A.D. regulate Psychotropic drugs. These drugs always need prescriptions to be dispensed [118]. the Narcotic Act A.D. 2019 regulated narcotic drugs. Several of them, such as codeine, require prescriptions and are available only at hospitals. However, combination drugs contained narcotic drugs can be sold in pharmacies without prescription requirement, but patient names and citizen identification are requested to prevent drug abuse [119]. the Thai drug act, A.D. 2019 regulate the rest drugs. These drugs are subdivided by their active ingredients into four categories: controlled drugs, dangerous drugs, non-dangerous drugs, and household remedies [12].

1. Controlled drugs

Controlled drugs in Thailand require prescriptions to be dispensed. They are allowed to be distributed via hospitals and retailed pharmacies. Patients must always receive these drugs only under pharmacist supervision [11, 12]. DTC advertisements of these drugs are prohibited [115].

The criteria of controlled drugs can be found in the Thai FDA official website (in Thai) and from the presentation materials from the Thai FDA (in English). These criteria are described below.

(i) Correct drug use without physicians' supervision can lead to direct danger: high general toxicity, reproductive toxicity, genotoxicity, moderate-to-high frequency adverse drug reaction type A, low-to-high frequency adverse drug reaction type B, serious drug-drug interactions or food-drug interactions.

(ii) Correct drug use without physicians' supervision can lead to indirect danger from masking symptoms of serious diseases, such as cancers and heart disease.

(iii) Drug use should be under physicians' supervision to ensure correct use or drugs usually are misused widely.

(iv) Drugs are intended to treat symptoms that require a diagnosis from physicians

(v) Drug use can lead to negative impact to society, although they are safe enough to be classified as dangerous drugs, for example drug that often abused, drugs that usually used for illegal recreations, narcotics, and psychotropic substances [1, 11].

2. Dangerous drugs

Dangerous drugs in Thailand do not require prescriptions to be dispensed, however pharmacist supervision is still required [11, 12]. These drugs can be sold in hospitals or retailed pharmacies, but not retailers. DTC advertisements are prohibited [115].

The criteria of dangerous drugs can be found in the Thai FDA official website (in Thai) and from the presentation materials from the Thai FDA (in English). These criteria are described below.

(i) Drugs do not meet any criteria of controlled drugs.

(ii) Drug use can be explained or advice from pharmacists; while physicians' supervision is not necessary [1, 11].

3. Non-dangerous drugs

Non-dangerous drugs, known as non-dangerous and non-specially-controlled ready-packed drugs in Thailand, are drugs that governments do not announce to be designated in any schemes, or exempt from other schemes [11, 12]. These drugs can be sold in retailed pharmacies, both type 1 and type 2. They can be placed in the public area in the pharmacies. DTC advertisements are allowed for these scheme [115].

The criteria of non-dangerous drugs can be found in the Thai FDA official website (in Thai) and from the presentation materials from the Thai FDA (in English). These criteria are described below.

(i) Drugs do not meet any criteria of controlled drugs and dangerous drugs.

(ii) Drugs are not injection.

(iii) Drugs have low risk, supported by well-established evidence, in vulnerable people: children, pregnancy, lactating women, the elderly, and patients suffering from liver or renal dysfunctions.

(iv) Drug administration do not require instruction from healthcare professionals; patients can administer drugs by following labels or package inserts [1, 11].

4. Household remedies

Household remedies are drugs that can be widely sold in retailers and over the internet. The supervision from healthcare professionals are not required [11, 12, 107]. DTC advertisements are permitted in this country [115].

The criteria of household remedies can be found in the Thai FDA official website (in Thai) and from the presentation materials from the Thai FDA (in English). These criteria are described below.

(i) Drugs do not meet any criteria of controlled drugs and dangerous drugs.

(ii) Drugs are not injection.

(iii) Drugs are intended for symptoms that can be self-diagnosed, without healthcare professionals' involvement.

(iv) Drugs have low risk, supported by well-established evidence, in vulnerable people: children, pregnancy, lactating women, the elderly, and patients suffering from liver or renal dysfunctions.

(v) Drug administration do not require instruction from healthcare professionals and are easy to administer by patients when follow labels or package inserts [1, 11].

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