ANTINEOPLASTIC DRUG ACCESS IN THAILAND

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การเข้าถึงยาต้านมะเร็งในประเทศไทย

นางสาวพรสรวง เสรีกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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พรสรวง เสรีกุล : การเข้าถึงยาต้านมะเร็งในประเทศไทย (ANTINEOPLASTIC DRUG ACCESS IN THAILAND) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ภญ. ดร. รุ่งเพ็ชร สกุลบำรุงศิลป์, 213 หน้า.

การเข้าถึงยาต้านมะเร็งเป็นเรื่องหลักที่ส่งผลต่อผู้ป่วยโรคมะเร็งในการวางแผนการรักษาเช่นเดียวกับค่าใช้จ่ายในการรักษา การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อประเมินและเปรียบเทียบสถานการณ์ของการเข้าถึงยาต้านมะเร็งระหว่างประเทศไทยและประเทศเทียบเคียง รวมทั้งการสำรวจปัจจัยที่มีอิทธิพลต่อการเข้าถึงยาต้านมะเร็งในประเทศไทย โดยทำการศึกษาจากข้อมูลทะเบียนยาต้านมะเร็งที่ได้รับอนุมัติในช่วงปี 1982 ถึงเมษายน 2016 ที่ได้มาจากเว็บไซต์ของหน่วยงานกำกับดูแลยาของประเทศที่ทำการศึกษาได้แก่ประเทศไทย, สิงคโปร์, มาเลเซีย, สหรัฐอเมริกา, สหราชอาณาจักรรวมทั้ง หน่วยงานกำกับดูแลยากลางของยุโรป (EMA) ผลการศึกษาพบว่า ยาต้านมะเร็งที่ได้รับอนุมัติทะเบียนในประเทศไทยมีจำนวน 88 รายการจากจำนวนที่บันทึกไว้ 180 รายการโดยองค์การอนามัยโลก ซึ่งเทียบกับจำนวน 130 รายการที่ได้รับอนุมัติทะเบียนยาในสหรัฐอเมริกา จำนวน 119 รายการในสหราชอาณาจักร จำนวน 75 รายการจาก EMA จำนวน 92 รายการในสิงคโปร์และ 68 รายการในประเทศมาเลเซีย นอกจากนั้นพบว่าใน 88 รายการได้รับอนุมัติทะเบียนในประเทศไทย มีเพียง 38 รายการอยู่ในบัญชียาหลักแห่งชาติ (NLEM) สำหรับการเข้าถึงยาของผู้ป่วย สำหรับเวลาที่ล่าช้าคิดจากช่วงเวลาที่ต่างกันระหว่างวันได้รับอนุมัติทะเบียนในประเทศไทยกับในประเทศเทียบเคียงอื่น ซึ่งพบว่าโดยเฉลี่ยประเทศไทยใช้เวลาเพื่อให้มียาต้านมะเร็งที่มีอยู่ในตลาดล่าช้ากว่า สหรัฐอเมริกา 37.26 เดือน สหราชอาณาจักร 4.52 เดือน EMA 12.22 เดือน สิงคโปร์ 10.73 เดือนและมาเลเซีย 6.51 เดือน จากการวิเคราะห์แสดงให้เห็นว่า การเข้าถึงตลาดของยาต้านมะเร็งได้มีการปรับปรุงการในแต่ละช่วงเวลา พบความล่าช้า 87.59 เดือนในช่วง 1983-1990 และมีความล่าช้าเพียง 23.62 เดือนในช่วง 2007-2016 อย่างไรก็ตาม พบความล่าช้าในการเข้าถึงยาของผู้ป่วยโดยเฉลี่ย 88.05 เดือน สำหรับผลิตภัณฑ์ที่ได้รับการระบุไว้บัญชียาหลักแห่งชาติหลังจากที่ได้รับอนุมัติทะเบียนยาในประเทศไทย การวิเคราะห์ตัวปัจจัยการเข้าถึงตลาดชี้ให้เห็นว่ามีเพียงปัจจัยสำคัญเดียวที่อธิบายการเข้าถึงตลาดของยาต้านมะเร็ง คือระดับความใหม่ของตัวยา ที่ระบุไว้เป็นความใหม่ระดับ 2 หรือ ระดับ 3 ซึ่งพบว่าจะเข้าสู่ตลาดไทยได้เร็วขึ้นกว่าความใหม่ระดับอื่นๆ ในยาประเภทเดียวกัน การศึกษาสรุปได้ว่าในช่วงเวลาที่ผ่านมา การเข้าถึงตลาดของยาต้านมะเร็งในประเทศไทยมีการพัฒนาดีขึ้นเทียบเคียงได้กับสิงคโปร์และมาเลเซีย แต่กระบวนการสำหรับยาต้านมะเร็งที่จะได้รับการระบุไว้บัญชียาหลักแห่งชาติ สำหรับการเข้าถึงยาของผู้ป่วยนั้นจำเป็นต้องได้รับการพัฒนาและปรับปรุง

ภาควิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต .....

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5377107033 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS: MARKET ACCESS, PATIENT ACCESS, ANTINEOPLASTIC DRUG / TIME LAG

PORNSROUNG SAEREKUL: ANTINEOPLASTIC DRUG ACCESS IN THAILAND. ADVISOR: ASST. PROF. RUNGPETCH SAKULBUMRUNGSIL, Ph.D., 213 pp.

The access to antineoplastic drugs has been a major concern affecting cancer patients on treatment plan as well as treatment costs. This descriptive study aimed to assess and compare the situation of access to anticancer drugs between Thailand and benchmarked countries, and to explore determinants influencing the accessibility of antineoplastic drugs in Thailand. The data on drug registration information of antineoplastic medications approved during 1982 and April 2016 were acquired from websites of the drug regulatory agency of studied countries including Thailand, Singapore, Malaysia, US, UK, and EMA. The result showed that Thailand had registered 88 out of 180 active pharmaceutical ingredients (APIs) of antineoplastic listed by WHO, comparing with 130 APIs registered in USA, 119 in UK, 75 in EMA, 92 in Singapore, and 68 in Malaysia. Of 88 APIs registered in Thailand, 38 were listed under National List of Essential Medicine (NLEM) for patient access. The time lag, which was time difference between market authorization approval (MAA) date in Thailand and in the compared country, was reported that on average Thailand has anticancer drugs available in the market 37.26 months later than US, 4.52 months than UK, 12.22 months than EMA, 10.73 months than Singapore, and 6.51 months than Malaysia. Trend analysis illustrated that the market access of antineoplastic drugs has been improved overtime from 87.59 months during 1983-1990 to 23.62 months during 2007-2016. However, the longer waiting time for patient access was reported. It took 88.05 months on average for a product to be listed under the National List of Essential Medicine (NLEM) after registered in Thailand. The analysis on determinants of market access pointed that the only significant determinant explained market access of antineoplastic drugs was the novelty level. The API listed as the 2nd or 3rd me-too was found to enter Thai market faster than others of the same classification. The study concluded that market access of antineoplastic drugs in Thailand had been improved overtime and comparative with Singapore and Malaysia. It was recommended that the process for anticancer drugs to be listed under NLEM for broader patient access needed to be revised.

Department:	Social and Administrative Pharmacy	Student's Signature	.....
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Abbreviation	Explanation
ACE	Angiotensin Converting Enzyme
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirements
ADR	Adverse Drug Reaction
AIFA	Agenzia Italiana del Farmaco
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ASEAN	The Association of Southeast Asian Nations
ASG	Applied Sciences Group
ATC	The Anatomical Therapeutic Chemical
AUS	Australia
B.E.	Buddhist Era
BE	Bioequivalence
BIRC	Brazil, India, Russia and China
BLA	Biologic License Application
BODC	Board of Drug Committee
BPFK	Biro Pengawalan Farmaseutikal Kebangsaan
BSG	Blood Services Group
CAGR	Compound Annual Growth Rate
CDA	Centre for Drug Administration
CDE	Centre for Drug Evaluation
CDER	Center for Drug Evaluation and Research

Abbreviation	Explanation
CFM	Centre for Forensic Medicine
CFS	Centre for Forensic Science
CHMP	Committee for Medicinal Products for Human Use
CMDR	Centre for Medical Device Regulation
CMS	Concerned Member States
COMIS	Center-Wide Oracle-Based Management Information System
CP	Centralized Procedure or Centralized Authorization Procedure
CPA	Centre for Pharmaceutical Administration
CPM	Chinese Proprietary Medicines
CPMP	Committee for Proprietary Medicinal Products
CPP	Certificate of Pharmaceutical Product
CRP	Centre for Radiation Protection
CSA	Controlled Substances Act
CSMBS	Civil Servant Medical Benefit Scheme
CTD	Common Technical Documents
CTM	Centre for Transfusion Medicine
DC	Decentralized Procedure
DCA	Drug Control Authority
DESI	The Drug Efficacy Study Implementation
DMS	Department of Medicine Service
DP	Decentralized Procedure
DRG	Diagnosis-related Group
DRS	Drug Regulatory System

Abbreviation	Explanation
DS	Drug substance
DUE	Drug Use Evaluation
EEA	European Economic Area
EM	Essential Medicines
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EML-WHO	Essential Medicines list of WHO
EOB	Electronic Orange Book
EPAR	European Public Assessment Report
EU	The European Union
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	Federal Food, Drug and Cosmetic
FEO	For Export Only
GDA	Generic Drug Application
G	Generic Drug
GMP	Good Manufacturing Practices
GPO	Government Pharmaceutical Organization
GSL	General Sale List medicines
GST	Government and Services Tax
HAS	Health Sciences Authority
HC	Health Canada
HPRG	Health Products Regulation Group
HQ	Headquarter

Abbreviation	Explanation
HSG	Health Services Group
HTA	Health Technology Assessment
ICH	International Council for Harmonization
IND	Investigational New Drug
ITG	Innovative Therapeutics Group
KOLs	Key Opinion Leaders
LCD	Local Clinical Development
MA	Marketing Authorization
MAA	Marketing Authorization Approval
MAH	Marketing Authorization Holder
MAL	Malaysia
MHRA	Medicines and Healthcare Products Regulatory Agency
MOH	Ministry of Health
MOPH	Ministry of Public Health
MRP	Mutual Recognition Procedure
MS	Member State
MSM	Methyl sulfonyl methane
N	New Drug
NB	New biological drug
NCE	New Chemical Entity
NDA	New Drug Application
NG	New Generic Drug
NLEM	National List of Essential of Medicine
NMEs	New Molecular Entities

Abbreviation	Explanation
NP	Nation Procedure or National Authorization Procedure
NPCB	The National Pharmaceutical Control Bureau
OOPD	Office of Orphan Products Development
OTC	Over-the-Counter
P	Pharmacy-Only medicines
PBS	Pharmaceutical Benefits Scheme
PCC	Price Control Countries
PCS	Price Control System
PDMA	Prescription Drug Marketing Act
PDUFA	Prescription Drug User Fee Act
PHS	Public Health Service
PMPRB	Patented Medicine Prices Review Board
POM	Prescription-Only medicines
PRH	Product Registration Holder
PRP	Pharmaceutical Reference Price
PSD	Pharmaceutical Service Division
RLD	Reference Listed Drug
RMS	Reference Member State
SG	Singapore
SMP	Safety Monitoring Program
SSS	Social Security Scheme
TGA	Australia Therapeutic Goods Administration
TGC	Targeted Cell Therapy
TH	Thailand

Abbreviation	Explanation
Thai FDA	Thai Food and Drug Administration
THB	Thai Baht, the currency of Thailand
US	The United States
UC	Universal Coverage
USFDA	US Food and Drug Administration
USTR	United States Trade Representative
WHO	World Health Organization

CHAPTER I

INTRODUCTION

1.1 Background

Market access of medicines refers to the process by which a company gets a drug to the market; so that it turns out to be available for patients. Market access has been used to convey for various meanings. Some of them intend to use only as medicine availability on the market; whereas others extend its meaning to cover patients' ability to get needed medicines. In some countries, availability of medicines in the market or market authorization does not imply the accessibility by patients; if health benefit system plays an important role in reimbursement of drug expenditures.

In the past, the pharmaceutical industry relied on old conventional ways of building influence with key opinion leaders (KOLs), believing the key to the product success was merely conveying effective messages through efficient communication with physicians who prescribed the drug to patients. Currently, a need for new wisdom has arisen due to increasing types of hurdles for market and patient access. When confronted with a complex environment, in which multiple stakeholders come with multiple requirements, in addition to the costly health technology assessment (HTA); the pharmaceutical company needs a novel key to product success by initiating effective management program for payers (Cohen J, 2006). Market access for new pharmaceuticals can be successful with the awareness of various hurdles. In the past, for overcoming 3 hurdles of safety, efficacy, and product quality, in order to obtain regulatory approval entailed; the company needs to prove not only the safety and efficacy but also the quality of a product at launch. These three hurdles were sufficient to gain market access and patient access to new drugs and new biopharmaceuticals in a traditional system. The changing of drug pricing and reimbursement environment put more requirements in the process; before patient could access innovations in the containment system. Thus, the delay to access medicine is caused by time lag between applications for reimbursement approval and granting of marketing authorization. At

this moment, the fourth and fifth hurdles pertain to the reimbursement and pricing of approved drugs. The fifth hurdle to marketing access is pricing. Proving "value for money" has increased the need for "pharmacoeconomics", i.e., cost effectiveness and cost utility which brings up the sixth hurdle (Walley, 2004; Wilking & JönssonIt, 2006).

The requirement of proving for safety, efficacy, and quality of drugs, during the regulatory approval, has delayed the launch of new drugs to the market. The pricing and reimbursement environment policy of each country have intensified and extended the delay of patient access in many countries, as illustrated in the study on "Market access for cancer drugs and the role on health economics" studied by Wilking & Jönsson (Wilking & Jönsson, 2005). The impact on the "time lag or drug lag" was shown in Table 1

The delay in launching of new drugs is costly for consumers, who forego the benefits of the new drug. It is also costly for manufacturers, because drug patent life still continues to run; regardless of whether the product is on the market. From the product owners' point of view, each day of the delay is, thus, a day of on-patent revenues foregone; which can be worth millions of dollars for high volume drugs. More and more new drugs were experienced the launching delay before obtaining authorization to market the drug in the US; following the Kefauver Harris Amendment or "Drug Efficacy Amendment" which was 1962 amendments to the Food, Drug, and Cosmetics Act, after the thalidomide tragedy. The Food, Drug, and Cosmetics Act required that manufacturers have to show the proof of efficacy in addition to the safety and the good manufacturing practices (GMP). This delay, even considering as a safety measure for consumers, was documented as "drug lag" relative to other industrialized countries; and was confirmed by several studies in the year 1970s and 1980s. The similarity of these measurement has, later, been adopted by other countries (Popper & Nason, 1994; S. O. Schweitzer, H. Salehi, & N. Boling, 1985).

Table 1: Average time delay in day between marketing authorization approval (MAA) date and the lunching dates as market access after final pricing and reimbursement (during Jun 2000 – Jun 2004)

Average time delay in days between marketing authorization and market access (2000 - 2004)				
Countries	Number of products	Average time delay between approval & market access	Time delay between approval & market access	
			Maximum time	Minimum time
Austria	69	82	994	0
Belgium	69	435	1094	28
Cyprus	6	130	250	0
Czech Republic	62	389	1461	31
Denmark	61	54	1084	0
Estonia	41	131	958	0
Finland	76	226	1293	0
France	55	431	1393	58
Germany	82	0	0	0
Greece	73	427	1039	39
Hungray	20	214	548	76
Ireland	69	170	1372	0
Italy	66	345	1049	26
Netherlands	58	259	1201	56
Norway	31	302	1071	20
Poland	106	2190	2190	2190
Portugal	64	361	1524	0
Slovakia	40	453	914	31
Spain	64	327	1382	0
Sweden	68	122	1173	0
Switzerland	42	159	676	26
UK	86	0	0	0
USA	100	0	0	0

Source by: Wilking, N., & Jönsson, B. (2005). Market access for cancer drugs and the role of health economics. A pan-European comparison regarding patient access to cancer drugs (pp. 70-85). Karolinska Institutet in collaboration with Stockholm School of Economics

A social drug lag, or the delay of patient access to medicine, was found in U.S. during 1970-1980. This lag is the delay between the time that a drug is approved for market by the US Food and Drug Administration (USFDA) and the time that a drug is available to indigent population of state through the Medicaid program (S. Schweitzer, H. Salehi, & N. Boling, 1985). The launch delay of new drugs has been a major public alarm in

Japan; although it is recognized that the delay results from industrial R&D manners and regulatory conditions in the global market (Hirai et al., 2012). The median for the approval time lag for Japan (41 months) was more than 3 years longer than that of US; and for EU about 2.7 months longer than that of US (Tsuji & Tsutani, 2008).

However, the delay for launching new cardiovascular drugs in India, which is lagged as compared to the United States and European Union, has impacts on health outcomes remains to be established (Kataria, Mehta, & Chhaiya, 2013). The study of 20-year of data for six countries has revealed a certain extent of drug lag; which may have been resulted from national formula, National health plan, generic substitutes, and patent protection and regulation (Popper & Nason, 1994). The key regulatory barriers of 'Western Approval' such as BIRC (Brazil, India, Russia and China) and 11-N counties, Local clinical Development (LCD), Certificate of Pharmaceutical Product (CPP), Good Manufacturing Process (GMP), pricing approval, document authentication and harmonization are identified (Wileman & Mishra, 2010).

The drug lag could be assessed by 2 dimensions: (a) the delay in time of innovation availability, and (b) the number of new drugs availability. The drug lag concept, by itself, implies the comparison by nature. The delay is occurred, when drug is available somewhere prior to the country of interest. Some studies use the number of new drugs, available in the country, as an indicator to measure the extent of drug lag. The higher the number of drugs available; the lesser the degree of drug lag the country is facing. The number of drug available could, also, be measured in the form of either absolute or relative. The absolute drug lag is defined as the number and the percentage of approved new drugs in each region/country (EU, US, Japan), out of a total of new drugs approved in the other regions/country; whereas the relative drug lag is defined as the number and percentage of first approvals in the regions/country, compare to a total of new drugs approved either in the other regions during the study period. The other variable was the approval lag against the first approval granted to each drug in each region. Tsuji and Tsutani (Tsuji & Tsutani, 2010) reported the absolute drug lag, in their study that during the years 1999-2007, from the total 398 new drugs which were approved in US, EU and Japan; 325 (81.7%) were approved in US, 314 (78.9%) in EU, and 220 (55.3%) in Japan. On the other hand, the relative drug lag was illustrated that US had the first

approval 202 (50.8%) out of the 398 new drug while EU had 139 (34.5%), and Japan had 52 (13.1%). The median of approval time lag for the US, the EU, and Japan was found 0 month, 2.7 months and 41.0 months, respectively. Bhaven C. and colleagues (cited in (Kataria et al., 2013) recounted the absolute drug lag in their study, that during the years 1999-2011, of the total 75 new cardiovascular drugs approved in US, EU and India; 61 (81.33%) were approved in US, 65 (86.66%) in the EU, and 56 (74.66%) in India. They, also, revealed the relative drug lag; that the US was the first to approve 35 (56.45%) from the 75 new cardiovascular drugs, meanwhile the EU 24 (38.71%), and India 3 (4.84%). The median approval lag for India (44.14 months) was, substantially, higher as compared to the United States (0 month) and EU (2.99 months).

The study of P. Russo, F.S. Mennini, P.D. Siviero and G.Rasi in Italy revealed the time delay patient to access medicine is 2.3 years. Some processes, such as price regulation and reimbursement submission, delay patient to access for cancer drug (Russo, Mennini, Siviero, & Rasi, 2010)

In Thailand, the delay of launching drugs in the market was, rarely, reported. The study by Burapadaja, Kawasaki, Charumanee, and Ogata (Burapadaja, Kawasaki, Charumanee, & Ogata, 2007) revealed the significant effects of essential medicines (EM) on the patterns and values of cardiovascular products available for the market in Thailand. This study confirmed the impact of National List of Essential of Medicine (NLEM) on patient access to medicines in Thailand. Essential medicines (EM) were, originally, defined by the World Health Organization (WHO) as the medicines that fulfil the needs of the majority of the population. Therefore, they should be available at all times, in adequate amounts, in suitable dosage forms, and at a price the individual and community can manage to pay for (WHO, 2013). In Thailand, as a general concept, the selection of essential medicines is usually a two-step process.

1. The first step involves regulatory approval; which is based on a review of safety, efficacy, including the quality of medicines. Based on these registered products, essential medicines under the therapeutic class stand, then, drug was selected by the basis of comparative safety and efficacy including cost of drug.

2. The second step is to guarantee that list is the widest acceptance. The selection process needs the involvement from stakeholders, prescribers, dispensers, academics, health facilities, civil society, professional organizations, and others.

Since the year 1981, Thailand created its first National List of Essential Medicine (NLEM); based on the World Health Organization (WHO) of minimal drug list concept. The current 2016 NLEM (the 11th version) classified essential medicines into sub-lists C, D, and E(2); whereby Drug use evaluation (DUE) must be introduced for the use of sub-list D (Thai-FDA, 2013). More than 34 years of NLEM available in Thailand, a limited range of carefully selected essential medicines has been introduced while the advance technology of treatment has increased double. The dilemma of NLEM in Thailand has always been between better health care for patients and better drug management for the country. There has been no study to address NLEM assessment, in terms of the delay patient access to medicines. Knowing whether there is absolute delay or relative delay would benefit Thailand; and they could use to improve the NLEM management system.

Various factors limit the access of medicines in Thailand; such as financial factor, procurement of medicines, and regulation on medicines for use (Chalongsuk, 2007). As Thailand is a developing country, the fast moving of Pharmaceutical market contains large proportion of items. Since 1989, the new regulation on new drug registration has been enforced in Thailand. There are 453 items by trade name or registration number of new drugs with Safety monitoring program (SMP) condition (Thai-FDA, 2012a) and 1240 items of new drugs without SMP condition available until the end of December 2012 (Thai-FDA, 2012b). Among all of new drugs, the drug delay to the market is not a concern; whether or not, there is an impact on the accessibility to medicine in Thailand. Even at the health policy level which is under the budget constrain, the effort is focused more on mechanisms to list items on NLEM. But how soon they will be listed has never been raised as the major concern. The delay of new drugs to be listed under National List of Essential of Medicine (NLEM) has never been explored; and the impact on patient access is, thus, unknown.

The pressure from the United States Trade Representative (USTR), since the year 1986, forced the country to open its Tobacco market; and accepted product patent in 1992 (Wibulpolprasert, 1999). The delay of the new generic drug (NG) launching to the market is even intensified in Thailand; due to the patent protection and the new regulation of Bioequivalence (BE) study requirement imposed in 1997-1998. During the first NG approval in 1999, until the end of 2012, there were 594 items counted by the registration number approval or marketing authorization (Thai-FDA, 2012c). The launching of NG in the market seems to be a factor expediting the new chemical to be listed on NLEM in Thailand.

The drug expenditure in Thailand, reported by National Drug Account in 2010, showed that the value of the domestically manufactured drugs (excluded repacking) was 46,895.78 million Baht (THB); whereas the import value was 99,663.79 million THB, and the export value was accounted for 12,077.48 million Bath (THB) (NDA-TFDA, 2010, Kessomboon, N., Sakulbumrungsil, R., Kanchanphibul, I., Udomaksorn, S., & Jitraknatee, A., 2012). (NDA-TFDA, n.d.)

Antineoplastic Drug is classified as one of 16 groups of products by the Anatomical Therapeutic Chemical (ATC) classification system. Up until present, the domestic manufacturers cannot manufacture antineoplastic (anticancer) drug; all of anticancer drugs has thus been relied on importation. The imported values of antineoplastic drugs were ranked 5^{th}-7^{th} during the period before the turn of the century; and they were ranked second in 2010, with anti-infective were all time highest expenditures. The imported value of antineoplastic group has increased from 682.71 million THB (6.54% of total imported value) in 1997 to 12,404.24 million THB (12.83%) in 2010; which accounted for 25.0% compound annual growth rate (CAGR), or growing over 17 times in values whereas the average CAGR of all importation was 18.7% as shown in the Table 2. (Thia-FDA, n.d.).

Table 2: The value of imported product during year 1997-2010 (one million Thai baht per unit).

No.	Items of Anatomical Therapeutic Chemical (ATC) classification system	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	GAGR%
1	ALIMENTARY TRACT AND METABOLISM	1,441.76	1,385.42	1,812.55	1,790.99	1,954.28	2,434.19	3,296.02	4,403.83	5,279.86	6,256.95	7,074.46	8,274.67	7,079.91	9,925.30	16.00
2	BLOOD AND BLOOD FORMING ORGANS	804.27	1,099.24	1,277.17	1,277.17	1,557.37	1,578.08	2,285.46	2,905.97	3,462.65	5,033.74	5,514.62	6,154.49	9,178.66	12,345.51	23.38
3	CARDIOVASCULAR SYSTEM	1,398.49	1,776.03	1,833.69	1,864.41	2,464.99	2,508.32	3,011.29	3,287.18	4,155.38	4,685.82	5,991.93	6,599.85	6,933.53	10,835.92	17.06
4	DERMATOLOGICALS	300.42	328.60	441.12	440.92	457.64	515.38	563.50	667.60	811.30	886.29	1,090.76	1,033.19	6,933.53	1,831.17	14.92
5	GENITO-URINARY SYSTEM AND SEX HORMONES	585.86	716.44	1,273.47	1,273.47	1,634.35	1,890.10	2,474.43	2,349.34	2,873.41	1,915.43	4,027.69	3,275.51	3,843.59	5,573.81	18.92
6	SYSTEMIC HORMONAL PREPARATIONS	183.92	193.51	182.95	237.88	307.21	382.05	467.41	512.58	610.93	817.39	934.16	1,156.65	1,036.80	1,081.40	14.60
7	GENERAL ANTI-INFECTIVES-SYSTEMIC	2,502.72	3,514.64	3,804.57	3,790.01	4,332.98	3,777.10	4,697.33	5,401.48	7,517.71	8,021.90	9,056.62	10,865.73	13,788.92	15,074.74	14.81
8	HOSPITAL SOLUTIONS	302.76	447.59	478.35	489.67	442.89	392.23	619.20	718.91	841.37	1,108.94	1,122.50	1,126.55	1,468.16	2,298.96	16.88
9	ANTINEOPLASTICS	682.71	1,348.62	1,262.30	1,207.37	1,591.27	1,727.04	2,722.84	3,355.84	4,278.87	5,601.62	5,571.24	7,361.15	7,858.66	12,400.24	24.99
10	MUSCULO-SKELETAL SYSTEM	443.68	518.02	645.91	646.57	875.10	937.61	1,171.99	1,706.02	2,079.66	2,618.13	3,410.26	4,120.92	5,612.01	7,427.41	24.20
11	CENTRAL NERVOUS SYSTEM	575.72	836.25	926.10	919.92	1,160.90	1,369.02	1,856.13	2,019.91	2,715.47	3,705.17	4,050.78	4,776.91	5,504.22	8,376.05	22.87
12	PARASITOLOGY	112.41	38.36	36.11	36.11	76.10	35.59	36.55	38.78	37.47	53.83	50.41	58.44	45.25	67.15	(3.89)
13	RESPIRATORY SYSTEM	645.20	1,474.28	1,778.75	1,078.05	2,232.92	1,226.02	1,665.79	1,680.62	1,803.45	2,334.21	2,572.09	3,164.68	3,712.40	4,258.04	15.62
14	SENSORY ORGANS	295.06	349.58	477.37	487.77	568.06	809.71	801.18	1,055.36	1,177.62	1,578.74	1,712.75	2,124.34	2,400.78	3,325.77	20.48
15	DIAGNOSTIC AGENTS	114.06	111.98	210.41	218.05	230.11	268.04	244.66	286.25	427.80	170.86	667.86	575.21	565.78	1,251.23	20.23
16	VARIOUS	46.29	80.77	78.98	67.04	87.17	75.06	110.85	103.47	225.84	205.67	245.36	316.37	382.13	577.01	21.42
Total import (all 16 groups)		**10,435.34**	**14,219.31**	**16,519.79**	**15,825.40**	**19,973.32**	**19,925.53**	**26,024.62**	**30,493.12**	**38,298.77**	**44,994.69**	**53,093.49**	**60,984.66**	**76,344.33**	**96,649.71**	**18.68**
Percentage of Antineoplastic drug (%)		**6.54**	**9.48**	**7.64**	**7.63**	**7.97**	**8.67**	**10.46**	**11.01**	**11.17**	**12.45**	**10.49**	**12.07**	**10.29**	**12.83**	**5.32**

Source of data: the Thai FDA's Statistic data "Import and manufacturer information" , accessed date on April 12, 2016, retrieved from http://drug.fda.moph.go.th/zone_search/sea001.asp

During the critical period of budget constrain in the year 2012, the nine groups of non-NLEM which possessed high value of prescribing, were watched up; and the limitation on dispensing original branded product has been imposed. Anticancer drug group was ranked at the ninth position of concerned government budget as in the listed below. (MOPH, 2011).

Nine groups of non-NLEM with high value of prescribing include:

(1) Antiulcerant/Variceal bleeding

(2) NSAIDs/Anti-osteoarthritis

(3) Antilipidemic

(4) Angiotensin converting enzyme (ACE) inhibitors

(5) Angiotensin-II receptor blockers: ARBs

(6) Antiplatelet

(7) Glucosamine

(8) Drug affecting bone metabolism

(9) Anticancer

Based on the information of Global Cancer Facts & Figures: 3rd Edition by American Cancer Society in 2015 (American Cancer Society, 2015), cancer deaths were found increase each year. The cancer causes of death was found more deaths than the combined causes of AIDs, tuberculosis, and malaria. From data in 2012, cardiovascular diseases were the first leading cause of death worldwide, in the meantime cancer was the second. Ranked by income level, leading causes of death global in 2012, revealed that cancer deaths were still the second leading causes (25%) in high-income group behind cardiovascular diseases (38%) as the first. However, in low and middle - income group, cancer deaths were ranked the third leading causes of death (12%) after infectious and parasitic diseases (14%) as the second and cardiovascular diseases (30%) as the first.

The five commonly deaths cancers of worldwide were lung, liver, stomach, colon and prostate in males; and breast, lung, colon, cervix, stomach and liver in females. There were (a) lung cancer accounted for 1.6 million people of the total for both men and women, (b) stomach cancer accounted for 0.7 million of the total for both genders, (c) liver cancer for 0.7 million, (d) colorectal cancer taking 0.69 million more people, and (f) female breast cancers in 0.5 million women of the total for women. See the table 3 below:

Table 3: The estimate death case worldwide for the leading cancer site 2012 (American Cancer Society, 2015)

Male		**Female**	
Lung, bronchus & trachea	1,098,700	Breast	521,900
Liver	521,000	Lung, bronchus & trachea	491,200
Stomach	469,000	Colon & rectum	320,300
Colon & rectum	373,600	Cervix uteri	265,700
Prostate	307,500	Stomach	254,100
Esophagus	281,200	Liver	224,100
Pancreas	173,800	Pancreas	156,600
Leukemia	151,300	Ovary	151,900
Urinary bladder	123,100	Esophagus	119,000
Non-Hodgkin lymphoma	115,400	Leukemia	114,200
All sites*	4,653,400	All sites*	3,548,200
Note*: Excluding non-melanoma skin cancers. Estimate may not sum to worldwide total due to rounding.			

Modified from: Global cancer, Facts and Figure, 3rd Edition, American Cancer Society-2015

Cancer is also an increasing health problem in Thailand. Trends in number of cancer cases, from the years 1990 to 2008 for the five cancer sites (positions) such as colon-rectum, liver, lung, breast-cancer and cervix-uteri, were revealed (Sriplung, Wiangnon, Sontipong, Sumitsawan, & Martin, 2006). See the information in the Table 4. Because of the high cost of antineoplastic drug, as well as the nature of the disease that needs close monitoring; all of the approved Marketing Authorization Applications (MAA) was the special control medicine; classified by Thai FDA (TFDA), which were required to be sold only in hospitals and clinics. The given status of special control medicine required antineoplastic to be prescribed for patients only by specialist physicians. There

were very few study that addressed the drug lag in Thailand causing the delay access to medicines particularly for cancer patients. The study, thus, was interested to analyze medicine access to antineoplastic drugs on the basis of four reasons:

1. It had high value of the expenditure. The data showed that anticancer drugs had the second highest imported values and highest compound annual growth rate during 1997-2010.
2. It has been one of the nine controlled prescribing groups listed by the Ministry of Public Health.
3. Cancers have been one of the leading cause of death not only Thailand but globally; and the cost of illness and treatment were unaffordable for most people.
4. Antineoplastic drug was classified as special control status by TFDA; which could be prescribed only by specialists and available only in hospitals.

Table 4: Number of cancer cases in Thailand form year 1990-2008 (Sriplung et al., 2006)

	1990	1993	1996	1999[1]	2002[2]	2005[2]	2008[2]
Male							
Colon-recturn	1,638	1,940	2,529	3,258	3,896	4,711	5,666
Liver	7,463	8,241	9,020	9,571	10,527	11,652	12,928
Lung	4,480	5,079	5,844	6,435	7,412	8,500	9,792
All sites	27,610	32,096	35,405	41,114	46,756	53,482	61,393
Famale							
Colon-recturn	1,280	1,679	1,963	2,847	3,365	4,208	5,155
Liver	3,072	3,733	3,669	4,107	4,574	5,128	5,798
Lung	2,295	2,555	2,786	3,038	3,476	3,985	4,560
Breast	2,931	3,516	5,161	6,750	8,321	10,194	12,370
Cervix uteri	4,696	4,665	5,531	6,488	7,026	7,823	8,756
All sites	24,842	28,863	33,298	40,425	47,000	54,910	63,852

[1] Estimated based on projected rates of cancer in Bangkok. [2] Projected from statistical model

Source by: Hutcha Sriplung, S. W., Sineenat Sontipong, Yupa Sumitsawan, & Martin, N. (2006). Cancer Incidence Trends in Thailand, 1989-2000. Asian Pacific Journal of Cancer Prevention, 7, 239-244.

The aim of this study was to explore the drug lag in Thailand for antineoplastic drugs; looking from the perspectives of both the market access and patient access, and also examined the factors that influenced the antineoplastic drug access.

1.2 Research questions

1. What was the antineoplastic drug lag situation in Thailand?
2. How was the antineoplastic drug lag different among ASEAN Country?
3. What were factors that influenced the accessibility of antineoplastic drugs?

1.3 Objectives of study

1. To assess market access and patient access of antineoplastic drugs in Thailand
2. To compare accessibility of antineoplastic drugs among selected ASEAN countries
3. To analyze the association between determinants and access to antineoplastic drugs

1.4 Conceptual Framework

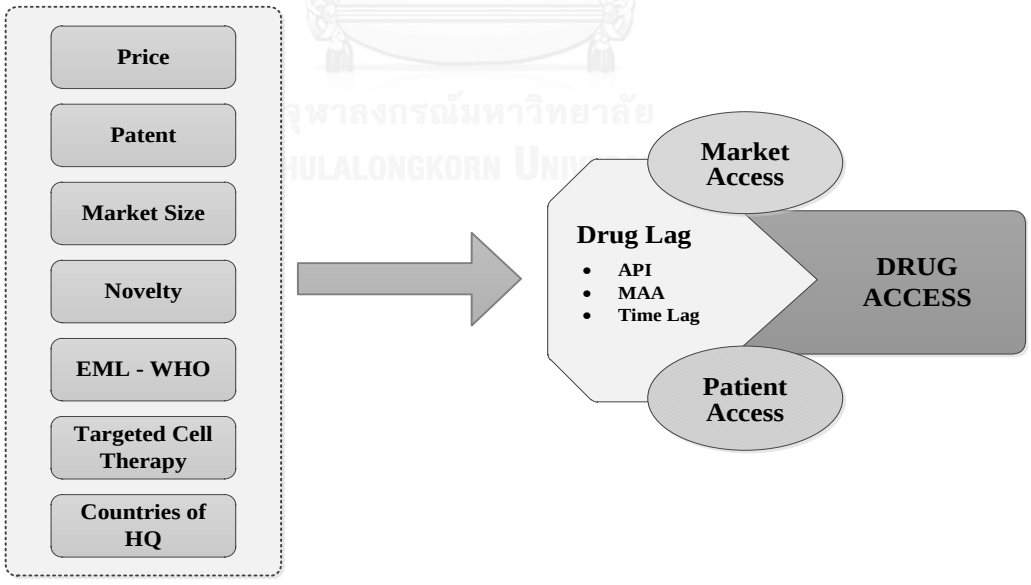


Figure 1: The conceptual framework

Based on this conceptual framework, the drug access consists of two main accesses. One is the market access defined as the existing of drug in the market. The other one is

patient access defined as the reaching of medicine of patient. The measurement of drug access is the time lag or drug lag, number of drug or active pharmaceutical ingredient (API) including number of marketing authorization application (MAA). The factors that may influence to drug lag such as drug price, drug patent, market size and priority list of drug, will impact to the drug access

1.5 Expected contributions

1. The access to antineoplastic drugs situation could be learned as an example of high cost care.
2. The Food and Drug Administration could use the results from the study to strengthen the drug registration system and speed up the process to assure the appropriated drug access in Thailand.
3. The NLEM committee could improve patient drug access by taking into consideration all associated determinants contextualized by the study.

1.6 Word interchangeable used:

In this study, the many words are used interchangeable between:

- Chemical substance or active substances or active pharmaceutical ingredient (API) and anatomical therapeutic chemical (ATC) name
- Medicine and drug
- Antineoplastic drug and cancer drug
- Active pharmaceutical ingredient (API) and new chemical entity (NCE)

CHAPTER II

LITERATURE REVIEW

The interest of the research was about the antineoplastic drugs and their market. How the drugs can penetrate the market with self-completion to the patients in Thailand. In this literature review, the pathway and the view of these topics was described by 10 sections as follows:

- Situation of cancer disease
- Situation of anticancer drug
- History of drugs and regulations, and pathway to market in Thailand (TH)
- History of drugs regulations and drug registration (legislation) process in other countries
- Related research: drug access, market access, patient access, drug lag, price, patent and targeted cell therapy

2.1 Situation of cancer diseases

Cancer was a kind of diseases, characterized by uncontrolled cell growth. There were more than 200 different types of cancer; and each type was classified by the type of cell, that was, initially, affected (Cancer Research UK, n.d.; National Cancer Institue, 2015). Cancer troubles the body when damaged cells were divided, nonstop, to form masses of tissue called tumors, excluding leukemia, where cancer prohibits standard blood function by irregular cell division in the blood stream (National Cancer Institue, 2015).

Cancer was also a foremost cause of death global; and it was estimated that 7.6 million cancer deaths happened, worldwide, in 2012. Lung cancer was found around 1.6 million for men and women; meanwhile stomach cancer was 0.7 million for men and women. Additionally, liver cancer caused 0.7 million for men and women, colorectal cancer effected 0.69 million for men; and women and female breast cancers were about 0.5 million. These five cancers were the most common causes, presenting more than

half of all cancer deaths. Table 3 (Chapter I) provided the information of estimate death cases, worldwide, by cancers (American Cancer Society, 2015).

In Thailand, cancer was also the problem which the value of cancer drugs (Antineoplastic and immunomodulation Agents) was approximately 15,264.47 million THB in year 2010 (NDA-TFDA, n.d.). Cancer was also an increasing health problem in Thailand. Trends in number of cancer cases from the years 1990 to 2008 for the five cancer sites (positions) such as colon-rectum, liver, lung, breast-cancer and cervix-uteri were revealed and the total of cases was estimated to be 63, 852 in year 2008 (Sriplung et al., 2006) as shown in Table 4 (Chapter I).

A study in Thailand since the year 1982 (Miller & Somboonchaeroen, 1982) revealed that the pattern of cancers, in Thailand, were different from pattern of cancers in the United States. The environmental situation was a significant factor; which they were differences in dietary and smoking behaviors, and the distribution of certain environmental carcinogens. Several cancers expected to be prevented by the nationwide campaign of health education to do the prevention. Many plan such as setting up the cancer centers in all regions in Thailand; especially in the provinces where an university hospital was not available (Vatanasapt, Sriamporn, & Vatanasapt, 2002).

2.2 Situation of anticancer drug

The common types of cancer plan for treatment are: surgery, chemotherapy, radiation therapy; and many others depend on the type and stage of cancer. Chemotherapy treatment (or treatment by drug/ anticancer agents) was discovered, mainly, by inhibiting metabolic pathways crucial to cell division (Narang & Desai, 2009).

A major new innovation in model development had occurred in the early 1910s; when George Clowes of Roswell Park Memorial Institute (RPMI) (in Buffalo, New York) developed the first transplantable tumor systems in rodents. Then, the first anticancer, nitrogen mustard for lymphoma, was introduced to the world in 1964. Until now, the treatment has been changed from the conventional of treatment to be target cell therapy after the discovery of molecular targets. This targeted cell therapy had brought a new

period in anticancer drug research since 2007 (Eckhardt, 2000; Vincent T. DeVita, 2008).

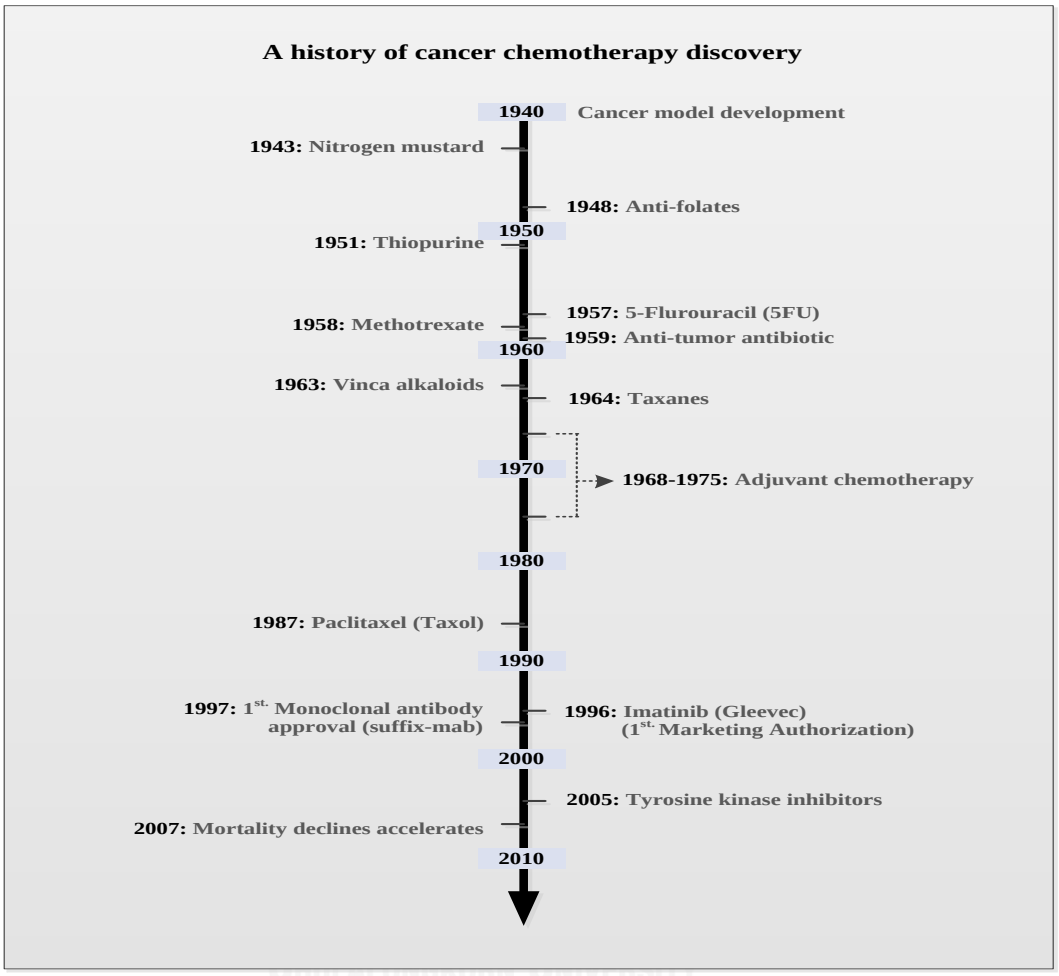


Figure 2: Key advances in the history of cancer chemotherapy (Modified from: History of cancer chemotherapy of Vincent T. De Vita, 2008)

The chemical agents of anticancer drug classification were established according to their mechanism of actions and the sequence by time of products discovery. It is similar to the ATC-code system of WHO classification. Active Pharmaceutical product (API) is chemical substance which is classified by WHO ACT-code system (WHO, 2011). “Antineoplastic and immunomodulating agents” are classified as group L in the ATC code first level. Antineoplastic drug (L01) is therapeutic group: the level 2 of the ATC classification, and from this level, it is separated in five pharmacological groups as a level 3 of the classification system.

1. Alkylating agents (Level 3: L01A)
2. Antimetabolites (Level 3: L01B)
3. Plant alkaloids and other natural products (Level 3: L01C)
4. Cytotoxic antibiotics (Level 3: L01D)
5. Other cytostatic (Level 3: L01X)

By counting, there were 180 chemical substances, 23 chemical groups, and 5 pharmacological groups of antineoplastic drugs; which were revealed to the world by ATC-code of WHO at the end of 2015. According to the time of product discovery, new chemical entity in group is normally described by 01 which defined as the breakthrough in group. Then, when the second, third and fourth product in the same chemical group are discovered, it becomes 02, 03, and 04 as a sequence. This later chemical substance in the same group is defined as "me too" product (WHO, 2015).

Table 5: Classification ATC-code in five levels, modified from structure and principle of ATC-code (WHO, 2011)

L	Antineoplastic and immunomodulating agents (1st level, anatomical main group)
L01	Antineoplastic drugs (2nd level, therapeutic subgroup)
L01A	Alkylating Agents (3rd level, pharmacological subgroup)
L01AA	Nitrogen mustard analogues (4th level, chemical subgroup)
L01AA01	Cyclophosphamide (5th level, chemical substance)

Source from : WHO. (2011, Last updated: 2011-03-25). Structure and principles. Retrieved from http://www.whocc.no/atc/structure_and_principles/

2.3 History of drug, the drug registration process and pathway in Thailand

The medicine is known to import to Thailand long time ago without any office record. However, the drug registration regulation was changed and forced to be recorded in the database since 1982. Consequently, the change of law and regulation of drug, in each period, may change the first marketing authorization approval of drug. The review of history of drug entry and the drug registration process and pathway, thus, is necessary for this study and it can help to understand drug system and provide clearly vision and to this study.

2.3.1 History before 1982

The entry of modern medicine or western medicine in Thailand was in Ayutthaya period during the years 1518 – 1752 by European visitor; such as Portuguese and following with French as missionaries who had experience in the medicine and treatment. There was a small area under the Catholic Church "St. Joseph Church" known as a functional hospital in the King Naria decade. The modern medicine, which was different from the traditional medicine, was acknowledged by Thai people for treatment of their illness since then. (Charuluxananan & Chentanez, 2007).

The treatment by the modern medicine was face out; due to the relationship between Thailand (or Siam) and western countries did not flourish during the late Ayutthaya era and Thonburi era. The modern medicine came back to be well known again in the beginning of the Chakri Dynasty in the year 1828; by the American missionary who constructed the hospital to help Thai people from the suffering of illness.

After the great plague of cholera in Thailand in 1881; The King Rama V made decision to establish 48 functional hospitals in Thailand; as a government hospital to manage the epidemic disease at that time. His daughter was, also, killed by this epidemic disease "Cholera". The King had donated land and money for the construction of Siriraj Hospital to be the memorial of the lost daughter in 1887. This hospital was established with an objective to help Thai people from the suffering of illness.

The modern medicine for illness treatment has known in Thailand long time ago without any record; since the king Rama V established hospitals. The management of the hospital functions, at that time, was set up under the control of the Ministry of Interior, during the King Rama VI.

However, the treatment of illness according to the new technology came to Thailand in the early 1900s. At that time, due to the need of patients, many pharmaceutical companies imported modern medicine for sale in Thailand; and many small drug stores were set up in Bangkok and in big provinces of Thailand. During that periods of time (before 1909), the modern medicines were freely sold without any control of Thai government (Thia-FDA, 2004).

Under the consumer protection activities established to protect the food and drug from the physical and chemical hazardous for Thai citizen; the laws and regulations were, gradually, developed starting from the following years and events below (Thai-FDA, 2010):

1. **1909 (B.E. 2452 or roh-sor 127):** the protection of food and drug contamination was promulgated, for the first time, in 1909. This was the first era, in Thailand, called

   "Any adulterated food and drug for consumers. It is wrong and will be punished with imprisonment for a term not exceeding two years and a fine not exceeding five thousand baht"

2. **1913 (B.E. 2456):** The enactment of morphine and cocaine was issued as the first act in 1913 (B.E. 2456); which was main law to lunch Thailand's second act to control narcotic drug in 1922.

3. **1922 (B.E. 2465):** After Siam (name of Thailand during that time) joined an international agreement at The Hague regarding opium. Drug control had started, for the first time in Thailand; under the Division of Narcotic Drug, Ministry of the Interior.

4. **1929 (B.E. 2472):** The government of Thailand announced that the duties for manufacturing and dispensing medicines were assigned to pharmacists; which created the new professional "pharmacist" in Thailand.

5. **1936 (B.E. 2479):** During the reign of King Rama VIII, the medical education in Thailand was more developed. However, many modern medicines, still, were sold in Thailand without any control. Therefore, Thai government, at that time, launched the first law, related to drug, as "The Selling Drug Act" in 1936 (First version). This act did help setting the direction for selling of medicine in Thailand in right direction. It required the sale license for selling drug in Thai market; according to three categories as follows:
   - **Category A** sale license: By Pharmacist level 1 who had the right to sell dangerous drugs and meanwhile has the right to produce the medicine
   - **Category B** sale license: By Pharmacist level 2 who had the right to sell dangerous drugs, only to health professional's modern first-class or organization in the government.
   - **Category C** sale license: By not pharmacist

6. **1939 (B.E. 2482):** At that time, there were no big scale drug productions according to the global pharmaceutical manufacturing industry in Thailand. Most medicines were imported from abroad at the high prices. Thai government thought that if Thailand could produce drugs; it could help Thai people to have medicine for treatment at economic cost. Thai government, then, decided to build the first pharmaceutical factory in Phayathai district, in January 1939 (GPO, n.d.).

7. **1941 - 1942 (B.E. 2484 - 2485):** During pacific war, pharmaceutical factories in Thailand were controlled under The Pharmaceutical Division, Department of Medical Science, Ministry of Health on April 7, 1942 (B.E. 2485). A government pharmaceutical factory was officially opened on June 24, 1942 (B.E. 2485). Twenty-four years later, the Government Pharmaceutical Organization (GPO), was established under the Ministry of Public Health on August 5, 1966. The GPO was created according to the Government Pharmaceutical Organization Act, AD 1966 signed by Her Royal Highness Princess Srinagarindra, (the Princess Mother of the

King Rama IX). In the same year 1966, Thailand “Food and Drug Division” was set up under the Department of Public Health, Ministry of Public Health.(GPO, n.d.)

8. **1950 (B.E. 2493)**: After founding of Ministry of Public Health in 1942 (B.E. 2485), all activities of medical affairs and public health were separated into three departments: The Department of Food, the Department of Drug Control and Department to Promote Food. Furthermore, there was the announcement of new updated version of Selling Drug Act 1950; which had an assortment of selling license, clearly, into four categories. A "Control Board Dispensary” was also set up to control selling drug in Thailand (Thai-FDA, 2010).

   According to this Act, before drug was sole in Thai market, the drug products were required to be registered; therefore, the drugs whether from the local pharmaceutical manufacturing or import from other countries had to apply for a drug registration. It was the first legislation of the drug registration in Thailand.

9. **1953 (B.E. 2496):** Thailand Food and Drug Division was renamed to “Food and Drug Control Division” and then was transferred to be under the control of the Office of Permanent Secretary, Ministry of Public Health.

10. **1955-1962 (B.E. 2498-2505):** Since 1909 (B.E. 2452), several medicines were imported and produced in Thailand by many institutes and hospitals; so they were needed to be controlled under the law and regulation to cover many activities of medicine in Thailand. Therefore, during 1955-1962 period, the Selling Drug Act 1950 (secondary version) was reviewed and updated, many time, to cover all drugs selling activities in Thailand as the below listed.
    - the Selling Drug Act 2499 (Third version)
    - the Selling Drug Act 2500 (Fourth version)
    - the Selling Drug Act 2505 (Fifth version)

11. **1965 (B.E. 2508):** The control of Drug has been started for the first time in Thailand under the Division of Narcotic Drug, Ministry of the Interior.

12. **1967 (B.E. 2510):** Some periods from the beginning, there had been many counterfeit medicines around Thailand. Thus, the consumers had been harmed by

counterfeit medicines. The mission of the Division of the Food and Drug Administration, at that time, was to focus on the issues of combating with counterfeit medicines. Therefore, the Selling Drugs Act in 1950 (B.E. 2493) included the amended the 5th edition was canceled. In order to have committed and complete control, the Act 1967 (B.E. 2510) was implemented instead of the previous act; and became the primary drug act in Thailand. The Ministry of Health was in charge of the law and also setting "the drug committee" to consider and provide the principles and guidelines for the drug productions and drugs imported into the Kingdom. This Drug Act provided a major change in drug control. The Act had separated drugs in two categories: modern medicine and traditional medicine. It also separated approval licenses in five licenses: the manufacturing license, the imported license, the sale license including the sale license for OTC and the sale license for animal drug. It became the major change and originates regulation in Thailand until now.

13. **1961-1982 (B.E.2504 to 2525):** During this period, hospitals in Thailand had been developed; together with the items of medicines had been produced which were important point to organize National List of Essential medicine (NLEM) in 1981.

    13.1) 1961 (B.E. 2504): In 1961, after hospitals were set up and organized in almost every province in Thailand; the difference drug items of each hospital were an issue for the government to solve and to maintain the same budget for each hospital. In order to have the same main list of drugs for most of hospitals, Department of Medicine Service (DMS), which had 91 hospitals under its control, decided to create "the main hospital formulary". Under the team of Department of Medicine Service and Pharmacist Chavee Bunnag (Professor Emeritus, PhD); the main hospital formulary was completed on December 7, 1962 (B.E.2505). This main hospital formulary, then, was implemented in 1963 (B.E.2506) as a "Hospital formulary: version Department of Medicine Service (DMS), Ministry of public Health 2506". It is the first hospital formulary for all hospitals under the control of Department of Medicine Service (DMS). The list was expected to be updated every two years. However, there was no updated version of hospital formulary until 1973. Nine items of drugs were categorized

under the antineoplastic drug groups presented in this hospital formulary as in the table 6 (MOPH, 1963).

Table 6: List of antineoplastic drug in the first hospital formulary of 1963 (B.E. 2506)

	Drug name	Indication	Company
1	Bismuth Sodium Triglycollamate tablet	Anti-treponemal	Bristrimate (Smith, Miller & Patch)
2	Busulphan	Antineoplastic drug	Myleran (Burroughs Well W.)
3	Chlorambucil tablet	Nitrogen mustard derivative (Anti-neoplastic drug)	Leukeran (B.W.)
4	Mechlorethamine HCl for in injection	Cytotoxic	Mustagen (M.S.D.)
5	Mercaptopurine Tablet	Neoplastic suppressant	Puri-Nethol (B.W.)
6	Metrotrexate U.S.P.	Neoplastic suppressant	Metrotrexate (lederle)
7	Sodium Radio-Iodine Solution	For radiation	[a]
8	Sodium radio-phosphate solution	For radiation	[a]
9	Urethan Tablet	Neoplastic suppressant	[a]

[a] Information is not available

13.2) 1973 (B.E.2516): All of rural hospitals that were under control of Department of Medicine Service (DMS) were transferred to be under controlled of the Office of Permanent Secretary, Ministry of Public Health. The hospital formulary, therefore, was transferred to be updated by the Office of Permanent Secretary. The process of revising for a second version of the hospital formulary started in April 1973 and finished in December 1976. Then, it was updated again in 1976 (B.E. 2519) for all hospitals under listed for Ministry of public Health (MOPH). There were 17 items of drug under "antineoplastic drug" were found in this formula as in table 8.(MOPH, 1976)

13.3) 1978 (B.E. 2521): There were several changes in 1978 with the laws and regulations related to medicine such as:

- ❖ The MOPH launched a new regulation for procurement of medicines and medical supplies. In this regulation, hospitals had to purchase drugs from the GPO by using the generic name and with the government purchasing budget.
- ❖ The WHO launched the List of Essential Drug. The objective of this list was to be a suggestion list for the development countries that had forty percent (40%) of government budget for drug treatment.
- ❖ During 2519-2521, there were many new drugs launched in Thailand market and were not found on the Hospital Formulary of 1976. The antineoplastic drugs were found on the list as in the table 7.

13.4) 1979 (B.E. 2522): MOPH decided to set up the committee to revise and update the hospital formulary of 1976. However, the list of drugs was finished in 1979. It was called "Drug List of MOPH" instead of "Hospital Formulary of MOPH". This Drug List of MOPH was presented as the single active ingredient and avoided using the fix dose combination. MOPH had designed to do renewal this Drug List for every 1 or 2 years. From this Drug List, we found 18 items are the antineoplastic agents which included the steroidal hormone as well (MOPH, 1979).

Remark: At that time, the steroidal hormone for the immune suppressive was classified in the same classification of antineoplastic. But it was separated in a year later by WHO classification.

13.5) 1981 (B.E.2524): The development of National List of Essential Medicine (NLEM) was started and its first version was preceded in 1981. The NLEM was developed in order to serve the policy of the government, at that time, to provide the list of basic essential drugs for treatment of various diseases. Antineoplastic drug was, also, listed as the one group of drug in the NLEM in this year. Since the first list of NLEM until 2016, the 11^{th} versions of NLEM was implemented and 38 antineoplastic drugs were on the list. The details in the table 8.

Table 7: List of antineoplastic drug in the hospital formulary of 1976 (B.E. 2519)

	Drug name	Indication	Company
	Alkylating Agents (7 items)		
1	Busulfan	Anti-treponemal	Myleran (Burroughs Wellcome)
2	Chlorambucil	Antineoplastic drug	Leukeran (B.W.)
3	Cyclophosphamide	a	Endoxan (Asta Werke
4	Melphalan	a	a
5	Mustine hydrochloride	Cytotoxic	a
6	thiotepa	a	a
7	Uracil mustard	a	a
	Antimetabolites (3 items)		
1	Fluorouracil	Efudix	Roach
2	Mercaptopurine	Puri-nethol	Burroughs wellcom
3	Metrotrexate U.S.P.	-	lederle
	Steroidal hormones (3 items)		
1	Androgens	For radiation	a
2	Estrogens	For radiation	a
3	Progestogens	Neoplastic suppressant	a
	Plant alkaloids (2 items)		
1	Vincristine Sulfate	a	a
2	Vinblastine sulfate	oncovin	Eli Lilly
	Antibiotics (3 items)		
1	Chromomycin A3	Toyomycin	Takeda
2	Dactinimycin (Actinomycin-D)	Cosmegen	MSD
3	Mitomycin C	Mitomycin-C	Kyowa

Note: * Information is not available

Source by : MOPH. (1976). Hospital formulary: version MOPH MOPH.

Table 8: Number of Antineoplastic drug counted by API in each version of NLEM in Thailand

Number of Antineoplastic API in each version of NLEM in Thailand				
Version number	**Implemented year**	**Counted by drug substance or API**	**Counted by dosage form**	**Antineoplastic drug by API**
1	1981 (B.E.2524)	370*	408*	11
2	1986 (B.E.2529)	[a]	[a]	11
3	1987 (B.E.2530)	373*	417*	11
4	1992 (B.E.2535)	348*	390*	13
5	1996 (B.E.2539)	388*	556*	17
6	1999 (B.E.2542)	634*	932*	28
7	2004 (B.E.2547)	629	882	26
8	2008 (B.E.2551)	637	892	26
9	2013 (B.E.2556)	676	1021	31
10	2015 (B.E.2558)	688	736 (74 as herb)	36
11	2016 (B.E.2559)	[a]	[a]	38
* from Areya Sripairol, Sripen Tantivess and Viroj Tangcharoensathien: The implications of 1999 National Essential Drug List on Public Hospital in Thailand, URI: http://hdl.handle.net/11228/165, Health Policy and Planning Journal, 3,3(2543): 20-40				
[a] Information is not available				

14. **1982-1983 (B.E. 2525-2526**): Based on the limitation of authority staffs and the increasing of drug registrations after 1975; Thai Food and Drug Administration (Thai FDA), at that time, considered to cancel the renewal of product licenses in 1979 (B.E. 2522) in order to reduce the task work. Thus, the Drug Act of 1967 (B.E. 2510) was updated in 1979 (B.E. 2522), and assigned to cancel the product license renewal process or Marketing Authorization (MA) renewal process every five years, like other countries.

The result of Thai FDA decision caused the product licenses or marketing authorization approvals (MAAs) certificate of product registrations were no valid from the date of issuance after 1982 (B.E. 2525). Therefore, we could not find any record of drug registrations during year 1967 to 1982 in current Thai FDA database. The information of MAAs (such as drug registered number, company name, imported license holder,

manufacturer name and etc.) have been recorded in 1983 (B.E. 2526) until now (Thai-FDA, 2010)

Products, which were registered up to 1982 (before 1983) and expired, are needed re-registration under the new system of drug registration. Thus, all drugs and cancer drugs that were first registration before 1983, will have no actual first year of MA approval. In this study, we assumed that the first year of product available in Thailand will be the granted/approved years of MA only in Thai FDA database since 1983. The records of drug registration were started in 1983; therefore, some data of first Active Pharmaceutical Ingredient (API) before 1983 was lost.

2.3.2 History since 1982

Actually, in the beginning, the control system of food and drug was developed as a small unit in Ministry of Public Health. However, the Division of Food and Drug Control was endorsed to be the Office of Food and Drug Administration (FDA), and ranked as one department of Ministry of Public Health in 1974 (B.E. 2517). Drug registration and regulation in Thai FDA which, previously, were under the control of a drug control unit. At that moment, it was changed to be “Bureau of drug control”. The Drug Act of 1967 (B.E. 2510) is, currently, still in effect; and the revised of the Drug Act of 1987 (B.E. 2530) are, thorough, used until now.

The drug registration process, now, becomes necessary to guarantee quality, safety and efficacy drugs before lunched into Thailand market. Therefore, in Thailand, the process of authorized licensees is required to apply for product registration. Manufacturing plants, where drugs are manufactured, are also need to be complied with the Good Manufacturing Practice (GMP) requirements; either the manufacturing site is in Thailand or foreign country. The registered drug license or MAA document is provided by Thai FDA as a lifelong commitment.

After a lifelong commitment of MAA (no valid of MAA) was considered for drug registration system, transition period 1979-1982; the first drug registration approval record was found in 1983, Until 1989 (B.E. 2532), many new innovative drugs were launched in US and other countries. The information to support the innovative drug

registration had, also, to be difference from the earlier drug registration. Meanwhile, the reference countries such as US, the drug registration did not have to be only one type of drug registration process. Therefore, by drug committee announcement, vary in degrees of control and dossier submission, the registration procedure of modern medicine was accountable by two categories “Generic Drug” and “New Drug”

Generic Drug (G-group):

The definition of generic drug (G-group), in Thailand, may not be exactly the same as in other countries. Thai FDA defined “Generic Drug” as the following:

1. It is not a new drug by definition of Thai FDA.
2. A drug substance or active ingredient that has been registered in Thailand during 1983-1989
3. The product must be the same active ingredients and the same dosage forms as those of products which was registered in Thailand during 1983-1989, but manufactured by different manufacturing site.
4. The registration requires only dossiers on product manufacturing and quality control along with product information.
5. After marketing authorization (MA) is granted, the drug register number will be in the format such as 1C 53/2526 or 1A 44/2526

Remark: In this study, we also call the “generic drug” as the “G-group”

New Drug (N-group):

It is defined by Thai FDA as:

1. New chemical entity, new combination, new indications, new dosage form, new delivery system or new strength and new route of administration.
2. After MA is granted, the drug register number will be in the format that has the ending of: (NC), (N) (NB), (NBC); such as 1C 53/2526 (NC) and after 1C 44/2526 (NC)

The first new drug registration had already been approved MA since 1991 (B.E. 2534). (Thia-FDA, 2007)

Based on safety concept, the clinical studies of new drugs have, mostly, studied in the limit number of patients, and the studies did not be performed in Thailand. The limitation of testing, like this, may cause patients to have a risk of adverse drug reaction (ADR); when using new drug. For the safety alarm of using new drug, during first 2 year of lunching in the country; new drug has to be approved under the condition of SMP. Therefore, on May 31, 2537, Board of Drug Committee (BODC) of Thai FDA had updated guideline of new drug and implemented the Safety Monitory Program (SMP) for approval new drug (Limpananont, n.d.). During the SMP condition period, the medicine was, mandatory, to be used, only by the doctors in hospitals and clinics at least two years. They cannot be sold via drug stores. The condition of SMP will be released, only after, there is no concerning of ADR report in the critical level. A company has to get an approval from Thai FDA for the releasing SMP out from the condition; then the drug registered number will be changed from 1C 45/2556 (NC) to be 1C 45/2556 instead.

During 1991-1994, after new drugs as the innovative products, were lunching in Thai market; there were copies of the innovative products attempted to be registered in Thailand. To guarantee for an equal product, Thai FDA, by the BODC, implemented the guideline for the Bioequivalence study; which was required for new generic drug (NG) registration. Bioequivalence study is the study to weigh the expected the equivalence of two brand-named preparations of a drug. If two products are believed to be bioequivalence; it means that new generic drug would be expected to be the same for all intents and purposes of original product. The new generic drug seems to be developed since then; and the guideline of New Generic Drug were also updates in year later in 2001 (B.E. 2544).

New Generic Drug (NG-group):

It is a drug product that is comparable to new drug registration in Thailand as a brand/reference drug product in dosage form, strength, quality and performance characteristics, and intended use and those of the new compounds (new chemical entity) registered after 1991. In addition to the required documents for generic drug

submission, the new generic registration requires bioequivalence studies as well as literature supporting for the safety and efficacy of the product.

In 2000 (B.E. 2543): the guideline of Biological product registration was implemented in Thailand to help drug registration to, completely, classify into four types of product group as in other countries. (Thai-FDA, 2000)

In 2004 (B.E. 2547): The notification of Thai FDA for N-group and NG-group registration, the accelerated or priority review as a fast track channel, was announced and implemented on Aug 3, 2004. It was implemented in order to help accelerate approval of the life threatening drugs such as HIV drug, cancer drug and others as Thai FDA consideration. The process time line is at least 100 -130 official/working days (Thai-FDA, 2004)

In 2007, (B.E. 2550): ASEAN drug registration guideline was adopted by Thai FDA to implement, fully, in Thailand starting from 31 December 2006. However, Malaysia and Singapore had implemented it ,one year, before Thailand (Thai-FDA, 2006).

Between 2012-2014 (B.E. 2555-2557): According to the policy of government to accelerate New Generic Drug Lunching in Thai market, bioequivalence (BE) from foreign countries were allowed by Thai FDA for submission in 2012 (Thai-FDA, 2012d). However, this policy was phase out in 2014, due to the change of government policy.

In 2015 (B.E. 2558): Since the Licensing Facilitation Act, B.E. 2558 (2015) was implemented and became effective on 27 July 2015 in Thailand; Thai FDA has lunched the new guideline and pathway for drug registration. The committed timeline for the number of days after received date was granted from Thai FDA. For example, N- group expected to be within 280 working days, G- group expected to be within 210 working days and New Generic drug expected to be within 155 working days.

2.3.3 Drug registration process in Thailand

There were three main processes for drug registration: (1) the GMP accreditation approval process, (2) the license to import or manufacture drug sample process and (3)

the drug registration submission process as show in the below flow-chart figure 3. This figure provided the new drug registration process in 2016.

A product, that needs to be applied for drug registration in Thailand, needs to have the guarantee of manufacture. Therefore, oversea manufacturer needed to have a GMP accreditation approval by Thai FDA; before applying for drug registration application. GMP accreditation could be waived for the old manufacturing site; which information of that manufacturer has already been in Thai FDA database according to the FDA notification in 2014. Thus, this means that new manufacturing site needs to get approval of GMP accreditation by Thai FDA before starting to apply drug registration submission.

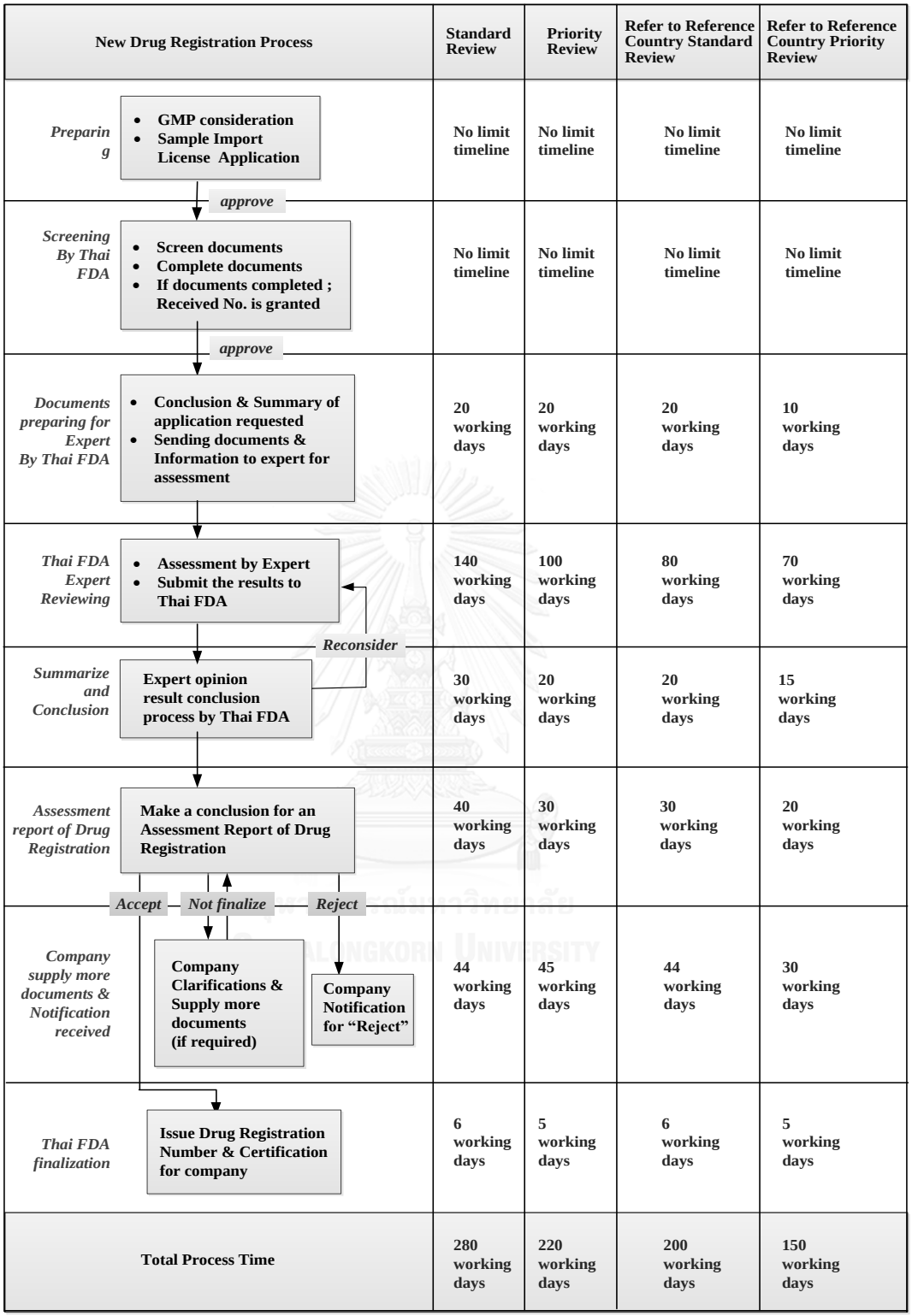
The company, that planned to have a drug to be registered in Thailand, needed to have the drug sample import license to be approved as the second step of drug registration application.

The documents for drug registration had to be prepared according to the classification of drug registration: Generic Drug, New Drug, New Generic drug and Biological product, according to the ASEAN guideline as follows:

Generic Drug: Documents of drug registration for Generic Drug had to prepare according to the guideline of Thai FDA "The manual of registration of Generic Drugs and Procedure of Generic Drugs Registration" as stated in ASEAN Harmonization implementation on 1st January 2009 (B.E.2552) (Thai-FDA, 2009b)

New Drug: Documents of drug registration for New Drug had to prepare according to "the manual of registration of New Drugs and Procedure of Generic Drugs Registration" as stated in ASEAN Harmonization implementation on September 2007 (B.E.2550) as a version 1 (Thai-FDA, 2009c)

New Generic Drug: Documents of drug registration for New Generic Drug had to prepare according to "The manual of registration of New Generic Drugs and Procedure of Generic Drugs Registration" as stated in ASEAN Harmonization implementation on September 2007 (B.E.2550) (Thai-FDA, 2007)



Modified from "Guideline for new drug and new biological product registration: version 27 July 2015 (Abridged evaluation under the Benchmark/Reference agencies)"

Figure 3: Registration Pathway of New Drug Registration in Thailand, year 2015 (Thai-FDA, 2015)

Biological product: Documents of drug registration for Biologic product had to prepare according to The manual of registration of New Generic Drugs and Procedure of Biological Drugs Registration" as ASEAN Harmonization implementation on September 2009 (B.E.2552) (Thai-FDA, 2009a)

2.3.4 Drug evaluation types

Drug evaluation type of drug registration was based on the classification of drug registration: New Drug, New Generic Drug, Generic Drug and Biological Product. However, Thai FDA also provides two options processes to use as the following:

1. **Full option:** The full dossier option was used for New Drug and new Biological Product that the documents have full of three parts of document: quality part, manufacturing part and non-clinical & clinical part.
2. **Waive non-clinical & clinical part:** This option was for the Generic Drug and New Generic Drug that the non-clinical & clinical part is not required for drug registration

Timeline of the process (exclusive screening process):

1. New Drug and Biological Product: 280 working days
2. Generic Drug: 210 working days
3. New generic drug 155 working days

General requirements: In accordance to ASEAN ACTD/ ACTR

2.3.5 Drug registration number system (or Product License No.)

Drug registration number, issued by Thai FDA, has three parts that consists of number and letter. The registration number starts with first part of two digits such as 1C. It follows by second part which has seven digits such as and 45/2556 and it ends with the third part which present the letter in the parenthesis "( )"

First part of a drug registration number (two digits) consists of number and letter/phablet. The first position has to be either number "1" or "2". Then, it follows by the one letter: A or B or C for the human medicine as a second position. The meaning

of the number and the letter in the first part of drug registration number are defined as follows:

Number:

"1": Single active pharmaceutical ingredient.

"2": Combination of active pharmaceutical ingredient.

Letter:

"A": Represent of drug that is produced domestically or manufacturing products, in Thailand.

"B": Represent of drug that is repacked domestically from the manufacturer in Thailand

"C": Represent of drug that is imported from the foreign country

Second part of a drug registration number (seven digits) consists of two groups of numbers. The first group is the sequent number of drug registration running according to the sequent of drug approval that is approved within the endorsement year. This number is started from 1 and counted until the end of the year. This number is placed after the letter "A"," B" or "C" which is separated type of drug registration. Then it is followed with the slash symbol ("/") and followed with the endorsement year. For an example, 1C 45/2556 (NC), 45 is the sequent number of drug registration at 45 of 1C and 2556 is the endorsement year of drug registration in Buddhist Era (B.E.) as a Thai year.

Third part of drug registration number consists of: one or two or three alphabets in the parenthesis at the end of a drug registration number such as: "N", "NC", "NBC", "NG" or "NB". There is no the third part of drug registration number for Generic Drug

"N" is defined as the New Drug without the condition of SMP (Safety Monitoring Program)

"NC" is defined as the New Drug with the condition of SMP (Safety Monitoring Program)

"NB" is defined as the New Biological Product without the condition of SMP (Safety Monitoring Program)

"NBC" is defined as the New Biological Product with the condition of SMP (Safety Monitoring Program)

"NG" is defined as the New Generic Drug

2.3.6 Drug searching

The information of drug registration was searching via the Thai FDA website http://fdaolap.fda.moph.go.th/logistics/drgdrug/Dserch.asp

2.3.7. Maintain of drug registration

The registered drug license or MAA document is provided by Thai FDA as a lifelong commitment. There is no renewal process regulation of drug registration in Thailand. The MA approval will be validated without expiry date. However, if the registered product is found no imported or manufacturing for two consecutive years, MA approval of product will be automatically cancel Thai FDA.

2.3.8 Fee for drug registration

Fee for drug registration was only THB 2,000 for all types of drug registrations. The fee was for MAA paid when the company got the product license. The fee was not for the application submission. If the submission was rejected and product was not approved, the company did not have to pay for this fee. It means that this fee is only one charge throughout the process of drug registration in Thailand.

2.4 History of drugs regulations and drug registration (legislation) process in other countries

To find out an appropriate country to be considered as the first drug registration in the world for being a comparable country to calculate the time lag. A selected comparable

country to calculate the time lag, was often to be either the US or the EU. Therefore, the drug registration (legislation) process and pathway of the US and the EU were necessary to be reviewed. Moreover, this study was aim to compare antineoplastic drugs among selected ASEAN countries; thus, Singapore and Malaysia were selected to be reviewed for the case of comparable country in ASEAN.

2.4.1 The United States

2.4.1.1. History of drug registration

The United States Food and Drug Administration (USFDA) was considered as the most stringent for drug registration in the world, at this moment. USFDA was, also, considered by many countries to be as a reference agency for drug registration of the world. Thai FDA also accepts USFDA to be as the agency reference model for New Drug, New Biological Product registration, including Generic Drug Registration. Therefore, in this study, drugs approved in The United States (US) expected to be considered for our reference as the first products approved in the world.

The USFDA was very respectable for a drug registration system. The pathway of drug registration was developed since 1820; when the U.S. Pharmacopeia was set up as the first standard for drug and the Federal Food, Drug and Cosmetic (FDC). FDC Act of 1938 was implemented in the US as the new system for drug registration that required the approval on the elementary of the safety. However, after the Thalidomide crisis, the US Congress had passed the Kefauver-Harris Drug Amendments to require the mandatory of drug makers to verify their product before the Marketing authorization is granted for sale in 1962. This law helped the system of drug registration in the US became stronger in the safety of product. In the years 1962 – 1984, USFDA had lunched many acts and regulations in order to help the effectiveness marketed product such as

- “Fair Packaging and Labeling Act” in 1966
- “The Drug Efficacy Study Implementation (DESI)” in 1968
- “Comprehensive Drug Abuse Prevention and Control Act” in 1970
- “Controlled Substances Act (CSA)” in 1970
- “The First Patient Package Insert” in 1970

- "Over-the-Counter Drug Review" in 1972

In 1984, in order to help US patients had access to medicine at economic price; Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) was issued by the US congress. The generic brand of new original medicine product could be approved by USFDA after a patent expired. This Act allowed brand-name companies had their patents protection extend up to 5 years from the normal time; when the Investigational New Drug (IND) application was counted as to start a patent protection year. The patent term of protection was opened to be seen by the public. This allowed generic companies to prepare their generic products to apply when the patent was expired.

In order to control prescription drug distributions in the US; the government at that time had implemented the Prescription Drug Marketing Act (PDMA) of 1987 as a legal safeguard to guarantee the safety and effectiveness of pharmaceuticals distribution. This law intended to prevent the selling of counterfeit products, misbranded products, sub-potency medicine, and expired prescription drugs. The important US laws were summarized in the below (US-FDA, 2009).

1. Federal Food, Drug, and Cosmetic Act (abbreviated as FFDCA, FDCA, or FD&C), 1938.
2. Comprehensive Drug Abuse Prevention and Control Act of 1970.
3. Controlled Substances Act (CSA), 1970.
4. Drug Price Competition and Patent Term Restoration Act (Public Law 98-417), informally known as the Hatch-Waxman Act, is a 1984 (Danzis, 2003).
5. Prescription Drug Marketing Act (PDMA) of 1987 (US-FDA, 2013).

2.4.1.2 Drug classification in the US (Forensic or legal classification)

In the US, the Center for Drug Evaluation and Research (CDER) is, now, a center to review and evaluate new drug applications in the US. The aim of this center is to guarantee safety and efficacy and to ensure that consumers can access the product, as quickly as possible, in order to reach for new treatments. Medicinal products approved for registration in US are based on the risk profile and their condition of treatment.

These medicines are regulated and classified under two legal classes by CDER as in the following:

- **Prescription Drug:** is defined as any drug product that requires a doctor agreement to use for the treatment.
- **Over-the-Counter Drug (OTC):** is defined as a drug product which can be used by the consumers without a doctor prescription

However, the application of drug registration was separated; due to the category of drug which was classified in three types of drug registration: New Drug Application (NDA), Abbreviated New Drug Application (ANDA) and Biologic License Application (BLA).

New Drug Application: The regulation to control new drugs in the United States is based on the New Drug Application (NDA). Since 1938, every new drug had to apply for new drug application (NDA). Furthermore, when marketing authorization (MA) was approved, it can be sold in US market.

The data resulted from the non-clinical studies and clinical study during the Investigational New Drug (IND) process has to be parts of the new drug application. The documentation required by NDA is supposed to inform about what the ingredients of the drug are, how the drug behaves in the body, and how it is manufactured, processed and packaged.

Abbreviated New Drug Application: In the US, the application of generic drug is called “Abbreviated New Drug Application (ANDA)”. A generic drug, defined by USFDA, is a drug which is the same as a brand name drug. In order to guarantee that a generic drug can be replaced its brand name drug; "therapeutic equivalence” is needed to declare to USFDA. The application of generic drug needs a scientific demonstration of bioequivalent data to prove that its product performs in the same characteristic as the innovative product. Even this generic drug may differ in characteristics such as shape, release mechanism, excipients (including colors, flavors, and preservatives), by the US law, a generic drug must have identical amounts base on three criteria:

- same active ingredient(s)

- same dosage form and route of administration
- identical in strength or concentration

The preclinical study (in animal) and clinical study (in human) data, which is done to establish safety and effectiveness, can be waived when submission. Generic product can be manufactured and marketed only when approval by the authority.

Biologic License Application (BLA): Biological products (biologics) can be medical products. They, normally, come from a variety of natural sources such as human, animal or microorganism. Similar to drug products, biological products are used for treatment of some diseases, or to relieve medical conditions, or to prevent disease. They are known as vaccines, some cancer drugs, gene therapies, tissue transplant products, etc.

In US, under the provision of the Public Health Service (PHS) Act, a firm, who manufactures biological product for sale, must apply for the product license. After the marketing authorization is approved by USFDA; this biological product can be, then, sole in US market. Due to the requirement of USFDA, the specific information such as the manufacturing processes, quality control methods, pharmacology, clinical pharmacology and the medical effects of the biologic product are needed to applying for Biologic License Application (BLA). After evaluation, if it meets the USFDA requirements, the application will be approved and a marketing authorization approval (MAA) is granted.

Over-the-counter (nonprescription) drug (OTC-drug)

Over-the-counter (nonprescription) drug (OTC drug) is defined as a drug that is harmless and effective to be used by patient or consumer without an opinion of health professional or prescription. OTC drug, now, is an important role for health care system of the country. In the US, there are two processes for OTC drug registration. First process is to be approved under the applications similar to new drug application or prescription drugs. On the other hand, the other process is, legally, marketed without an application or USFDA reviewing and it only require to meet the regulation called an OTC drug monograph (US-FDA, 2016e)**.** Furthermore, new coming products that are met with a final monograph, may be marketed without further USFDA review.

However, if they do not conform, they must be reviewed via the New Drug Application and process. The drugs, which needed an NDA process or a drug which was intended to switch from prescription drug (Rx) status to OTC product, have to provide the contents and format of application similar to the requirements for prescription drug.

2.4.1.3 Drug registration number (or FDA application number)

A drug application number is, actually, a “drug registration number”. Its number can be classified by the category of drugs such as NDA or ANDA or BLA. It is the key for finding information of a drug product. The USFDA Application No. is shown as below examples:

- (ANDA) 078729
- (NDA) 201292
- (BLA) 103792

The format of Drug Registration Number or USFDA Application Number, is started with groups of alphabet, ANDA, NDA, BLA for each type of product. Then, they are followed by ‘six digits’ number, which is assigned by USFDA to each application for using until the marketing authorization approval is granted in the United States. In case of the drug has different dosage forms or routes of administration, the application number will be more than one number. This number will be used for finding the first drug registration in USFDA database and to confirm the patent information if patent is not expired (USFDA, 2012)

2.4.1.4 Drug searching in USFDA

There are two main channels of searching for drug approval in US (US-FDA, 2016d) :

1. By Drug@FDA via website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
2. By Electronic Orange Book (EOB) via website http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm

Searching by Drug@FDA

The drugs approved by USFDA, such as brand name and generic prescription including over-the-counter human drugs and Therapeutic Biological products (BLAs) approved by CDER are, all, in the USFDA database. This database can be searched via http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm for searching Drug@FDA. Drug approved information, that were stored in the database, have already been started since 1939. However, the information, labels, approval letters, reviews, and other information have been included in database, later, since 1998. Furthermore, some information inside database of Drugs@FDA overlaps with the Orange Book, but it is not intended to replace each other. In fact, it also contains some information of:

- Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)
- Center-wide Oracle-based Management Information System (COMIS).

The information of COMIS that can be searched by "Drug@FDA" are: the acceptance and evaluation status of investigational new drug applications (INDs), new drug applications (NDAs), and abbreviated new drug applications (ANDAs)

Updated Database: The database has provided the information of Drug approved information since 1939. It is, usually, updated every day.

Searching by Electronic Orange Book (US-FDA, 2016a)

Approved drug products with Therapeutic Equivalence Evaluations was, first, recorded as a print book called "The Orange Book" in October 1980. The information inside this Orange Book can be searched via the USFDA website as the Electronic Orange Book (EOB). It provides the information starting on October 31, 1997 onward. Then, in February 2005, Electronic Orange Book (EOB) started to include a daily update of new generic drug approvals.

Updated Database: The content of Electronic Orange Book (EOB) includes the information of New Drug Application (NDA) which is monthly update and the information of Abbreviated New Drug Application approvals (ANDA or Generic drug)

which is a daily update. The EOB also includes the information of all product changes received and processed; which have, monthly, update and the information of discontinued products which are updated according to the date of publication. Moreover, the patents information is also included in the EOB and is updated daily and monthly; and Data exclusivity also is included in this EOB and has monthly update. The comparison of content from Drugs@FDA and the Electronic Orange Book (EOB) was in table 9

Table 9: The comparison of content from Drugs@FDA and the Electronic Orange Book (EOB)(US-FDA, 2015a)

Items	Information	Drugs@FDA.	Electronic Orange Book (EOB)
	Content		
1	All drug item listed	yes	yes
2	Tentative Approvals and "Chemical Type 6" approvals.	yes	no
3	Links to documents and web pages related to the approval history, drug safety, and patient information	yes	no
4	Therapeutic biological products (BLAs) approved by CDER	yes	no
5	Patent and exclusivity information	no	yes
6	Updated daily for new generic drug approvals and patent. Updated monthly for other information.	no	yes
	Features		
7	Tables of therapeutic equivalents grouped by product.	yes	no
8	Tables, grouped by product, showing over-the-counter drugs containing the same active ingredient	yes	no
9	Drug approval histories	yes	no
10	Links to documents and web pages related to the approval history, drug safety, and patient information	yes	no
11	Date-range searches	yes	no
12	Drug approval reports by month	yes	no
13	Search by applicant	no	yes
14	Search by patent	no	yes
15	Search by type: prescription (Rx), over-the-counter (OTC), and discontinued	no	yes

Source from : 1. Drug@FDA via website http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
2. Electronic Orange Book (EOB) via website http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm

2.4.1.5 Drug approval process:

The USFDA has one standard review program and five expedited programs for drug approval as in the table 10.

Table 10: The review program of standard review (S) and five expedited programs of drug approval in US (US-FDA, 2015b)

Program name	Year instituted	Characteristics of qualifying products	Does it formally change evidentiary standard ?	Phase during which it exerts most direct effect
Orphan drug	1983	Treats disease occurring in <200,000 people per year in US	No	Drug development
Fast track	1988, 2007	Treats life threatening or severely debilitating diseases	Yes; can approve after single phase 2 of study	Drug development and FDA review
Standard review drug (*)	1992	A drug that appears to have therapeutic qualities similar to those of an already marketed drug	-	-
Priority review	1992	Seems to offer therapeutic advance over available therapy	No	FDA review
Accelerated approval	1992	Treats seriu or life threatening illnesses	Yes; can approve on basis of surrogate endpoint reasonably likely to predict patient benefit	Drug development and FDA review
Breakthrough therapy	2012	Treats serious disease for which preliminary clinical evidence suggests substantial improvement over existing therapies on one or more clinically important endpoints	No	Drug development and FDA review

(*) : Apply from Standard Review Definition of USFDA

Source by : US-FDA,2016d, 14/09/2015. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. Retrieved from

The Drug approval process is an important factor that impacts directly to the product approval for launching in the US market. If it takes a long time; patients will, also, have to access the medicine late. The benefit for treatment of patients to reach new technology is, also, lost due to the time spending during the process of registration. Normally, the average time to review for a product registration by authority agency is difference due to the drug product characteristic, chemical types and review classification. In 1992, to improve drug review times, a two-tiered system of the drug approval process was implemented in USA under the Prescription Drug User Fee Act (PDUFA) as the following:

Standard Review: A Standard Review is applied for drugs which are similar to those drugs that are existed marketed. In 2002, after the amendments of PDUFA, the goal for a Standard Review period was expected to be within 10 months.
Timeline: 10 months

Priority Review: A Priority Review is designed to use with drugs that offer a new treatment that no suitable therapy existed before or offer a major advance in treatment. The goal for a Priority Review period is within 6 months.
Timeline: 6 months
The speeds for the availability of drugs, that can provide the treatment of serious diseases, are in everyone interest; especially when there is the first available treatment, or if the new drug has advantages over existing treatments (Kesselheim, Wang, Franklin, & Darrow, 2015).

Orphan Drug Program: An Orphan drug is defined as a pharmaceutical product that has a mechanism for treatment of disease or medical condition, which is rare to therapy. To develop the orphaned drug takes time and need to have a lot investment. In 1983, Orphan Drug Act was implemented in order to motivate the development of orphan drugs for rare disease areas. A rare disease is defined as a disease that affects people not more than 200,000 at that time. The law offers 7-years data exclusivity to sponsors of approved orphan products. Moreover, a sponsor can get the opportunity to waive a tax credit of 50 percent of the cost of conducting orphan drug, and research grants for clinical testing of new therapies to treat orphan diseases (US-FDA, 2016b)

Beneath the USFDA, Office of Orphan Products Development (OOPD), products such as drugs, biologics which have potential to treatment of rare diseases/medical condition, have motivation evaluation in drug registration. It looks like incentives programs of OOPD for sponsors to develop products for rare diseases.

Timeline: The average time for the OOPD to approve a product decreased to 160 days in 2000, from a high of 267 days in 1996 (US-FDA, 2001)

Fast Track Program: A Fast track program is the process for drugs that are intended to treat Life-Threatening and Severely Debilitating Illnesses. USFDA issued the Interim Rule for Investigational New Drug, Antibiotic, and Biological Drug Product as a Regulations "Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses" in 1988 (53 FR 41516, October 21, 1988) and it was organized into law in 2007 (US-FDA, 2012, 2014).

Furthermore, by USFDA, a Fast Track program is defined as a process intended to simplify the development, and to accelerate the review of drugs for treatment of serious conditions. A Fast track program is set up in order to fulfill an unmet medical need. The rate of communication assures that questions and issues are resolved quickly. It, often, leads to earlier drug approval and access by patients. A Fast Track designation has to be requested and initiated by the drug company at any time during the drug development process. USFDA will review and make a decision of the request within 60 days. The decision is based on, whether or not, the drug has fulfilled an unmet medical need in a serious situation. Once a drug receives Fast Track term, a drug company is required to have frequent communication with the USFDA, all the way through the entire drug development and review process.

Timeline: 60 days

Breakthrough Therapy Program:

If a drug is chosen for the treatment of a breakthrough therapy, USFDA will speed up and review of this drug quickly. It will be reviewed within 60 days of receipt, and then USFDA will provide approval or rejection the request (US-FDA, 2014, 2015b)

A new drug can be considered as a breakthrough therapy by USFDA; when it is developed to treat a serious or life-threatening disease or to provide the improvement over existing therapies. In USA, The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed in order to support a drug that considered as breakthrough therapy to be registered faster. The breakthrough therapy designation is designed to convey all of the fast track program features including of intensive involvement from USFDA for an efficient drug development program; an organizational commitment involving senior managers, and eligibility for rolling review and priority review.

Accelerated Approval Program:

The Accelerated Approval process was performed in 1992 and implemented later in law. This process helps to accelerate approval of drug that treats serious or life-threatening diseases. This regulation allows to drugs (for serious conditions that had an unmet medical need) to be approved based on a surrogate endpoint. Furthermore, Accelerated Approval will be given on the condition that sponsors have to conduct post-marketing clinical trials to verify the anticipated clinical benefits. If these trials fail to demonstrate the anticipated benefits, the approval can be cancelled

Timeline: not available

2.4.1.6 Drug registration process

New drug registration (US-FDA, 2016c):

1. **First**, **Investigational New Drug Applications (INDs)**: It is pre-clinical research development, including animal testing approval; which can take from one to three years. After that, once a company submits an investigational for a new drug application with authority; Phase 1 of clinical studies is proceeded to examine the drug's toxicity and pharmacology in 20 to 100 volunteers. This stage requires several months in order to finish. Then, the drug is tested with larger groups of patients; who have the disease that the drug is intended to treat. Phase 2 of clinical studies is required to have as many as several hundred patients, which might last

from several months to two years. Phase 3 is to investigate the drug using with several hundred to several thousand patients for one to four years. Then the results of these 3 phases are used to the form a new drug application.

2. **Second**, **New Drug Applications (NDAs**): the new drug application is reviewed by an authority over an average of two years. Advisory committees of scientists, health care professionals, and consumer representatives outside the agency are required to consult on drug reviews. However, the final decision rests with USFDA authority. The MAA will be granted to lunch the product in the market.
3. **Third**, after the agency has approved the drug and MAA has been granted; the post-marketing surveillance will continue after the medicine is on the market, in order to control as the normal risk management process.

Therefore, it will give the lag time to launch the product to the market in US.

Generic drug registration

Generic drugs are approved by using an Abbreviated New Drug Application (ANDA). This ANDA does not require all of the clinical trials; normally as required for a new drug in an NDA. Only Bioequivalent are needed to be in the reference listed drug (RLD). However, a New Drug Application (NDA) must be, previously, approved and listed as the reference listed drug (RLD). RLD is, generally, the innovator brand and defined as the listed drug identified by USFDA after a previously approved NDA.

Generic drug approval process in the US by Hatch-Waxman Act of 1984 (Danzis, 2003)

However, an approval ANDA is related to the Hatch-Waxman Act which was implemented in 1984. Hatch-Waxman Act is issued to provide the balance of consumers benefits, the innovative brand name pharmaceutical industry and the generic drug industry; in order to make economic cost generic drugs to be more available, and to create a new motivation for increasing R&D expenditures of certain products that are subject to require for pre-market approval. It is separated into 2 titles.

Title I of Hatch-Waxman Act: For this section of Hatch-Waxman Act, approved marketing of generic drugs is allowed after the authorization of Abbreviated New Drug

Application (ANDA). Furthermore, after submission of a full NDA; the application under ANDA can be approved after the submission of evidence that have the active ingredient of the generic drug is the “bioequivalent” with innovative drug previously approved by USFDA. This can be done without having to submit studies establishing the safety and efficacy of drug.

Title II of Hatch-Waxman Act: This section is to provide the specific extensions of patents to cover the drugs and other products that are subject to “regulatory review” by the USFDA and government agencies. It was intended to balance the benefits of ANDA practice by providing brand name drug companies with the portions of the restoration terms of their drug patents that were lost during the testing period, which are required for approval of the drugs. However, these patent term adjustments and patent extensions are implemented within 10 years after the announcement of Hatch-Waxman Act.

Types of Certifications: The pathway for approval of generic drugs by the Hatch-Waxman Act, begins with the certification procedures. There are four options for application to apply for generic approval. The first three options are to avoid litigation or legal action. Option1 stated that the patent information which is related to innovator patent has not been filed. Option II stated that the related patent has already expired. Option III stated that the generic drug cannot be marketed until after the patent expires. Option IV, the generic drug manufacturer should certify that an applicable patent is invalid or will not be infringed with the generic product that is applied for the approval.

ANDA approval process

Initially, as a standard review and inspection, product company must show that the conditions which use to identify within its proposed labeling have been previously approved in the listed drug that the ANDA is based. According to this act, ANDA has to incorporate the same labeling set with the previously approved for the listed drug; which can be excepted for any changes required because of the differences are approved on the basis of a suitability petition. If the effective patent and data exclusivity of RLD is expired and there are no any legal issues related; the complete approval will be

granted. A tentative approval will be provided; if USFDA found the unexpired patent and data exclusivity of innovative brand product or RLD

Timeline: 2-3 years

2.4.1.7 Maintain the marketing authorization approval (MAA)

There is no renewal process; MAA must be maintained by submitted the safety report to USFDA including annual report. Without the annual report, the notification will be reported not to continue.

2.4.1.8 Fee of drug registration

Table 11: The US drug registration user fee year 2014 – 2016 (Mezher, 2015)

Activity	Registration Fee		
Prescription Drug User Fee Act (PDUFA)	**2014 (US $)**	**2015 (US $)**	**2016 (US $)**
New Drug Application (With Clinical Data)	2,169,100	2,335,200	2,374,200
New Drug Application (Without Clinical Data)	1,084,550	1,167,600	1,187,100
New Drug Application Supplement With Clinical Data	1,084,550	1,167,600	1,187,100
NDA Establishment	554,600	569,200	585,200
Annual Product Registration	104,060	110,370	114,450
Generic Drug User Fee Act (GDUFA)	**2014 (US $)**	**2015 (US $)**	**2016 (US $)**
Abbreviated New Drug Application	63,860	58,730	76,030
Prior Approval Supplement	31,930	29,370	38,020
Drug Master File	31,460	26,720	42,170
Finished Dosage Form Facility (Domestic)	220,152	247,717	243,905
Finished Dosage Form Facility (Foreign)	235,152	262,717	258,905
Active Pharmaceutical Ingredient Facility (Domestic)	34,515	41,926	40,867
Active Pharmaceutical Ingredient Facility (Foreign)	49,515	56,926	55,867
Biosimilar User Fee Act (BsUFA)	**2014 (US $)**	**2015 (US $)**	**2016 (US $)**
Biosimilar Application (Requiring Clinical Data)	2,169,100	2,335,200	2,374,200
Biosimilar Application (Not Requiring Clinical Data)	1,084,550	1,167,600	1,187,100
Biosimilar Supplement (Requiring Clinical Data)	1,084,550	1,167,600	1,187,100
Biological Product Development (Initial)	216,910	233,520	237,420
Biological Product Development (Annual)	216,910	233,520	237,420
Biological Product Development (Reactivation)	433,820	467,040	474,840
Establishment Fee	554,600	569,200	585,200
Product Fee	104,060	110,370	114,450
Each year, FDA adjusts the rates of these fees to keep up with inflation and the agency's workload. The table above shows the rates to be charged for FY2016, which take effect on 1 October 2015.			

Source from : FDA Unveils User Fee Rates for FY2016
http://www.raps.org/Regulatory-Focus/News/2015/08/04/22960/FDA-Unveils-User-Fee-Rates-for-FY2016/

These registration fees and related fees were adjusted based on their workload and a sustained increase in the general level of prices for services in each year.

2.4.2 The European Union

The European Economic Area (EEA) consists of 28 the European Union (EU) member countries plus Iceland, Liechtenstein and Norway. The medicine regulation system has been harmonized and implemented in the EEA. This system has set the unique regulation system for the EU community including the UK (EMA, 2013; Kohler, 2011)

2.4.2.1 History of drug registration in the EU

The first Pharmacopeia in the EU was the pharmacopeia from Spain, called "Pharmacopoeias". It was published in 1581; and is still acknowledged until now. Then, London Pharmacopoeia was followed only in 1618.

The research and development of modern drugs were established in the 19th century to support the Second World War. However, the modern medicines regulation was not started, precisely, at that time. The tragedy of the using thalidomide (in 1962) had triggered each EU countries to start thinking for the development of modern medicines regulation.

The Council Directive 65/65/EEC (26 January 1965) was the first European pharmaceutical directive that was developed by the triggered of thalidomide tragedy. It was developed with the aim to harmonize the directions & frameworks for approving processes of drug registration within EU. However, the drug registration, still, had to be with each national government. After 1975, there were adoptive the harmonization of national regulatory manners and started to introduce the multistate procedures which had become as the mutual recognition procedures in EU such as:

- **Detective 83/570/EWG of 1983**: the community procedure of drug registration was modification to be the procedure of multistate
- **Detective 87/22/EWG of 1987**: Granting the nation marketing authorization of innovative drug through the Concentration Procedure, it was amendatory to get the opinion of Committee for Proprietary Medicinal Products (CPMP).

- **Detective 2309/93/EEC of 1993 and Detective 93/39/ECC of 1995 (in force)**: The Centralized Procedure (CP) and Decentralized and Mutual Recognition Procedure (DP/MRP) were implemented to use among the EU members. Furthermore, the European Medicines Evaluation Agency (EMEA) was established to manage the evaluation of drug application, including performed CPMP back again to provide the advice and conclusion about the scientific assessment then provide the opinion of the agency for the centralized procedure.
- **1998:** Replacement of Decentralized Procedure and Mutual Recognition Procedure to National Application was completed for EU community.
- **Detective 2001/27/EC of 2001:** The clinical test requirement was standardized for EU community. Requirements for the conduct of clinical research in the EU were also provided in this Detective.

2.4.2.2. Drug registration process

The European Medicines Evaluation Agency (EMEA) started to operate in 1995. It was set up as a part of the reformation of the regulatory procedures for the marketing of pharmaceuticals in the EU. Until 2004, the EMEA was reorganized and the abbreviation of name was changed to be the European Medicines Agency (EMA). It is now act as a European Union agency for the evaluation of medicinal products.

Objectives of EMA is not only to reduce the €350 million annual cost drug companies incurred by having to win separate approvals from each member state; but also is to eliminate the protectionist tendencies of states unwilling to approve new drugs that might compete with those already produced by domestic drug companies of their countries.

Before launching each medicine in EU market, it must be authorized by the agency in the EU. According to European legislation, there are two procedures for specific product types to choose: Centralized Authorization Procedure (CP) and National Authorization Procedure (NP)

Centralized Authorization Procedure

Within the centralized authorization procedure, a pharmaceutical company can submit a single marketing-authorization application to European Medicines Agency (EMA). Once, Marketing Authorization Approval (MAA) is granted, pharmaceutical product can sell in all of the EU Member States plus Iceland, Liechtenstein and Norway.

Scope of Centralized Authorization Procedure

According to the centralized authorization procedure, the following medicines are required to apply for drug registration:

- New chemical entity medicines for treatment such as HIV, AIDs, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, viral diseases
- Medicines derived from processes of biotechnology, such as genetic engineering
- Advanced-therapy medicines, such as somatic cell-therapy, gene-therapy, tissue-engineered medicines
- Orphan Medicines for rare diseases
- Veterinary medicines that are used as growth or yield enhancers.
- Other medicines which are not specified above and are interested by public at the EU level.

Today, there are a great number of new and innovative medicines have passed the centralized authorization procedure in order to be marketed in the EU.

Process of Centralized Authorization Procedure

In order to obtain a Marketing Authorization for all 31 countries, a drug registration application must be applying to the European Medicines Agency (EMA). An evaluation result will be provided by the Committee for Medicinal Products for Human Use (CHMP). The European Commission will receive opinions within 210 days and drafts a decision on a Community marketing authorization (MA). Then, the MA is granted under the centralized authorization procedure (CP, which is valid for the entire EU

market. The MA will have 5-year validity, which is counted from the date of notification of the Commission Decision to the marketing authorization holder (MAH).

National authorization procedure

Medicines existing in the EU are, normally, approved by national procedures of each country in EU. Each country has its own national authorization procedures. The information of these national procedures is available on the websites of each national competent authority. If the companies prefer to get the marketing authorization in several EU Member States for their medicines which are out of the criteria of the centralized procedure; the medicines can, then, be applied in one of the following procedures:

- The Mutual Recognition Procedure (MRP)
- The Decentralized Procedure (DC), whereby a medicine that has not yet been authorized in the EU, can be simultaneously applied and authorized for several member states of EU.

Mutual Recognition Procedure

For Mutual Recognition Procedure (MRP), when a marketing authorization (MA) is granted in one-member state of EU; it can, then, be recognized in other EU countries. This means that, a medical product must have a national license in one of EU member countries before submission for a MRP application. However, MRP is compulsory for all medicinal products since Jan 1998. This procedure is, also, introduced in order to help the previous registration products (as a national level) can be certified by other member's state (MS) when renew the registration (due to the compulsory in 1998). Furthermore, an application for mutual recognition procedure can be submitted to one or more member countries of the EU. (EMA, 2015; SUKL, n.d.):

The country of the first authorization for "national marketing authorization" will become the Reference Member State (RMS). On the other hand, the other countries of EU that are selected by the applicant are considered as the Concerned Member States (CMS). An assessment report has to be prepared by the Reference Member State (RMS). Then, according to MRP, this report must be evaluated by the other states of

CMS within 90 days. A decision for approval or rejection will be made in 90 days. See Figure 4 for the flow chart of MRP. According to the Mutual Recognition Procedure, the following products are within the scope to apply for drug registration (Bianchetto, n.d.) :

- Medicinal products having new active substances, but it is not being under the scope of centralized procedure
- OTC (over-the-counter) products
- Homeopathic medicinal products
- Generic products (also generic versions of products Authorized by the Centralized Procedure before November 2005, with the exception of biotechnology-derived ones)
- Abridged applications, well-established use products, which are the line Extensions of "old Mutual Recognition Procedure" approval such as new indications, new dosage form, new combination etc.

Decentralized Procedure

The Decentralized Procedure (DC) has influenced for drug registration in the EU since 2005. The aim of this procedure is to support the products that are unmet with the criteria of centralized procedures. This procedure helps the products that, also, want to obtain the marketing authorization in several Member States (MSs) of EU. Using this procedure, a company can apply for synchronize authorization in more than one of EU countries; if the product has never been authorized in any the EU country before. The steps of the process to apply for this procedure are as the following:

1. The applicant (company) has to send an application to the competent authorities of each EU member states that the company is expected to launch the product in the markets of these EU countries.
2. The applicant has to choose a country to act as the Reference Member State (RMS) and the Concerned Member States (CMS).
3. The criteria of a company to select a Reference Member State (RMS) depends on many aspects including its workload, its previous experience, interests, and the acceptance of the dossier by the selected RMS.

4. As a state of RMS, it has to review/consider the registration documents and prepare the assessment report to both all CMSs and applicant within 70 days.
5. If all CMSs agree to approve the assessment report; each marketing national authorization will be granted from the RMS and each of CMSs.

See the flow chart of Decentralized Procedure of drug registration as in Figure 5

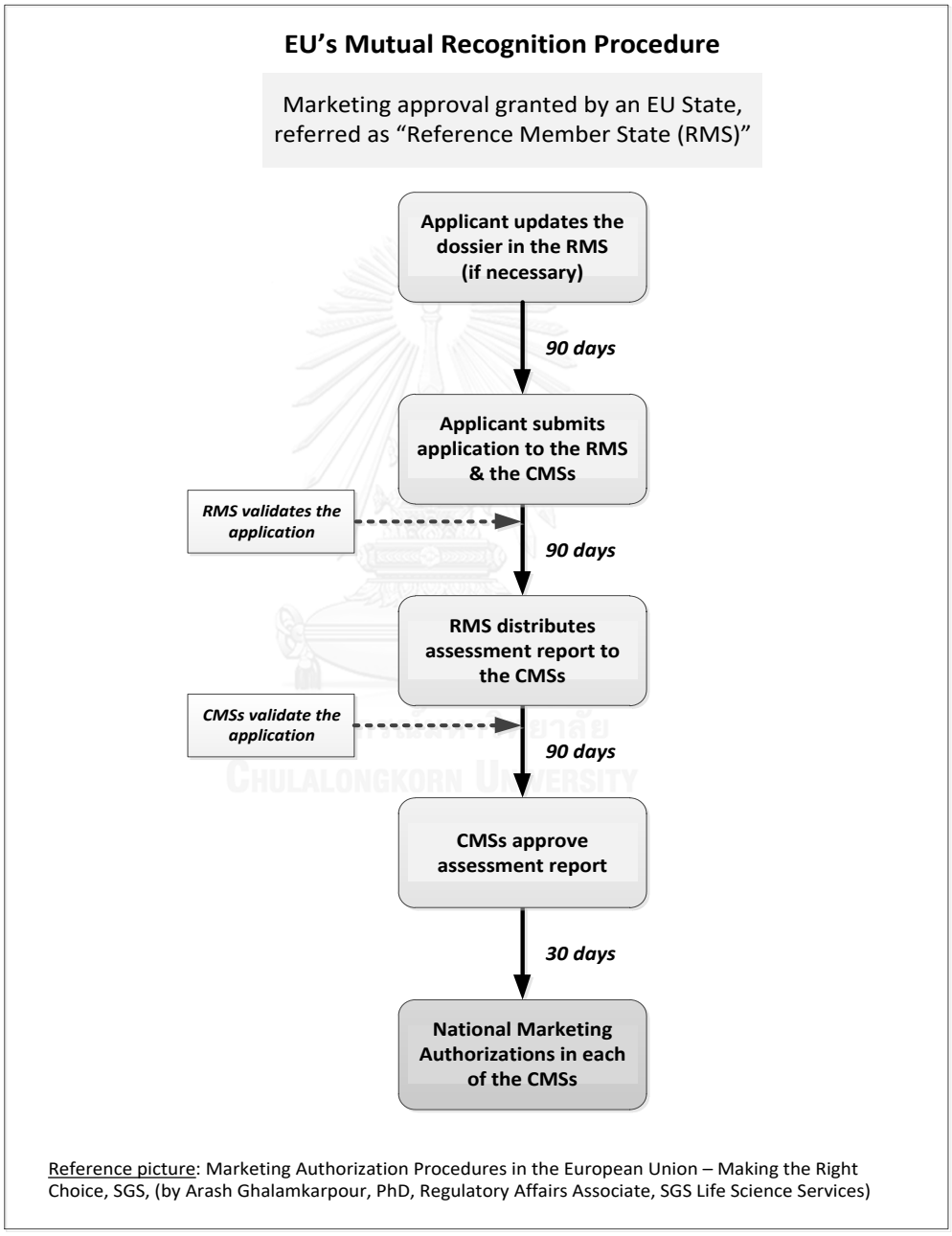


Figure 4: The flow-chart of the Mutual Recognition Procedure (MRP) of drug registration in the EU (Ghalamkarpour, 2009)

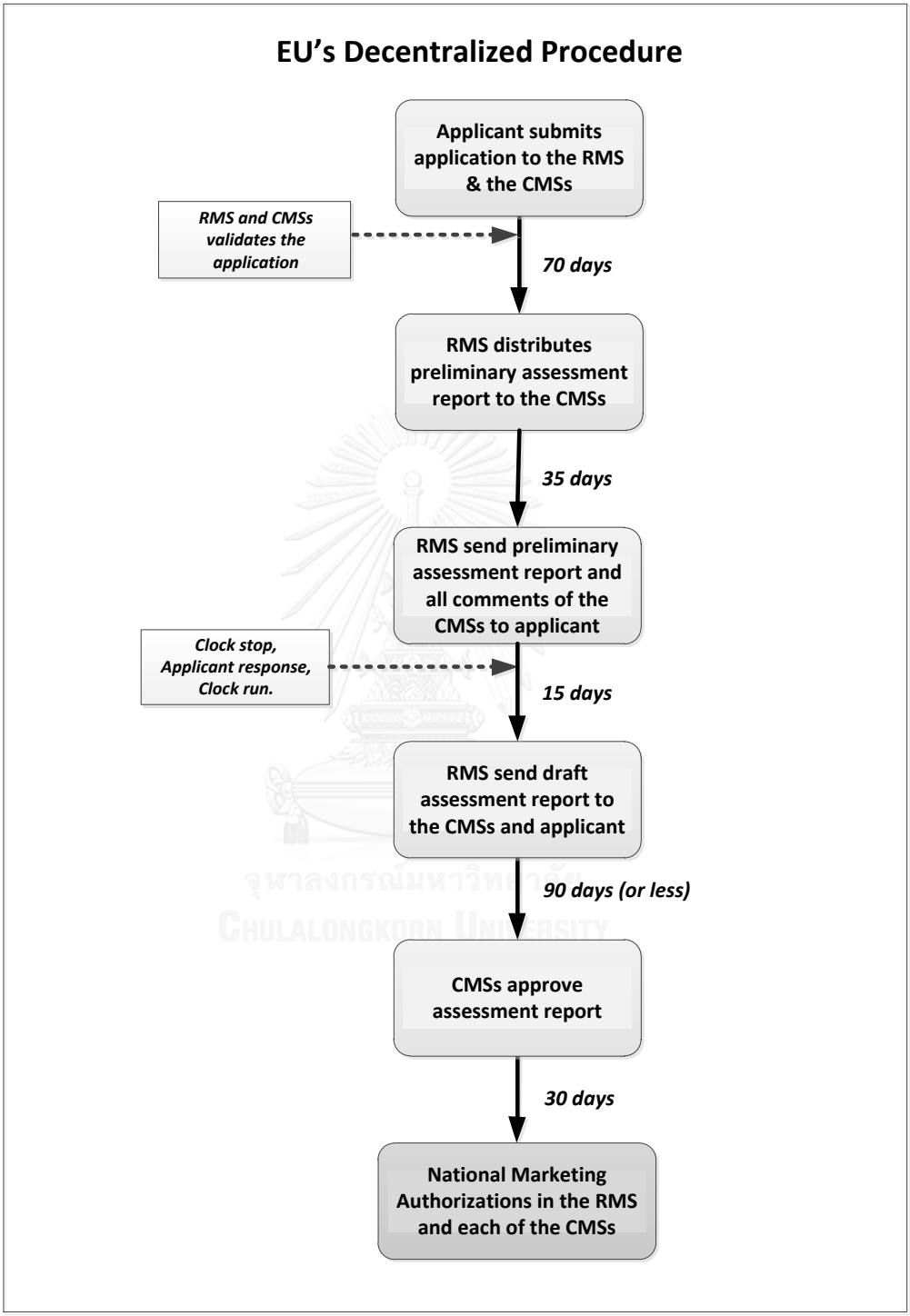


Figure 5: The flow-chart of Decentralized Procedure (CP) of drug registration in EU(Ghalamkarpour, 2009)

2.4.2.3. Maintain drug registration/marketing authorization

Normally, the product license or marketing approval (MA) in EU has 5-year validity. It needs to be renewed only once at five years after the first MA is granted. The MA renewal application must be started at least six months before the expiration date.

2.4.2.4. Drug searching from EU

As the limited information on EMA website, the registration information before 1995 is not available for searching. Only information of every medicine granted for a central marketing authorization (the centralized procedure) by the European Commission at the EU level are available for searching. The information of registration for products via the nation route cannot be searched. For the other products registered via the national route, the searching has to get from the website of the national health authority of each country, where the products are registration (EMA, 2013)

- Drug approval under the centralized authorization procedure can be searched via website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (EMA, n.d.)

- Drug approval under the National authorization procedure such as United Kingdom (UK) can be searched via http://www.mhra.gov.uk/spc-pil/ (MHRA, n.d.)

2.4.2.5 Fee for drug registration

The fees were adjusted based on their workload and a sustained increase in the general level of prices for services as annual fees for authorized medicines. The explanatory note on general fees for all related fees of the European Medicines Agency was presented in the website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp. Some basic fees for the process of drug registration by EMA were listed in the table 12.

Table 12: Basic fee for drug registration fee in EMA (EMA, 2016)

Fee type	Human medicines (€)
Marketing-authorisation application (single strength, one pharmaceutical form, one presentation)	From 278,800 €
Extension of marketing authorization (level I)	83,700
Type-II variation (major variation)	83,700
Scientific advice	From 41,800 to 83,700 €
Annual fee (level I)	100,000
Note : The Agency charges fees for applications for marketing authorization, and for variations and other changes to marketing authorizations, as well as annual fees for authorized medicines	

Source from : European Medicines Agency : Fees payable to the European Medicines Agency, retrieved data : April 2016
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000327.jsp

2.4.3 Singapore

2.4.3.1 History of drug registration and drug regulatory system in Singapore

Drug regulatory system in Singapore

Western Drugs, actually, were imported for sale in Singapore long time ago. However, prior to 1987, the drug registration was not recorded in the recognizable system. During 1987 to 1991, the Drug Regulatory System (DS system or DRS), under the ministry of health (MOH) of Singapore, was started to implement, gradually, step-by-step for four years of hard work. (HSA, 2015a)

After implementation of DRS, during 1991-1997, Drug registration regulation was set up to strengthen drug registration process. The process of drug registration was adjusted to be flexibility, clarity, and forcefulness. Also, some agencies, under the MOH, were developed to support the pharmaceutical products during this period.

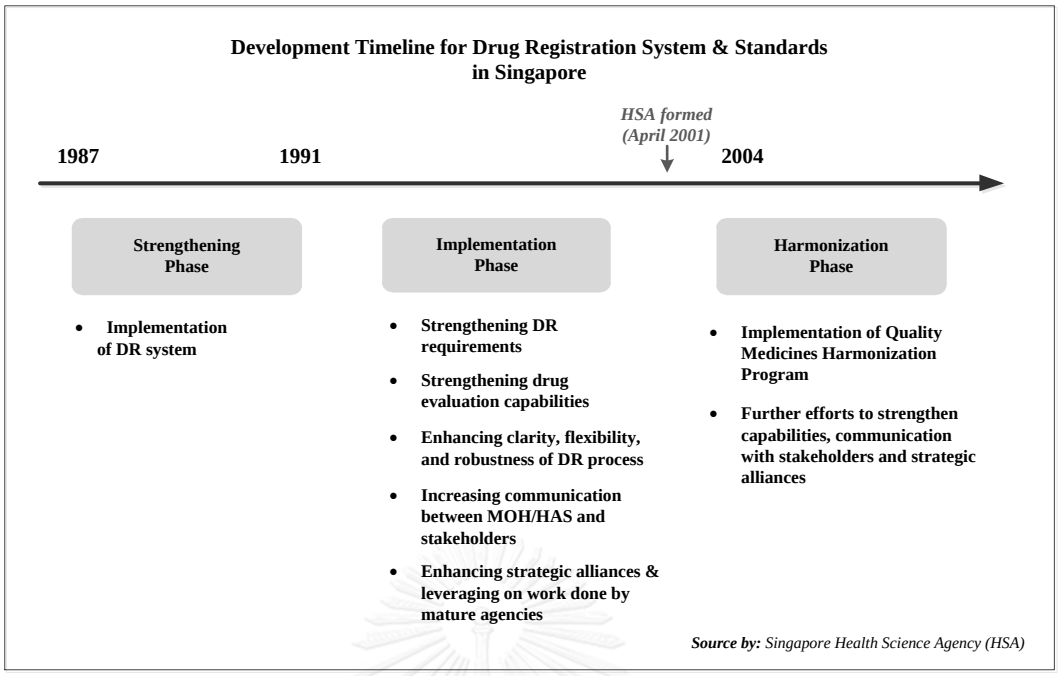


Figure 6: Development timeline for the drug registration system (HSA, 2014a)

In order to support evaluation of the new drug registration, the Centre for Drug Evaluation (CDE), or known as Innovative Therapeutics Group (ITG) at that time, was established under the MOH in 1998. The CDE was set up to facilitate all functions related to drug registration within the same unit. It was set up by combined teamwork of the Ministry of Health (MOH) and the National Science and Technology Board, which is now known as the Agency for Science, Technology and Research.

Phase I:

In order to cover all activity of pharmaceutical products; Health Sciences Authority (HSA) was set up as a legal board of the Singapore Ministry of Health (MOH) in April 2001. The HSA consisted of 5 agencies in Phase-I for development of following:

- Centre for Drug Evaluation
- Institute of Science and Forensic Medicine (Applied Science)
- National Pharmaceutical Administration (Corporate HQ)
- Product Regulation Department (Health Product Regulation)
- Singapore Blood Transfusion Service (Blood Service)

Phase II:

In Phase-II, these 5 agencies, developed in Phase-I, were reorganized into 8 professional centers as the following:

- Centre for Pharmaceutical Administration (CPA)
- Centre for Drug Evaluation (CDE)
- Centre for Radiation Protection (CRP)
- Centre for Medical Device Regulation (CMDR)
- Centre for Transfusion Medicine (CTM)
- Centre for Forensic Medicine (CFM)
- Centre for Forensic Science (CFS)
- Centre for Analytical Science (CAS)

The objective of HAS is to guarantee the quality, safety and efficacy of medicine, medical devices, cosmetics, and other health related products selling in Singapore. In January 2004, the harmonization phase of drug registration system began, Centre for Pharmaceutical Administration (CPA) was merged with Centre for Drug Evaluation (CDE) in order to form the Centre for Drug Administration (CDA). However, at that time, the CDA was positioned under the HAS in order to provide the accountability for the all requirement for new drug registration. It seemed that a new pathway of Western drugs registration was introduced in Singapore at this time. The approval process is obtainable in a shorter time when compare to the previous pathway.

In 2007, in order to facilitate their services, HSA, which was restructured into 8 professional centers previously, was reorganized these professional centers into three main professional groups.(HSA, 2014a, 2015a, 2015b)

The Health Products Regulation Group (HPRG):

Centre for Medical Device Regulation (CMDR), Centre for Radiation Protection (CRP) and Centre for Drug Administration (CDA) were joined together to form the Health Products Regulation Group (HPRG).

The Health Services Group (or the Blood Services Group (BSG) in 2008):

CTM was regrouped under the Health Services Group (HSG). Then, in 2008, the Health Services Group was renamed the Blood Services Group (BSG)

The Applied Sciences Group (ASG):

The Centre for Forensic Medicine (CFM), Centre for Forensic Science (CFS) and Centre for Analytical Science (CAS) were combined to form the Applied Sciences Group (ASG).

Health Products Regulation Group (HPRG) was established in 2007 to ensure that drugs, innovative therapeutics, medical devices and health related products in Singapore are wisely regulated to meet appropriate standards of safety, quality and efficacy. In summary, the laws and regulations which have been implemented for pharmaceutical products in Singapore are:

- The Medicines Act (Chapter 176), enacted in 1987, to ensure that marketed medicinal products in Singapore meet with appropriate standards of safety, efficacy and quality.
- The Poisons Act (Chapter 234). (Original Enactment: Ordinance 39 of 1938). Revision edition of 1999. (30th December 1999).
- The Sale of Drugs Act (Chapter 282) (Original Enactment: Ordinance 15 of 1914), revised version 1985 (30th March 1987).
- The Misuse of Drugs Regulations – subsidiary legislation under the Misuse of Drugs Act (Chapter 185).
- The Medicines (Advertisement and Sale) Act (Chapter 177), (Original Enactment: Act 22 of 2008) and Revised edition 2010 (31st March 2010).
- The Health Products Act, enacted in 2007, to expand regulatory practice to include all health products, such as medical devices, cosmetics, traditional Chinese medicines and supplements used for health purposes. (Singapore-Government, 2001)

Reference agency of Singapore

The Standard Reference Agencies which are accepted by HSA for drug registration consists of five agencies as following:

- Australia Therapeutic Goods Administration (TGA)
- Health Canada (HC)
- US Food and Drug Administration (USFDA)
- European Medicines Agency (EMA) via the Centralized Procedure
- UK Medicines and Healthcare Products Regulatory Agency (UK MHRA)

However, one of the two regulatory authorities must be declared as the primary reference agency for drug registration submission

Good manufacturing practice

Beneath the Medicines Act, the manufacturers for medicinal products and Chinese Proprietary Medicines (CPM) in Singapore have to comply with PIC/S of Good Manufacturing Practice (GMP) standard and they must be licensed with Health Sciences Authority (HSA). Therefore, new oversea western products, which are not found in registration information in Singapore database before 1st April 2004, have to be applied for the GMP assessment by HSA.

2.4.3.2 Drug registration process

Drug Classification (Forensic or legal classification)

Medicinal products are approved for registration, in Singapore, are based on the risk profile and their conditions. These medicines are regulated and classified under three legal classes as the following:

1. Prescription-Only medicines [POM]
2. Pharmacy-Only [P] medicines
3. General Sale List [GSL] medicines

Category or type of drug registration application

There are two categories of drug registration application. The first category is a new drug application (NDA) and the other category is a generic drug application (GDA)

New Drug Application (NDA): There are 3 types of new drug registration in Singapore as following:

- NDA-1: is defined as the application for new chemical or biological entity for the first strength of innovative product.
- NDA-2: is defined as the application for new combination, new dosage form, new routed of administration, new indication & dosage recommendation of registered chemical or biological entities. Moreover, it is a new drug product that does not fall under the requirements for NDA-1, NDA-3 or GDA.
- NDA-3: is defined as new strength(s) of a new drug product that has been registered or has been submitted as an NDA-1 or NDA-2

Generic Drug Application (GDA): The active substance(s) and strength(s) of a generic drug have to be the same as pharmaceutical dosage form as the Singapore reference product. There are two types of generic drug registration in Singapore.

- GDA-1: is defined as the first strength of a generic product.
- GDA-2: is defined as new strength(s) of the generic product that has a previous registration under GDA-1 type. The product name and pharmaceutical dosage form may be the same as that for the GDA-1, except strength of drug product.

Drug registration process and flow chart

Phase-1: The process, of this phase, is started with Pre- submission preparation; and then follows by Application submission and Application screening.

Phase-2: the process, of this phase, is started with Application Evaluation; and then follows by Regulatory Decision. Result of phase-2 will be only acceptance or rejection

Phase 3: This is a phase for Post – Approval changes. The process is for the post marketing and MAA that are needed to be changed

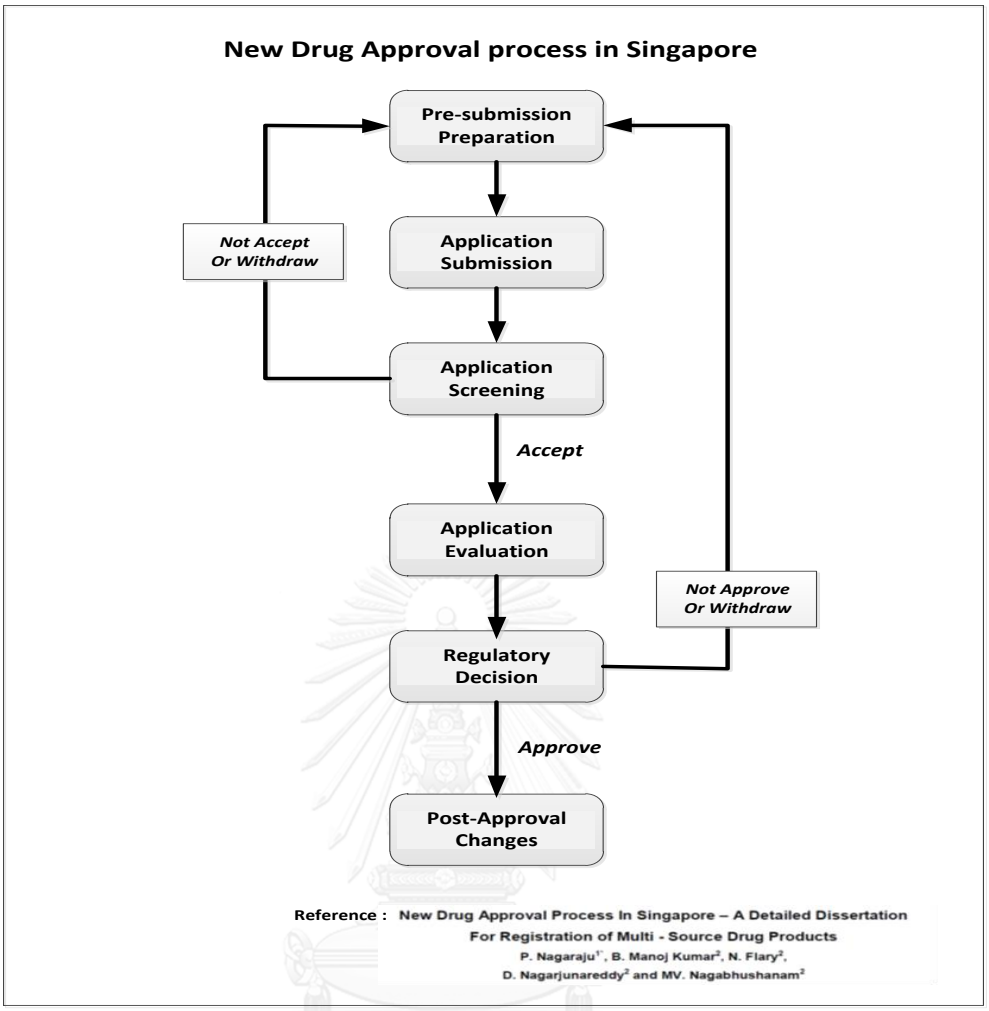


Figure 7: Drug registration process and flow-chart in Singapore (SG) (Nagaraju, Manoj Kumar, Flary, Nagarjunareddy, & Nagabhushanam, 2015)

2.4.3.3 Drug evaluation types and process

There are 3 types of evaluation routes for a drug registration in Singapore: full dossier, abridged dossier and verification dossier.

Full dossier: The full dossier option is for a product that has never been submitted in any country before; and it is the first submission in Singapore as a first country. Therefore, it can be applied to any product that cannot declare the reference country or the approval document from any drug regulatory agency at the time of submission. It is for NDA-1 process of submission.

Type product and timeline: NDA-1 is average timeline 270 working days

Abridged dossier: The abridge dossier option is for a product that had submitted in at least one country in the word and not with HSA reference drug regulatory agencies. Therefore, it can be applied to any product that can declare the reference country or the approval document from any drug regulatory agency at the time of submission in Singapore.

Type product and timeline:

NDA-2, NDA-3: 180 working days for branded patent drug
GDA: 240 working days

Verification dossier: The verification dossier option can be used with any product that has been evaluated and approved by HSA's reference drug regulatory agencies, or HSA's reference drug regulatory agencies from five authority agencies, or EMA (centralization process), or UK MHRA (the national procedure or where MHRA acted as the RMS for the MRP or Decentralized Procedures in Europe), or USFDA, Health Canada and Therapeutic Goods Administration (TGA) of Australia.

Type product and timeline: This will be the fastest; which is around 60 working days for branded patent drugs to get the approval which is based on the reference regulatory agency.

2.4.3.4 Drug registration number (Product License number or License number)

Since the drug registration system was implemented in 1987, the first product license or marketing authorization (MA) was approved on 16 October 1987. The First License No. was "SIN00001P" for Dextromethorphan Linctus 15 mg/5 ml. Since then, the format of the product license number has been the same throughout this study period. The format of registration number and license number are as following:

Product License No. Format: SIN 99999 P (E.g. SIN00001P)

Description:

SIN: Refer to "Singapore"

99999: Refer to a serial number for a product being registered since 1987

P: is unknown, may represent “Product”

2.4.3.5 Drug searching in Singapore

The “Product License Number” or “License Number” of approved products are kept in Health Products Database of HAS by the online Information Search via website: http://eservice.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load. The information of license number, Product name, the License holder, Approval date, Forensic classification, ATC Code, Dosage form, Route of Administration, Manufacturer, Country of manufacturer, Active ingredients and Strength can be provided specific to your search request. A complete listing of the database, which is extracted biannually (in January and July) into Excel files, can also be downloaded for this website.

2.4.3.6 Maintenance the registration

All medicinal products imported and sold in Singapore are required to be licensed by the Health Products Regulation Group (HPRG), Health Sciences Authority (HSA).

The regulation requires the company to be registered, locally, in Singapore; and it has responsibility to apply, maintain and update information of its medicinal product, in order to secure a product license. In other words, it has to provide the safety, quality and efficacy of the product based on the requirement of the regulation, regularly.

Product license must be renewed every year. By a system-generated, the renewal notice will send to the license holder at 2 months before the expiry date. A one-year validity period will be granted at each renewal. Each renewal of product license has one - year credibility period.

2.4.3.7 Fee of a drug registration

The fees charged for licenses and certificates of western medicines in Singapore, effective by 1 January 2010, are separated based on the drug registration process of

New Drug Application (NDA) and Generic Drug Application (GDA) in Singapore dollar in two process. The detail is in the Table 13.

Table 13: Drug Registration Fee in Singapore (SG) (HSA, n.d.)

Fee type	Cost (SGD)
Process 1: Screening (Payable upon submission)	
(i) Abridged/Verification Dossier (NDA & GDA)	550
(ii) Full Dossier (NDA)*	2,750
Process 2: Evaluation (Payable upon acceptance)	
New Drug	
(i) NDA Abridge Dossier (Chemical Drugs & Biologics)	
- NDA-1 & NDA-2	11,000
- NDA-3	5,500
(ii) NDA Verification Dossier (Chemical Drugs & Biologics)	
- NDA-1 & NDA-2	16,500
- NDA-3	5,500
(iii) NDA Full Dossier*	82,500
Generic Drug	
(iv) GDA Abridged Dossier	
- GDA-1	3,850
- GDA-2	2,200
(v) GDA Verification Dossier	
- GDA-1	10,000
- GDA-2	5,000
(vi) GDA Verification Dossier (CECA Scheme)	
- GDA-1	10,000
- GDA-2	5,000
Annual retention fee	300

Note : The fees charged for licenses and certificates of western medicines in Singapore, effective by 1 January 2010, are separated based on the drug registration process of New Drug Application (NDA) and Generic Drug Application (GDA) in Singapore dollar.
* Fees will be charged based on per submission (regardless of the number of strengths and/or dosage forms).

2.4.3.8 Special issue (patent, data protection, data exclusive)

Data protection: is indicated under the Medicines Act in 1998 which enable Singapore to comply with its obligations under Article 39 of the WTO TRIPS Agreement. It requires Singapore to protect the data of pharmaceutical product in contradiction of

leakage to the public and prejudiced profitable use. The period of protection is 5 years; starting from the date of approval.

Patent: Patent declaration is required for a new product registration or a new innovative drug in Singapore; according the Section 12A of the Medicines Act which was updated in 2004. In general, a confirmatory declaration is requested by HAS, when an approvable regulatory decision has to issue within the time frame.

2.4.4 Malaysia

2.4.4.1 History of a drug registration

The Law and Regulation of Drug, in Malaysia (MAL), has been developed and implemented by Ministry of Health of Malaysia (NPRA, 2015), as the following

1. Registration of Pharmacists Act 1951 (Act 371) & regulations
2. Dangerous Drug Act 1952 (revised 1980)
3. Poisons Act 1952 (Act 366) & regulations
4. Sale of Drugs Act 1952 (Act 368)
5. Control of Drugs and Cosmetics Regulations 1984
6. Medicines (Advertisement and Sale) Act 1956 (Act 290) & regulations
7. Patent Act 1983
8. Wildlife Conservation Act 2010 (Laws of Malaysia Act (716)
9. International Trade in Endangered Species Act 2008 (Act 686)

Pharmaceutical Service Division (PSD)

There are four dominate units, under the Pharmaceutical Service Division (PSD), Ministry of Health, which manage the pharmaceutical functions in Malaysia. They are:

- Pharmaceutical Practice and development unit
- Pharmacy enforcement unit
- Pharmacy regulatory unit (The National Pharmaceutical Control Bureau (NPCB)),
- Pharmacy management unit

The first acknowledge of pharmacy service was found in the country since 1951, under the enforcement of the Registration of Pharmacist Act 1951, Poisons Act 1952 and Dangerous Drugs Act 1952. The earlier service was to the procurement, storage and distribution of drugs that were imported from the United Kingdom through the Crown Agents (Pharmaceutical Services Division, 2013). Then, in January 1976, Pharmacy Enforcement Unit was established, under the Pharmaceutical Services Division (PSD), in order to bring out the prosecution of laws and regulation affecting to pharmacy and the pharmaceutical trade in Malaysia.

The National Pharmaceutical Control Bureau (NPCB) (As National Drug Regulatory Authorities in Malaysia)

The first acknowledge of the National Pharmaceutical Control Bureau (NPCB), or Biro Pengawalan Farmaseutikal Kebangsaan (BPFK), was the National Pharmaceutical Control Laboratory; which was established in October 1978 under the control of Pharmacy and Supply Program of PSD. It was acting as an institution that was set up to provide the quality control. After the gazette of the Control of Drugs and Cosmetics Regulations was lunching in 1984; the regulatory control of pharmaceuticals product was implemented as a systematic format, in order to guarantee the safety, efficacy and quality of pharmaceutical products in Malaysia. (NPRA, 2016)

The Drug Control Authority (DCA), which acts as the administrative group, was established under the Control of Drugs and Cosmetics Regulations 1984. In Malaysia, a drug is controlled by the Drug Control Authority (DCA). The National Pharmaceutical Control Bureau (NPCB) is, actually, the operational arm of DCA.

Furthermore, DCA is, also, performed as the licensing authority. Meanwhile, National Pharmaceutical Control Bureau (NPCB) acts as a secretariat to the DCA. NPCB, therefore, is National Drug Regulatory Authorities in Malaysia who take responsible to monitor product registration and the licensing system such as:

- Registration of pharmaceutical products and cosmetics
- Licensing of premises for importer, manufacturer and wholesaler
- Monitoring the quality of registered products in the market

- Adverse Drug Reaction Monitoring

The development regulation for drug registration staring from 1984 in each phase as the following: Figure 8

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Prescription Drugs	OTC	Traditional Medicine	Cosmetics	Veterinary	API
Registration Aug 1985	Registration 1988	Registration Jan 1992	Registration Feb 2002	Registration Aug 2007	Regulatory control of Active Pharmaceutical Ingredient
Licensing May 1987	Licensing 1992	Licensing Manufacturer Importers Jan 1999	Licensing Jan 2004	Licensing 1 Jan 2012	No Licensing Requirements As registration of API is linked to products

Figure 8: The development regulation for drug registration staring from 1984 in Malaysia (NPRA, 2015)

The Drug Control Authority (DCA) is the executive body established under the Control of "Drugs and Cosmetics Regulations 1984". The main task of this Authority is to ensure the safety, quality and efficacy of pharmaceuticals, health and personal care products that are marketed in Malaysia. (NPRA, 2015)

The applicant for product registration must be the Product Registration Holder (PRH) as a local company. This company must has the business related to pharmaceutical product.

2.4.4.2 Drug registration process

Process of drug registration in Malaysia was informed in the Drug Registration Guidance Document (DRGD), first Edition - January 2013 and revised version in 2015. The main step was study with the pre-submission of drug registration application (as an administration part). If it meets the requirement, then the product application will go to "Screening process" and throughout the process as in the figure 9.

2.4.4.2 Drug registration process

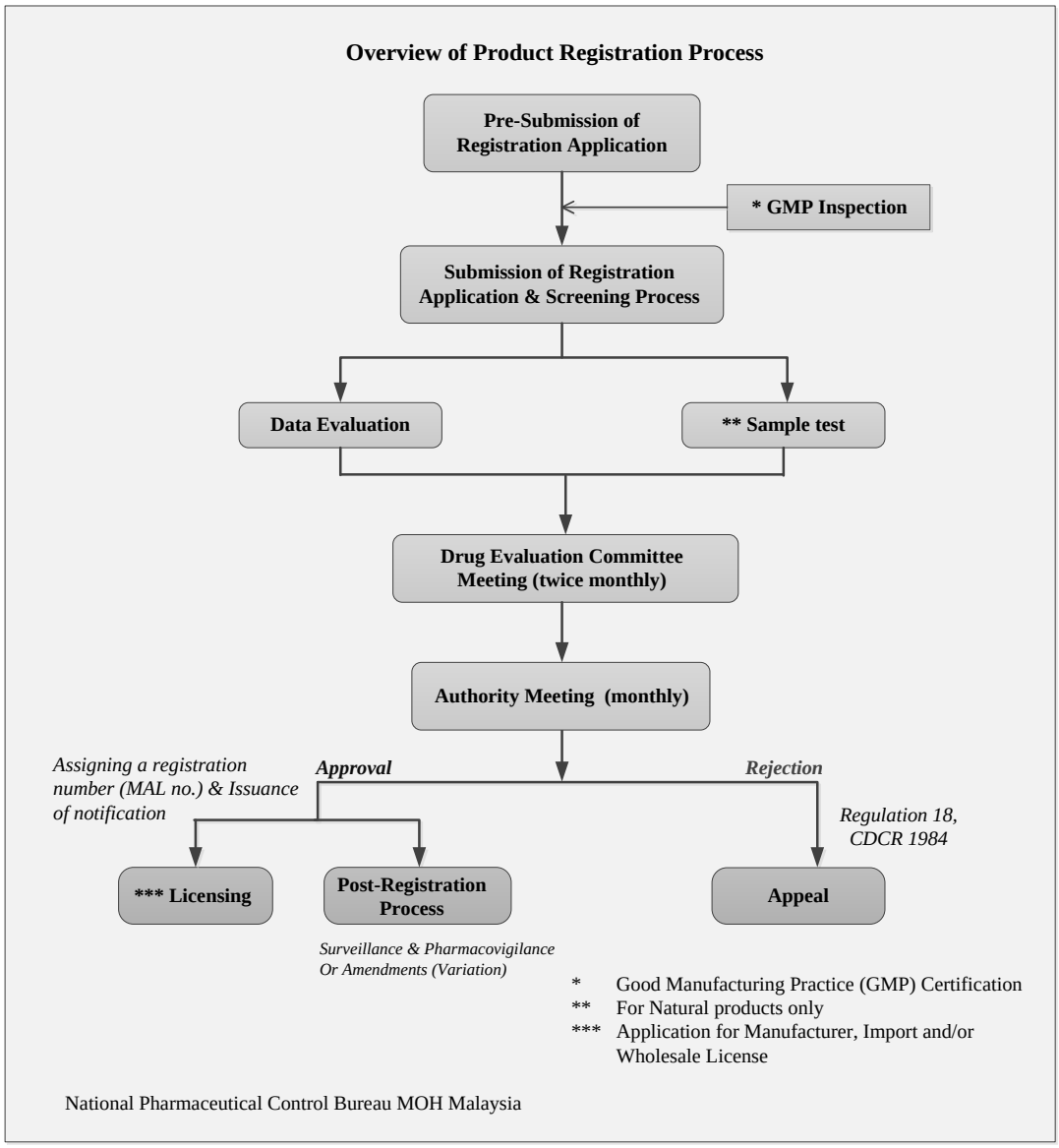


Figure 9: Drug registration Flow-Chart in Malaysia (NPRA, 2015)

2.4.4.3 Drug evaluation process

Malaysia has, already, been accepted the submission by the ASEAN-CTD since 2006; there are two types of evaluation routes for registration of a new product:

Full dossier: Applies to any product that has not been approved by any drug regulatory agency of ASEAN countries at the time of submission.

Type of product: New drug product, Biological product, Generic (Poison), Generic (OTC), Health supplement (disease risk reduction claim), Products containing Glucosamine (treatment indication)

Timeline (Inclusive screening process):

New drugs and biological: 245 working days

Generic: 210 working days

General requirements: In accordance to ASEAN ACTD/ ACTR or ICH guidelines

1. Part I: Administrative data and product information
2. Part II: Data to support product quality (Quality Document)
3. Part III: Data to support product safety (Nonclinical Document)
4. Part IV: Data to support product safety and efficacy (Clinical Document)

Submission: two steps of submission

1. Product validation (as product screening)
2. ASEAN requirements (as Part I, II, III, IV)

Abridged dossier: Applies to any product that has been evaluated and approved by at least one drug regulatory agency from other ASEAN countries.

Type of product: Generic (OTC), Health supplement, natural product, Products containing Chondroitin, Products containing MSM

Timeline: Timeline (Inclusive screening process):

Generic: 80 working days

Natural product and health supplement: 116 working days (single active ingredient), two or more 136 working days

Health supplement (high claim): 245 working days.

General requirements: not ASEAN ACTD/ ACTR or ICH guidelines

1. Section A: Product Particulars
2. Section B: Product Formula
3. Section C: Particulars of Packing
4. Section D: Label (Mock-up)
5. Section C: Particulars Product owner
6. Section D: Supplement document (GMP, CPP, etc.)

Submission: two steps of submission

1. Product validation (as product screening)
2. Full submission of general requirement (by all sections)

Table 14: Timeline of drug registration in Malaysia (NPRA, 2015)

Timeline		
No.	**Product Category**	*** Duration (inclusive screening process)**
(A)	**Full Evaluation**	
1	New Drug Products	245 working days
2	Biologics	245 working days
3	Generics (Scheduled Poison)	210 working days
4	Generics (Non-Scheduled Poison)	210 working days
* Upon recept of complete application.		

2.4.4.3 Drug searching

Like any other countries in ASEAN, the exiting of western drugs/modern drugs were not recorded when they came to market in Malaysia. The first drug registration in Malaysia was not records until the registration system was set up in 1984. This database is a collective list of drugs registered with the Drug Control Authority (DCA) of Malaysia since 1985.

A format of records in this list consists of: drug registration number, product name, name of product registration holder. Drug, which its marketing authorization (MA) was granted by DCA, can be searched from the website: http://quest3.bpfk.gov.my/QUEST3_SEARCH/

2.4.4.4 Drug registration number/code

Since drug registration system in Malaysia was implemented in 1985; the product license or marketing authorization (MA) was first approved in 1987. Also within the pharmaceutical product control and monitoring by Malaysian authorities; many

improvements have made constantly. For instance, the format of drug registration number has been changed several times. During this study, the format of registration number has changed from format 1 to format 2 as following:

Format 1: MAL YYYY$$$$@## (E.g. MAL 20071668A)
Format 2: MAL YYMM$$$$@## (E.g. MAL 12125046AZ)
MAL: states to "Malaysia"

YYMM: refers to year and month of registration, or

YYYY: refers to year of drug registration

$$$$: refers to a serial number for a product being registered

@: refers to category of product being registered i.e. A/ X/ N/ T/ H

- A= Scheduled Poisons
- X= Non-scheduled Poisons
- N= Health Supplement
- T= Natural Products/ Traditional Medicines
- H= Veterinary Product

Code (##): is for one or two alphabets

- C= Contract Manufactured
- E= For Export Only (FEO)
- R= Repacked
- S = Second source of manufacturer
- Y= Orphan product
- Z= Products listed under the National Essential Medicine List (NEML) for zero rated Government and Services Tax (GST)

2.4.4.5 Maintenance of registration

The drug, in Malaysia, has the marketing authorization (or product license) valid in 5 years, counted from the approved date. The renewal process must be done within 6 months before the expiry date of drug registration. The renewal application must be

started at 4 years and 6 month of product licenses lifetime onward. If it is no renewal, the Authority will automatically cancel the marketing authorization (MA).

In case, there are some change that affect to quality, safety and efficacy of product; the variation process is needed to be performed to the authority for approval, except the update package insert or product information, it can be submitted via the Post-Registration Center.

2.4.4.6 Fee for drug registration

Fees of drug registration in Malaysia were informed in the Drug Registration Guidance Document (DRGD), first Edition - January 2013 and revised version in 2015 as in the table 15.

Table 15: The Fees of the Drug Registration Process in Malaysia (NPRA, 2015)

No.	Product Categories	Processing Fees (RM)	Analysis Fees (RM)	Total Fees (RM)
1	Pharmaceutical (New Drug Products & Biologics)	1,000.00	Single active ingredient : 3,000.00	4,000.00
			Two or more activeingredients : 4,000.00	5,000.00
2	Pharmaceutical (Generics and Health Supplements)	1,000.00	Single active ingredient : 1,200.00	2,200.00
			Two or more active ingredients : 2,000.00	3,000.00
3	Natural Products	500.00	700.00	1,200.00
The processing fee is not refundable				

2.5. Related research

2.5.1 Drug access

Drug access is defined as Market access and Patient access

Universal medicine access is a major goal of the World Health Organization (WHO) and most countries with respect to medicine policy. The WHO defines medicines access as the equitable availability and affordability for essential medicines during the process of medicine acquisition (Paniz, Fassa, Maia, Domingues, & Bertoldi, 2010).

The pharmaceutical industry is important; because it is a major source of medical innovation. Once, a drug was discovered and approved by the Agency; the next step is to put the drug into the market and provide to a patient as the goal of treatment by medicine. Therefore, drug/medicine access is, commonly, understood by the term of market access and patient access**,** backward and forward due to the strong cornering of perspective.

Market Access is also used in Pharmacoeconomics. It refers to the process by which a company gets a drug to market; so that it becomes available for patients. However, since it is available for patients, how do patients can get easy for the medicine?

Recognizing "access" as a multidimensional concept; it, therefore, will be operationalizing in many dimensions related to markets and patients such as: market availability, including regulatory approval and time to reimbursement, insurer coverage, conditions of reimbursement; and patient out-of-pocket costs.

Georgi Iskrov and friends has defined "access" is an opportunity of timely and reimbursed medicinal treatment. When the EU, officially, approved and registered; orphan drugs are defined as "available". It will be "accessible" when effected reimbursement scheme and routinely used for treatment of patients in a selected country (Iskrov, Miteva-Katrandzhieva, & Stefanov, 2012).

To see the access to orphan drugs, the innovative medicine, breakthrough products in Bulgaria. The drug lag of 16 of 61 approved products in EU, since 21 Mar 2011, until it was accessible drug in Bulgaria, were need approximately 43±29.1 months. It was influence by the requirements and criteria of the relevant Bulgarian legislation on registration, pricing and reimbursement of medicinal products in order to obtain the final list of the accessible orphan drugs in Bulgaria.

By the Nils Wilking and Bengt JönssonIt opinion, the reimbursement decision process delays the approved drug in EU to reach patients. France, Italy and Spain have time delay up to a year, and Poland has the worst record as no innovative drugs have been reimbursed over the past seven years. Only Germany, UK and the USA have no real reimbursement delay. (Wilking & JönssonIt, 2006).

Andrew Wilson and friends has defined “access” in terms of marketing availability, payer coverage, and patient out-of-pocket costs. This access is related to a patient to reach the medicine. (Wilson & Cohen, 2011). A patient can access new cancer drug in USA and Australia, differently; even though both country have the same pattern in reimbursement.

In the United States (US), even though, cancer drugs have fast tracks for approval by regulatory authority agency; patients access too costly for new cancer drugs are, still, concerned to patients, physicians, payers, developers, and policymakers. Because many, newly, approved cancer drugs have high per-unit prices. Therefore, MAA of products were granted, but the patients cannot reach them. Also in the Australia (AUS), the federal government operates a comprehensive national prescription drug reimbursement program known as the Pharmaceutical Benefits Scheme (PBS). Prescription drug coverage is provided to all residents and visitors through the PBS, which accounts for approximately 80% of all prescriptions.

In term of access above, between USA and AUS, the availability of products, between 2000 and 2009, the USFDA had approved 34 NMEs and biologics for the treatment of cancers. But there were only 19 (56%) approved by the Australian TGA. Furthermore, the price of 19 products, which are available in both countries, are difference due to the situation each country drug competition. Australian prices were lower than US prices. The key barriers to access in Australia appear to be marketing availability and coverage; whereas the key barriers to access in the US are patient out-of-pocket costs, i.e., ability to pay (Wilson & Cohen, 2011).

By Hans-Georg Eichler and friend, term ‘access’ is intended to signify the market access (available of MAA of product or product license) of a drug, more than ‘treatment access’ by individual patient (patient access). For many drugs, treatment access, also, involves a subsequent decision on reimbursement of an authorized drug by third-party players, such as Medicare in the United States or national health services in the European Union. (Hans-Georg Eichler, 2008). Furthermore, according to the Nils Wilking and Bengt JönssonIt opinion, the reimbursement decision process causes the delay of the approved drug to reach patients

In the pharmaceutical point of view, lack of an effective market access strategy is the most common reason of why new drugs fail to reach patients in a timely manner. At least 18 months ahead of an anticipated product launch (McGrath, 2010)

In Thailand, after the Marketing Authorization of product was granted, a drug product can be launched at any time according to the company strategic and plan launching. The price of product is set by company due to the competitor price available in the market. Innovative drug, such as cancer drug, is needed to be listed in the hospital when launching to the market. Therefore, there is no delay launching due to the price reimbursement approval like many countries in EU. Patient in Thailand can reach a drug product by their payment (self-payment), co-payment or by the three major health benefit schemes.

1. The Civil Servants Medical Benefit Scheme (CSMBS),
2. The Social Security Health Insurance Scheme (SSS)
3. The Universal Health Insurance Coverage Scheme (UC)

About 75% of the country's population was under the UC and approximately 22% was under the combined population of CSMBS and SSS together (Ngorsuraches & Kulsomboon, 2010). The product which was listed in NLEM is the drug of choice under the three major health benefit scheme. Therefore, the number of drug available on the NLEM list is the measurement patient access in Thailand.

In this study, **market access** was defined the availability of drug product in the Thai Market and **patient access** was defined as the availability of drug on the NLEM.

2.5.2 Drug lag

Drug lag is the term of time and availability.

Actually, "Drug lag" was known as a time lag after thalidomide tragedy hit the world in1962. This situation impacted the drug approval in USA. Thalidomide was the first released into the market in 1957 in West Germany and then became an over the counter drug in Germany around 1960. At that time, it could be bought without any prescription

to against nausea and to relieve morning sickness. Since the thalidomide tragedy hit the world in 1962; the United States took awareness for the safety concern of the drug to be approval. After the tragedy, the USFDA was granted the authority to judge drug efficacy, as well as safety of product registration. It effected to the time taken to approve a drug for MA appeared to increase (Reichert, 2003)

In Japan, drug lag is considered to be the result of three separate types of delay: 1) delay in the start of development, 2) delay in the progress of development, and 3) delay in review by regulatory authorities. These delays are the barrier for the product launch in market. (Hirai et al., 2012; Junichi Hashimoto, 2009)

Other Drug lag has occurred a 'social drug lag'. In US, Medicaid recipients are denied coverage for certain new pharmaceutical products, although the USFDA has approved them as being both safe and effective. This lag is the delay between the time that a drug is approved for marketing by the FDA and the time that it is available to the state indigent population through the Medicaid program. (S. Schweitzer et al., 1985)

Daniels and Wertheimer defined "drug lag" in two manners: first, the introduction of a number of new products in foreign countries compared with those of the United States; second, the time difference between the introduction of drugs in the United States versus foreign countries.(Charles E. Daniels, 1980)

Drug delay since submission to EMA until patient access is about 2.3 years (857 days) (P. Russo, F. S. Mennini, P. D. Siviero, Rasi, & 2010). The drug accessibility is referred to the Italian health care context studied by Russo P. and friends revealed the complex anonymous composed by

1. The different assessment criteria (EMA and domestic criteria).
2. The different market access strategies in European countries (depending on the comparison of domestic rules and hurdles).
3. The different market sizes.
4. The different regional perspectives (depending on their budget constraints and their health care organization and attractiveness).

The study of Russo, Mennini et al, revealed that the process before patients reach to oncology products took time and cost consuming. The study conducted based on the data of 20 oncology products approved by European Medicines Agency (EMA) between 2006 and 2008. The access to new oncology medicines were analyzed, in the view of time spending throughout the pathway starting from the completed R&D of drug to regional health care providers in Italy. The lag time was defined as the time difference between the endorsement date of drug registration application into the centralization procedure of EMA and the first obtaining date of same oncology product, by at least one health care public structure, in at least one Italy region. The factor that influenced time spending throughout the pathway were such as EMA time for drug approval, Pharmaceutical company time for launching decision and for price decision, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) time for approval of price and reimbursement, and Region time for 21 Italian regions to organize public tender for the purchase of medicines. It seemed that new drugs were needed a period of time after approval to penetrate into market and reach the patient. (Russo, Mennini et al. 2010).

K. Tsuji and friends, defined drug lag in terms of 'absolute drug lag' and 'relative drug lag' which refer to the number of drugs available in the region. (Kataria et al., 2013; Tsuji & Tsutani, 2010).

Absolute drug lag was defined as the number and the percentage of approved drugs in each region out of a total of new drugs approved, either in the three regions in the study period.

Relative drug lag was defined as two variables; one variable was the number and percentage of first approvals in the regions out of a total of new drugs approved in any of the three regions during the study period; and the other variable was the approval lag against the first approval granted to each drug in the three regions.

Drug lag is time delay in making a drug available in a particular market for the patients which can have very serious consequences. The other factor that influence the time delay, may come from several key regulatory barriers; which need to be targeted in

order to make further improvements such as: 'Western Approval', local clinical development (LCD), Certificate of Pharmaceutical Product (CPP), Good Manufacturing Practice (GMP), pricing approval, document authentication and harmonization. (Wileman & Mishra, 2010)

There was a considerable drug lag of approval for new cardiovascular drugs in India when compared with the first approval in the United States and European Union during 1999-2011. The drug lag was, also, considered in term of "absolute drug lag" and "relative drug lag" in the study of Kataria, Mehta et al. "Absolute drug lag" was measured by the number and the percentage of approved new cardiovascular drugs in each region. Its ratio calculated from the total approval in any of the three regions in the same period of study. "Relative drug lag" was measured by two variables. The first valuable was the number and percentage of first approvals in the regions out of a total of new cardiovascular drugs approved in any of the three regions in the study period. Meanwhile, the second variable was "time difference" between the first time approvals of each cardiovascular drug in the three regions.

Results of the 75 new cardiovascular drugs, 61 (81.33%) were approved in the United States, 65 (86.66%) in the European Union and 56 (74.66%) in India. The US was the first to approve 35 (56.45%) out of the 75 new cardiovascular drugs, the EU was the first to approve 24 (38.71%) and India was the first to approve 3 (4.84%). The median approval lag for India (44.14 months) was substantially higher as compared to the United States (0 month) and European Union (2.99 months). It seems that drug lag prevents Indian patients from accessing new drugs at the same time as patients in the developed countries such as USA and EU. (Kataria et al., 2013).

There was the study of Henry G. Grabowski and Y. Richard Wang about the launch of new chemical entities (NCEs) to during 1982 through 2003. This study found the moderately increases of first-in-class of NCE, and US was the first launch this product during 1993–2003 compare with during 1970-1980. In this study, the first API name as a NCE in a therapeutic class was identified "first-in-class" by the WHO Anatomical Therapeutic Classification (ATC) system. A total of 919 NCEs were introduced from 1982 through 2003. The results, 385 (42%) were global NCEs, 115 (13%) were first-

in-class NCEs, 90 (10%) were biotech products, and 69(8%) were orphan products. Consideration of the first launch NCEs, US had lag launching behind EU during 1982-1992, first 10 year of study. However, US could speed up in 1993-2003, and could overtake and went beyond EU country during 10 year later (Grabowski & Wang, 2006)

In this study, the researcher would like to use drug lag as a measurement variable of the drug access, therefore, the definition of drug lag will be “time lag” and “number of drugs” available in the country, described as Absolute drug lag/relative drug lag.

Form the study Taiwan by Chia-Jung Chung and Weng-Foung Huang (Chung & Huang, 2006), New drugs were found that products mostly were imported from the foreign countries. The average marketing lag was approximately within 30.5 months in Taiwan. Most of the new drugs were obviously classified as me-too product, meanwhile a few product was classified as breakthrough new drugs. The reimbursement lag revealed approximately 11.7 months for the patient to access the drug. To find out the relationship of main country of origin of import product and drug lag, country of origin was grouped into five categories: Taiwan, USA and Canada, European countries, Asia countries, and others. The regression model shows a significant difference in the marketing lag. For country of origin, the p values of foreign sources of origin countries showed a statistically significant difference to the control group.

2.5.3 Price

Price is a value that is used to purchase a finite quantity, weight, or other measure of a good or service. Medicine/drug price is, also, a value that is used to purchase not only quantity of drug but also the innovative of drug for safe life longer. Drug pricing, normally, is set by the pharmaceutical company for a medicine due to the costs increased in their discovery and development. The overall cost of one new drug launching can go beyond a billion dollars. In order to get a significant return on its investment, the price of a new drug tends to have very high price tags.

For the same drug in each country, pricing is set difference due to the situation of each country, market size, competitor, the effects of exchange-rate movement and policy. Patricia M. Danzon and Michael F. Furukawa had provided the comparisons of drug

prices in eight countries: Canada, Chile, France, Germany, Italy, Japan, Mexico, and the United Kingdom with the U.S. drug prices. Japan drug prices were found higher than U.S. drug prices and other countries' prices. Canadian drug prices were the lowest. The market structure of U.S. was performed with the higher prices of patent products and strong generic drug competition. (Danzon & Furukawa, 2003).

From the 25 major markets, including 14 EU countries, there were 85 new chemical entities (NCEs) that launched between 1994 and 1998. The price regulation of each country affects the launching delay. Countries, which have small markets that have lower expected prices, tend to have fewer products launched and longer delays for those products that are launched. Larger markets have higher expected prices and shorter launch delays. (Danzon, Wang, & Wang, 2005)

In many EU countries, the delay launching of new drugs are depended on using the price control which is the barrier to delay the patient access of medicine. The innovator companies mostly avoid launching their product in price regulation market; because the following market after launching in the prices regulation will result the lower price. Therefore, according to Kyle, M. study in 2007, indicated that price control in one country will impact the launching into other country. (Kyle, 2007)

The expectation of generic drug entry the market after the expired patent is the potential to drive the patient access the medicine easier in many countries. However, the timing of generic drug implementation in each country is suspended or delay due to the first country of generic drug lunching, the degree of competition and the expected market size. According to the study of Costa-Font, McGuire et al, in 20 main markets (US, Canada, Germany, Italy, France, Spain, UK, Greece, Finland, Austria, Turkey, Sweden, Japan, the Netherlands, Poland, Italy, Belgium, Switzerland, Finland and Portugal); the price regulation is the major influence significantly effect on reducing the time to launch of generics drug after the patent of innovative drug had expired. (Costa-Font, McGuire et al. 2014)

As we know, after drug patent had expired and the generic entry was expected to reduce innovative drug price, innovative company, therefore, try to maintain brand loyalty by

taking advantage of price increasing. The innovative drug prices may rise after patent expiration (Regan 2008)

Price Control

The control of pharmaceutical prices of each country is a mystifying diversity and tends to discourage rapid product entry the country. The Lower price by price control regulation will delay the introduction of new drugs in the country and the lack of access to new drugs has significant negative health effects in price control countries (PCC). Since the U.S. government had implemented the assumed price control regime/system in 1980, there were approximately 38 percent of new drug disappeared due to the study model by using the average of 43 new drugs per year. (Giaccotto, Santerre, & Vernon, April 2005)

Reference price system

Pharmaceutical reference price (PRP) is defined as the reimbursement ceiling price that set by the payers in the public or private sector. Payers will be covered or reimbursed only the cost of listed drugs up to the reference price. Beyond this level, patient has to pay the difference between the reference price and the actual price. The reference price is set by authorities due to price in their countries with reference to already existing prices for the same drug in one or more other countries.

There are two principal ways that is used to separate PRP from the price control system (PCS). First, the pharmaceutical company can sell above the reference price and leave the market share to the competition with cheaper while PCS cannot. Second, price control systems (PCSs) normalize selling prices product by product, while the reference prices are applied to subgroup of chemicals chemical substance or identical or similar drugs. (Dickson & Redwood, 1998; López-Casasnovas & Puig-Junoy, 2000)

Cost effective

When determining the price of a new drug, companies perform pharmacoeconomic studies to show that use of the new medicine can reduce overall healthcare costs.

2.5.4 Patent

The study of patent and the generic drug entry phenomenon, (Bae JP in 1997), found the 81 innovative drugs lost their patents protection and exclusive marketing rights during 1987-1994. The entry of generic drugs was only 62.7 percent by January 1995. The trend of generic entry rate was found based on: no relation of the market size and revenues, the number of exiting product in the same therapeutic group including the market place. Type of drugs such as generic drugs of chronic disease were trend be faster entry than generic drugs for treatment acute illnesses

Patents provide essential protection to costly research and development initiatives. Many innovative drugs, mostly, have a patent protection and also are more expensive than the older drugs that they replace in the same therapeutic group. Therefore, when determining the price of a new drug, the price is high to cover all investment of innovative drug as the healthcare costs.

It was described such a mechanism in Canada (Menon, 2001). Based on the setting criteria, the Patented Medicine Prices Review Board (PMPRB) regulated prices of patented drugs to make sure that prices were not “excessive”.

In term of innovative drug, the achievement of innovative product depends on many characteristics including the granted patents to protect their intellectual property. During the patented period, innovative drug was safe from the copy product when lunched into the market. At this time, product could completely get the financial recover from the investment as a monopoly sale. Generic drug is defined by WHO as a pharmaceutical product which was replaced to an innovator product, without a manufacturing license agreement from the innovator company. It can be marketed after the patent was expired (WHO, n.d.).

Moreover, a generic drug is, normally, a copy product of brand innovative. It is also comparable to a brand/reference product in dosage form, strength, quality and characteristics, and the intension of usage. Regarding with budget concerns, the adoption of generic drugs into a health care system may help to reduce the increasing pharmaceutical expenditure of government.

However, in order to extend the patent protection from the basic patent expiration, company organized the strategies to block generic entry by filling numerous patents seen the list on the orange book of USFDA. The cost saving due to the generic launching after patent expiration is now interested for government; since it is incentive for the country investment.

The cost of bioavailability study to perform a comparable generic with innovative drug, are significantly lower than investment to perform branded products. The price of generic drugs is average 20–80% lower than originators (Simoen & Coster, 2006; Suh, Schondelmeyer, Manning Jr, Hadsall, & Nyman, 1998)

Patent may delay and sustain the entry of generic drug to the country. One study in Malaysia, by using the patents data from the Malaysian and international patents databases and using drug registration data base from the Malaysian drug regulatory authority; the data of 12 prescription drugs which were loss of patents protection and having generic entry record during January 2001 to December 2009 were collected as a database for analysis. The time lag was calculated from the date of first generic equivalents approval minus the date of expiration of basic patent of innovator active drug substance. The study found 154 generic drugs, entry during the study period; and their time lag was 396.92 days in Malaysia. It is the significantly delayed from the day after basic patent expiration of innovator active drug substance. The delay impacts overall decreasing of drug price and health care expenditure (Fatokun, Ibrahim, & Hassali, 2013).

2.5.5 Targeted cell therapies

Traditional therapies against cancer known as chemotherapy and/or radiotherapy. It was found several limitations that lead to unsuccessful treatment. Finally, cancer was returned after the period of treatment.

Unsuccessful treatment was found related to systemic and local toxicity of cancer drug. Some cancer relapse due to drug resistance or self-renewal. The tumor cells which was called cancer stem cells (CSCs) was normally involved in cancer initiation, maintenance, metastasis and recurrence. To develop successful treatments, it is

important to develop drugs that can be specific and direct to the cancer cell and eliminate CSCs. For the time being, trend of cancer treatment is the combination therapy using conventional anticancer drugs with targeted cell therapies (TGC) as a strategy for management and treatment cancer (Dragu, Necula, Bleotu, Diaconu, & Chivu-Economescu, 2015).

The targeted cell therapy was defined as the treatment to stop growth of cancer cells as focus on specific characteristics and it provided generally more likely than chemotherapy to safe normal, healthy cells. Currently, targeted cell was chosen for cancer treatment instead of chemotherapy (National Cancer Institue, 2014).

Classification of targeted cancer agents (TGC) was generally categorized as either monoclonal antibodies or small molecules (Abramson, 2016). These drug were found significantly change the trend of cancer treatment above past 10 years. Targeted cell therapy drugs were known as a part of therapy for many common malignancies including lung cancers, breast cancers, colorectal cancers, pancreatic cancers and others such as lymphoma, leukemia, and multiple myeloma. Therefore, TGC seems to be the value trend of cancer treatment in the future (Gerber, 2008).

2.5.6. Country of headquarter

Headquarters (HQ) is normally defined as the location where the important functions of an organization are composed. The company headquarters mostly characterizes the top of a corporation taking full accountability to manage all company business activities. Multinational Pharmaceutical companies normally have a potential to get a portfolio of drug products for major diseases, including cancer, cardiovascular disease, neurological disorders, respiratory disease and etc. Then, drugs are plan to lunch in each country as per the company decision to increase the market based on the strategy of cooperated headquarter.

Antineoplastic drugs normally were exported from the foreign country to Thailand. Therefore, it was interested to known the country of origin innovator company. Research from Taiwan in 2006 (Chung & Huang, 2006), revealed that drugs were normally imported from foreign counties classified by the country of origin such as

USA and Canada, European countries, Asian countries, and other countries. By regression model, the relationship of main country of origin of imported product and drug lag was shown that the p values of foreign sources of origin countries presented a statistically significant difference to the reference group.

CHAPTER III

METHODS

This chapter explained the method of study that covered: study design, conceptualization and operationalization of study concepts and variables, data source, as well as, how data was retrieved, and analyzed.

Following three research questions brought up in Chapter I, including (1) what the cancer drug lag situation in Thailand was, (2) how the cancer drug lag was different among ASEAN countries, and (3) what factors that influenced the accessibility of antineoplastic drug were; the study conceptualized the framework as depicted in figure 1 with proposed three study objectives addressing both market access and patient access to antineoplastic drugs as followed.

1. To assess market access and patient access of antineoplastic drugs in Thailand
2. To compare accessibility of antineoplastic drugs among selected ASEAN countries
3. To analyze the association between determinants and access to antineoplastic drugs

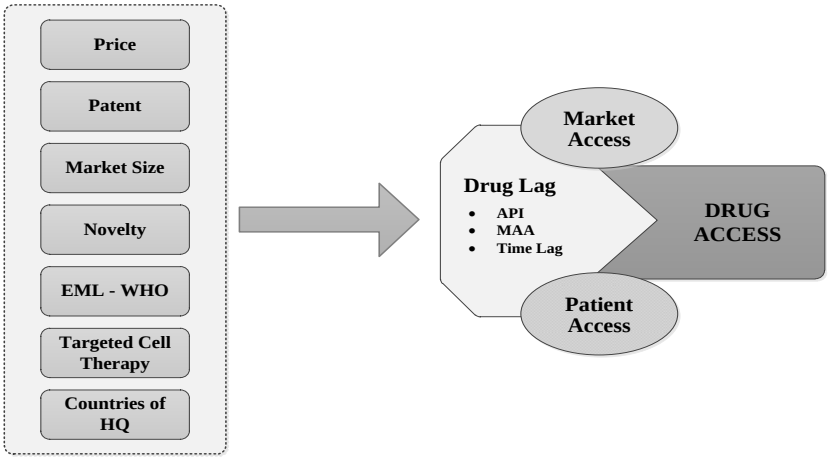


Figure 1: The Conceptual Framework

3.1 Study Design

The design of this study was a descriptive study, using secondary data such as marketing authorization approval (MAA) and related information of four countries and EU. The period of data was dated back as long as data available until April 2016. EU and four other selected countries for comparison with Thailand were Singapore, Malaysia, UK, and USA.

3.2 Operationalization of concepts, measurements of variables and source of data

According to the conceptual framework, major concepts included drug access and several independent variables.

3.2.1 Accessibility

In this study, drug access was defined as having medicines continuously in market and patient can reach those medicines for treatment. In many countries including Thailand, drug access was composed of two sectors: market access and patient access. Thus, this study chose to analyze the drug access from these two perspectives, market access and patient access.

Market access was defined as availability of a medicine item in the country without taking into consideration affordability issue. Market access represented the medicine that was succeeded in the first and foremost level of regulatory selection at the country level by getting the marketing authorization approval (MAA)

Patient access was defined as available of medicine items in the National List of Essential Medicine (NLEM). When the medicine was listed in NLEM, patients could certainly be able to access if needed. The patient access was, thus, considered for another level of medicine accessibility.

In this study, the extent of market access and patient access was conceptualized as ‘Drug Lag or the delay having medicines in the countries and delay adopting medicines on the NLEM of Thailand. Drug lag could be measured by 2 dimensions: time and number; variables representing drug lag thus comprise ‘time lag’ and ‘number lag’.

3.2.1.1 Measurement of number lag

The measurement of number was composed by two type of numbers. First type was the number of active pharmaceutical ingredients (APIs) and the second type was number of marketing authorization approval (MAA) in Thailand.

Number of API: the number of each different chemical substance in drug products that made the medications work.

Number of MAA: the number of the drug approval of each API in each country. By granting the MAA, the drug product was proved to have quality, safety, and efficacy. The document, showing the granting of 'marketing authorization', was also called product license or registration number. If 2 different drug products had the same chemical substance, number of MAA was counted as 2 but number of API was one.

Market access

Measurement market number lag

The market number lag by API was measured by 2 aspects: 'market absolute lag' and 'market relative lag'. The market absolute lag was measured by the number of approved active pharmaceutics ingredient (API) available in the country. The market relative lag was measured by number of API available in each country as a percentage of all APIs.

The market number lag by MAA measured by 2 aspects. One was "market absolute lag: the number of MAA available in the country" and the other was MAA/API ratio"

Patient access

Measurement patient number lag

Patient number lag by API was measured by the number of APIs listed under NLEM as a patient absolute lag. The number of API on NLEM as a percentage of all APIs was market relative lag.

The patient number lag by MAA measured by 2 aspects. One was patient absolute lag: the number of MAA listed under NLEM and the other was MAA/API ratio

3.2.1.2 Measurement of time lag

Market access

Selection the main comparator country

To investigate and select countries (the US or country in EU) as the main comparator country as a first country of MAA. Based on the barrier in language, the United Kingdom (UK) was selected to be the representative of EU in this study. The time difference between "the first MAA of US or UK" and "the first MAA of other countries, were calculated. The main comparator country must be selected by the confirmation with all positive time lag. The US was finally used as the main comparator since the information system was the most consistent and US had the most items of API available.

Measurement market time lag

Market time lag or another term of launch delay was measured by time difference between "the first MAA of drug available in US" and "the first MAA available in Thailand" including other countries.

Patient access

Measurement market time lag

Patient time lag was measured by time difference between the time first MAA available in Thailand and the time when the API was first listed in NLEM. Moreover, the additional to patient access was the time lag between the first MAA available in Thailand and the first new generic drug (NG) of the same API gets approved.

3.2.1.3 Source of data

Active Pharmaceutical Product

Active Pharmaceutical product (API) was chemical substance which was classified by WHO ACT-code system (WHO, 2011). In this study, the number API was obtained from WHO website https://www.whocc.no/atc_ddd_index/, last updated: 16 Nov 2015.

First level

The first level of the code indicates the anatomical main group and consists of one letter. There were 14 main groups. Antineoplastic drugs were classified under group L in the ATC first level as shown in table 16.

Table 16: The 14 Main Groups (ATC level 1) of Anatomical Therapeutic Chemical (ATC) classification system

ATC-Level 1	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

As presented in Table 5 (chapter 2), Example: '**L'** is the antineoplastic and immunomodulating agents

L	Antineoplastic and immunomodulating agents (1st level, anatomical main group)
L01	Antineoplastic drugs (2nd level, therapeutic subgroup)
L01A	Alkylating Agents (3rd level, pharmacological subgroup)
L01AA	Nitrogen mustard analogues (4th level, chemical subgroup)
L01AA01	Cyclophosphamide (5th level, chemical substance)

Source from : WHO. (2011, Last updated: 2011-03-25). Structure and principles. Retrieved from http://www.whocc.no/atc/structure_and_principles/

Second level

The second level of the code indicates the therapeutic main group and consisted of two digits. Under the Antineoplastic and immunomodulating agents, there were four ATC level 2 or drug therapeutic groups: Antineoplastic agents (L01), Endocrine therapy (L02), immunostimulants agents (L03) and immunosuppressants (L04)

Third level

The third level of the code indicated the pharmacological group and consisted of one letter.

Example: '**L01A'** was Alkylating Agents and 'A' was the first pharmacological group of this level. Then, 'B', 'C', 'D' and 'X' are the second, third and forth as sequential.

Fourth level

The fourth level of the code indicated the chemical group and consisted of one letter.

Example: '**L01AA'** was Nitrogen mustard analogues and 'A' was the first chemical group of this level. Then, 'B', 'C' and 'D' were the second, third and forth as sequential of this group.

Fifth level

The fifth level of the code indicated the chemical substance and consisted of two digits.

Example: '**L01AA01**' was Cyclophosphamide and '01' was the first chemical substance discovered of the Nitrogen mustard and analogues chemical group. Then, '02', '03' and '04' were the second, third and forth as sequential of chemical substance which was introduced in the world.

However, the last two digits in this level, '01' of chemical substance in each chemical group was defined as the breakthrough or first chemical substance discovered in the subgroup and others: '02', '03', '04' and etc. were defined as Me-too chemical substance which was introduced in the world. In this study, we defined the last two digits in this level as 'novelty code'

Marketing authorization approval

- Marketing authorization approval (MAA) information or drug approval information in the USA, the EU, Thailand (TH), Malaysia (MAL) and Singapore (SG) until the end of April 2016 were identified by their active pharmaceutical ingredient (API) as a generic name of product. The information such as date of approval, drug registration number, product owner, manufacturer, dosage from, were gathered, primarily, from the following sources:
- The US: 'CDER Drug and Biologic Approval Report', CDER, the FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) 'Products', CBER, the FDA (http://www.fda.gov/cder/products.htm), (US-FDA, n.d.)
- The EU: 'European Public Assessment Report' (EPAR), Committee for Medicinal Products for Human Use (CHMP), EMA (or EMEA) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (EMA, n.d.)
- The UK: for the MHRA for the searching the date of MAA in UK (MHRA, n.d.)
- Singapore: Homepage of Health Science Authority (HSA) for searching the drug license available in Singapore

http://eservice.hsa.gov.sg/prism/common/enquirepublic/SearchDRBProduct.do?action=load (HSA, 2014b)

- Malaysia: Biro Pengawalan Farmaseutikal Kebangsaan (BPFK), Product Search for the drug license http://www.bpfk.gov.my/Search/Search_product.asp (NPCB, n.d.)
- Thailand: home page of drug bureau http://wwwapp1.fda.moph.go.th/logistics/drgdrug/DSerch.asp (Thai-FDA, n.d.)

3.2.2 Price

Price was a value that was used to purchase a finite quantity, weight, or other measure of a good or service. In the study, price was defined as the value of an antineoplastic medicine which was set for sale by the company. Price of antineoplastic drug was obtained from the IMS database end of year 2014 in Thai Baht (THB).

Measurement of price:

Since price of drugs were presented in varieties of package size and strength, therefore price of the antineoplastic drug needed standardization for comparison purpose. Then, in this study, the cost per month was calculated to be the representative of price.

Cost per month = price (THB) per unit (mg) x dosage regimen of 12 week/2.77

The 12 weeks' dosage regimen of each API obtained from approved package insert by Thai FDA or summary product characteristic of drug of branded product including from the Drug Information Handbook to confirm dosage regimen. The high dosing regimen was selected for calculation.

Table 17: The average Thai size for calculation the cost pet month of product (Mosteller, 1987; NECTEC, n.d.)

Average Thai adult*	
Average weight adult	63.115 mg
Average height adult	163.23 cm
Body surface area (Calculated by Mosteller formula **)	1.69 square meters

Note*: "SizeThai" is form the website: http://www.sizethailand.org/region_all.html,
**: http://www.nejm.org/doi/full/10.1056/NEJM198710223171717

By using an “average” Thai size: adult weighing 63.115 kg or with a body area of 1.69 squared meters, a 12 week-dose regimen was calculated. Then it was divided by 2.77 to reach a cost per month of each API. The average 2.77 months was equivalent to 12 weeks (Bach, 2016).

Exception for clafarabine, drug for treatment of cancer in children 1-21 years, the dosage regimen was calculated by using the half BSA of adult. Since the price of the branded and generic products were different, the cost per month of each API was separately calculated according to drug regulatory classification: generic drug, new drug and new generic drug.

Source of data

Price was obtained from IMS database end of year 2014. The dosage regimen was from the approved drug package insert of Thai FDA and the Drug Information Handbook, 23rd edition (Lexi-Comp, 2014)

3.2.3 Patent

The term 'patent' was defined as a monopoly right; which was granted to a pharmaceutical company who had invented a new and useful pharmaceutical product, or an improvement of an existing product, or a new process of making product, or a grant of exclusive rights to an inventor or manufacturer and product according to the invented process for a limited period protection, approximately 20 years since submission date of new chemical entity.

In this study, patent information of drug registration in Thailand was not available in Thai FDA database, therefore searching from the Intellectual Property Thailand Department (IPT) was needed. It was not found patent information from searching via IPT by using API name. Name of product patented in the IPT database was not the same name as chemical substance name or API name of WHO. Consequently, the patent information in this study was obtained from USFDA database since the comparison was based on US drug registration.

Measurement of patent:

For each API, the following variables were created such as 1) patent of API was available in USFDA database or not at the time of study till April 30, 2016, 2) Patent expiry date of drug substance, 3) Type of patent claim available at the time of study: Drug product claim, Drug substance claim and Patent used claim. Under the USFDA orange book, the patent information was the current active patent. Thus, those medicines without patent information available at the study period could mean that all patents were expired or never had patent registered in the US. The latter case was quite uncommon, the condition that all patents being expired was then assumed.

Source of data

Patent information was main obtained from the USFDA database via the orange book searching website: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

3.2.4 Market size:

Market size of drug was defined as the sales volume of each API in Thailand. Companies was interested in knowing the market size before launching a new product or service in an area, based on: time period, geographic regions and epidemiology of disease. Calculating of market size was based on end users purchased during the period. Since sales in baht were sensitive to price level, the amount of use measured in term of patient-months was also calculated. Thus, the unit of measurement of sale value and patient per month (patient-month) of each year was used to be representative market size.

Measurement of market size:

It was measured in two forms: 1) antineoplastic drug sale values (THB) and 2) number of patient-months

Patient - month = Sales value of each year /cost per month

Source of date

The sale value was obtained from IMS database on sales during 2011 to 2014.

3.2.5 Novelty

Drug was classified using the Anatomical Therapeutic Chemical (ATC) classification system. Different APIs was identified by two digits of ATC code level 5, with the first to be discovered or synthesized coded as 01 and others in the same group were sequentially coded. The 01 designated as breakthrough or first-in-class treatment; meaning that the medicine targets at the certain disease or symptom in the way that no other drug had before. The other numbers, then, represented me-too medicines; which were structurally very similar to already known drugs, with some minor differences. The term "me-too" carried a follower connotation. However, me-too products created competition and drive prices down. Some me-too APIs showed improvement of safety and efficacy over the breakthrough. This study hypothesized that the newness of medicine or drug novelty could be a factor influencing medicine accessibility. Sequence of API at the ATC level 5 was used to represent the newness of a particular API.

Measurement of drug novelty

The sequence of API at the ATC level 5 was used to represent the newness of a particular API as a “Novelty code”

Source of data

The last two-digit number API was obtained from WHO website https://www.whocc.no/atc_ddd_index/. It was obtained from the API listed on the last updated: 16 Nov 2015.

3.2.6 WHO list of essential medicine

The WHO lists of essential medicines (EML-WHO) was the list of drugs which were set from the basis of national policies; concerning the chemotherapy to be offered in the light of the cancer problems in the country concerned. Generic forms of these drugs are also available as well. In this study, the priority list of antineoplastic drugs was obtained from the WHO list of essential medicine of 2015 as the priority list or the standard list of essential drug.

Measurement of cancer priority list:

The antineoplastic API on NLEM of 2016 was available in WHO essential drug list or not. The items of antineoplastic API of NLEM were compare to EML-WHO.

Source of data

The WHO list of essential medicine of 2015, 19th edition, listed in April 2015 and amended in Nov 2015

3.2.7 Targeted cell therapy

In this study, targeted therapies treatments were believed to stop growth of cancer cells as focus on specific characteristics and it provided generally more likely than chemotherapy to safe normal, healthy cells. Currently, targeted cell was chosen for cancer treatment instead of chemotherapy (National Cancer Institue, 2014). The advanced concept of treatment might influence the decision to enter market or to be listed under NLEM.

Measurement of targeted cell therapy

Antineoplastic active pharmaceutical ingredient in Thailand and on the NLEM was searched to find classification as a TGC. The number of API classified as TGC was report as absolute TGC' and 'relative TGC'

Source of data

The targeted cell therapies (TGC) for cancer drug classified by Abramson, R. in 2016 (Abramson, 2016)

3.2.8 Country of headquarter

The country of headquarter was defined as the country where headquarter (HQ) of product owner (product license holder in Thailand, drug manufacturer) was located. In this study, the first brand of antineoplastic API in Thailand was searched for product owner. Then, the country of HQ of product owner was obtained for country zone classification

Measurement of country of HQ

The headquarter country of the product license holder was searched and recorded, then was recoded according to geographical zones such as USA, EU and Asia.

Source of data

The Country of HQ of each API was obtained from drug registration information of Thai FDA database that searching via website http://wwwapp1.fda.moph.go.th/logistics/drgdrug/DSerch.asp (Thai-FDA, n.d.)

3.4 Data selection

In this study, all antineoplastic drug substances, at the API level, were selected with the WHO ATC-code listed last updated in 2015 as the reference of antineoplastic drugs available in the world. The Information about the name of approved drugs, indication and date of issue of marketing authorization approval (MAA), registration number, were retrieved from the data of the above sources.

Inclusion criteria:

- All antineoplastic drug APIs listed in ATC system are included.
- All antineoplastic MAAs in all dosage forms are included.

Exclusion criteria

- Combined drugs that do not include any antineoplastic API
- MAAs that contain antineoplastic API but approved for other indications

3.5 Data conditions

Thailand and Malaysia, the MAA approval date was not provided. Only the year of approval was revealed by the drug registration number system.

Thailand:

The approval time of drug registrations in Thailand was not provided in Thai FDA database, therefore, the year of approvals was obtained from the drug registered number granted by Thai FDA.

In order to be consistence with other country like USA, UK (as EU) and Singapore, and to reduce the gap of different time in year approval; the 1st date of July was assumed to be date and month for approval time of product for calculation of time lag resulted in date/month/year unit. For an example, drug registration number is 1C 134/2547 (N), therefore, the date and month were assumed as first of July, then followed with year from drug registration number "2547" (2004 BC). In this case, the approval time was assumed 01/07/2004. Moreover, some API, the first approval date (Date/Month/Year) was found on the special announcement list: the list of new drug and new biological product including new generic drug dated on 31 December 2014, the actual approval date was adopted to use for calculation. For the drug which was approved during the year 2016, since the study period was the end of April 2016, the date of approval was then assumed to be "16/April/2016"

Malaysia:

As the approval time of drug registrations in Malaysia was not provided in the database; however, the year of approvals was obtained from the Malaysia drug registered number. In order to be consistence with other country like USA, UK (as EU) and Singapore, and to reduce the gap of different time in year approval; the 1st date of July was assumed to be date and month for approval time of product for calculation of time lag resulted in date/month/year unit.

Without the information of date of drug products approval in the Malaysia drug search database (BPFK-database or NPRA-database); the year of first approval was obtained from product registration number of MAA. Two formats and systems of product registration number were found. For product registrations granted before 2011, only year of approval was present in product registration number. For those granted after 2011, years and months were available in the product registrations number. Since the date of drug approval was assumed from year of drug registration number such as MAL**2004**0232A, year of approval was 2004. Therefore, the date and month were assumed as first of July, then followed with year 2004. In this case, the approval time was assumed 01/07/2004. Furthermore, the 16th of month was assumed to be the date of the product which month and year could be obtained from the drug registration

number. To calculate time lag, three units of time lag, (date, month, year) were the unit presented in this study.

3.6 Data analysis

Descriptive statistics was used to characterize all of dependent and independent variables. Bivariate relationships between dependent and one categorical independent variable were analyzed by t-test or ANOVA. Regression analysis was conducted to explain the variance of time lag by hypothesized independent variables. This study performed the actions to analyze drug lag by number and time as the following:

1. Determine and describe the number lag by API of the four countries; in terms of 'absolute number lag' and 'relative number lag'
2. Determine and describe the number lag by API of the NLEM; in terms of 'absolute number lag' and 'relative number lag'
3. Determine and describe the number lag by MAA of Thailand; in terms of 'absolute number lag' and 'MAA/API ratio'
4. Determine and describe the number lag by MAA of the NLEM; in terms of 'absolute number lag' and 'MAA/API ratio'
5. Determine Time lag of the four countries with reference to US and NLEM with reference to Thai MAA
6. Determine bivariate relationships between dependent variable (time lag between TH and US) and one independent variable including the availability of patent, novelty level, cost per month, market size (sale value and patient-month), whether the drug was targeted cell therapy, country of HQ, and priority list,
7. Determine the multivariate relationship between dependent variable (time lag between TH and US) and independent variables: patent, novelty, cost per month, market size (patient – month and sale value), targeted cell therapy, counties of HQ and EML-WHO

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Introduction

The research questions of this study were what the drug lag situation in Thailand was, how the drug lag was different among ASEAN countries and what factors that influenced the accessibility of antineoplastic drugs were. The answers to these questions were presented in this chapter according to the three objectives, i.e, to assess market access and patient access of antineoplastic drugs in Thailand, to compare accessibility of antineoplastic drugs among selected ASEAN countries, and to analyze the association between determinants and access to antineoplastic drugs

The results of this study were constructed into three parts. The first part provided the descriptive analysis result of each variable and drug lag. The second part was the result of relationship between each variable and time lag including which included both market access and patient access. The last part presented the factors which influenced the time lag.

4.2 Descriptive analysis

4.2.1 Accessibility

In this study, the measurement of accessibility of antineoplastic drug was presented by the drug lag. Since drug lag could be measured by 2 dimensions: number of active pharmaceutical ingredients (APIs) available and time when the drug was available; variables representing drug lag were thus comprised of ‘number lag’ and ‘time lag’. Both number lag and time lag were also measured in terms of market access and patient access. The variables of drug lag then included market number lag, market time lag, patient number lag, patient time lag.

4.2.1.1 Number lag

The number lag could be measured by 2 aspects: ‘absolute lag’ and ‘relative lag’. The market absolute lag was measured by the number of approved active pharmaceutics ingredients (APIs) available in the country. On the other hand, the market relative lag was measured by number of drugs approved in each country as a percentage of all items listed under WHO ATC. Meanwhile, the patient absolute lag was measured by the number of approved active pharmaceutics ingredients (APIs) available in the NLEM. However, the patient relative lag was measured by number of drugs listed on NLEM as a percentage of all items listed under WHO ATC.

4.2.1.1.1 Number of active pharmaceutical ingredient by country

By WHO Anatomical Therapeutic Chemical (ATC) classification system, active substance or active pharmaceutical ingredient (API) to treat cancer was coded as ‘L01’. L represented level 1 of ATC (antineoplastic and immunomodulating agents) and 01 represent Level 2 of ATC (antineoplastic drugs). The third level of L01 consisted of 5 groups including A (alkylating agents), B (antimetabolites), C (plant alkaloids and other natural products), D (cytotoxic antibiotics and related substances), X (other antineoplastic agents). For the fourth level, there were 6 groups of alkylating agents, 3 groups of antimetabolites, 5 groups of plant alkaloids and other natural products, 3 groups of cytotoxic antibiotics and related substance, 6 groups of other antineoplastic agents. Each chemical substance at the fifth level was sequentially coded as 01, 02 and etc. The sequence was presumed to represent the order of market entry. At the fifth level of ATC, vocabularies that were used interchangeably, included chemical substance or active substance or active pharmaceutical ingredient (API) or ATC name.

There were some updates of WHO ATC from version 2013 to version 2015. Number of APIs was increased from 156 to 178 items at the end of year 2015. (Last updated 2015-12-16). Alemtuzumeb was also recoded from ‘L01XC04’ to ‘L04AA34’.

From 178 items of ATC code, ‘L01BC53’ was “tegafur, combinations”. Under this code, two products with difference fix dosage combinations were found. One product,

UFT, was tegafur combined with uracil and the other product, TS-ONE, was tegafur combined with gimeracil and oteracil. Under the same code 'L01BC53', two products with different API combinations were thus defined as two API names as in the below.

- Tegafur/uracil (UFT)
- tegafur/gimeracil/oteracil (TS-ONE CAPSULE)

Table 18: Number of antineoplastic APIs by WHO-ATC classification

Pharmacological group (ATC-Level 3)	Chemical group (ATC -Level 4)		Number of API (ATC-Level 5)
A: Alkylating Agents	ATC - L4	A: Nitrogen mustard analogues	8
		B: Alkyl sulfonates	3
		C: Ethylene imines	3
		D: Nitrosoureas	7
		G: Epoxides	1
		X :Other alkylating agents	4
	Total		26
B: Antimetabolites	ATC - L4	A :Folic acid analogues	4
		B :Purine analogues	6
		C :Pyrimidine analogues	12
	Total		22
C: Plant alkaloids and other natural Product	ATC- L4	A: Vinca alkaloids and analogues	6
		B: Podophyllotoxin derivatives	2
		C: Colchicine derivatives	1
		D: Taxanes	4
		X: Other plant alkaloids	1
	Total		14
D: Cytotoxic antibiotics and related substance	ATC- L4	A: Actinomycines	1
		B: Anthracyclines & related sub.	11
		C: Other cytotoxic antibiotics	4
	Total		16
X: Other antineoplastic agents	ATC- L4	A: Platinum compounds	5
		B: Methylhydrazines	1
		C: Monoclonal antibodies	21
		D: Sensitizers used in photodynamic /R-T	5
		E: Protein kinase inhibitors	33
		X: Other antineoplastic agents	37
	Total		102
Total active pharmaceutical ingredient (API) or chemical substance of antineoplastic drug			180

Therefore, 178 items of ACT code offered 179 API names in this study database. However, based on Marketing Authorized Approval (MAA) in Thailand, one API named “nimotuzumab” with uncompleted ATC code ‘L01XC__’ has been found in the Thai market since 2010. Even though, nimotuzumab did not exist in WHO ATC coding system at the time of the study, I decided to include under the L01XC group (Padfield, Ellis, & Kurian, 2015). with self-created code as ‘L01XC-16TH’. Therefore, the study included a total of 180 active pharmaceutical ingredients (APIs) as seen in table 18

The number of APIs available in each country as well as percentage of all items were summarized in the table 19. Comparative across countries, the more APIs available represented a higher level of market access to antineoplastic drugs in that country. While number of APIs listed under NLEM reflected the extent of patient access to anticancer medicines.

Table 19: Number of active pharmaceutical ingredient (API) available across countries

Country or Essential list	**Number of Active Pharmaceutical Ingredient (API)**	
	Total (available in April 2016)*	**Percentage (available in April 2016)***
WHO	180	100
US	130 (129)	72.22 (71.67)
EMA	75	41.67
UK	119	66.11
SG	92	51.11
MAL	68(63)	37.78 (35)
TH	88(76)	48.89 (42.22)
NLEM-TH	38	21.11
EML-WHO	34	18.89

Note: * number in the parenthesis denotes is the available APIs in April 2016

United States of America

From 180 APIs, one hundred and thirty (130) API names were found to have marketing authorization approval (MAA) in United States of America (USA), and only 129 APIs

were available in United States of America (USA) in April 2016. Gemtuzumab was canceled by company due to the product's safety in 2010

European country

According to reviewed literatures, the drug registration regulations of countries in the EU have already been harmonization, each country of EU members had two parts of drug registration: the nations procedure and the centralization procedure. In this study, based on country using English as the main language, the UK was selected as the representative country in the EU.

European Union agency

In the European community, under the centralized authorization procedure, based on 180 ATC names, 82 items of API were found approved by European Medicines Agency (EMA). From these 82 items of API, seven (7) items: busulfan, cladribine, cytarabine, doxorubicin, hydroxycarbamide, mercaptopurine and porfimer sodium, were the second approval in EU for the secondary dosage form with UK record for the first approval of marketing authorization (MA). Moreover, porfimer sodium was voluntary withdraw from EMA in 2012; due to the company reason. Thus, 75 API items remained obviously as the first API approval by EMA. Information of the date/month/year of approval times were obtained from EMA database by searching via EMA website.

United Kingdom

The United Kingdom (UK) government designated and confirmed to leave the EU in July 2016. However, this study was conducted during the United Kingdom (UK) was one of EU member states. Therefore, the drug registration system of UK was still based on EU regulation. Drug registration approval under the centralization process of the European Medicines Agency (EMA), can be applied for all 28 European Union Member States and the European Economic Area countries for three countries (Norway, Iceland and Liechtenstein). The UK was the one of 28 member countries.

Therefore, 75 items of API, first approval by EMA were also adopted to be the drug registrations in the UK.

Based on 180 APIs searching via "Medicines Information: SPC & PILs" of www.mhra.gov.uk and the electronic Medicines Compendium (eMC) of http://www.medicines.org.uk/emc/about-the-emc, Out of 119 items of API found to have MAA in the UK, 75 items were approved by centralized authorization procedure and 44 items by nation process of Medicines and Health Products Regulatory Agency (MHRA).

Information of the date/month/year of approval time was obtained from summary product characteristic (SPC) section, under the topic of "Date of first authorization"

Malaysia

Malaysia (MAL) regulated the renewed-process of drug registrations every 5 years. Thus, some products information may not be continued and absent from the Malaysia database. Since the information would not keep in the system if the product was discontinued, the date of first approval of API would not be found in case that MAA was expired and not renewed. While the other product with the same API, which MAA was dated later (not the first MAA), still maintained for MAA, then the information of these first MAAs of product were still kept in the system and would be regarded as the first of API in Malaysia.

In the pre-study phase, two sources of database were selected and the information of drug registration was obtained. The first data source was Malaysia drug search website (the accessed time during January 2014 and April 2016). The second source was the Malaysian drug code (MDC) list of 2010, 6th edition. This list assisted to confirm the antineoplastic drugs available in Malaysia and was able to find the exact date of the first API approval. Data from the first search in Jan 2014 including the final search of 180 APIs in April 2016 via the Malaysia drug search website, sixty-eight (68) APIs were found, and only 63 items were active MAAs in April 2016.

Thailand

From Thai FDA, 88 APIs found having MA approval in Thailand (TH) and only 76 APIs were still active in April 2016. Meanwhile, there were 12 APIs that the registrations status was canceled as of 31 April, 2016. However, the same as other country, two APIs (5FU combination: 5FU combined with salicylic, and celecoxib) were found MAA in Thailand. But these 2 APIs were not used for only cancer treatment; thus, they were excluded from this study.

Singapore

Singapore had approved 83 APIs in Health Sciences Authority (HAS) database. The total 83 APIs was still available till in April 2016. This was accounted for 51.11 percent of all 180 APIs.

Essential medicine list of WHO

To afford the quality medicines was the fundamental health care system in many countries including Thailand. WHO had organized and published the fundamental list of drug which was called “essential medicines”. WHO encouraged many countries to establish their own list which was appropriate for their countries. Therefore, a model list of essential medicines of WHO, was now become the protocol to draft or adjust the essential list or a minimum list of essential drug in many countries including Thailand. The Essential Medicines list of WHO (EML-WHO) was normally updated every two years. The current version was the 19th version which was implemented in 2015 and revealed 34 APIs on the EML-WHO.

In this study 34 APIs were set as a priory list of antineoplastic drug as a standard list to compare with National list of essential medicine in Thailand. This minimum list contained 18.89 percent of all 180 APIs and had the least items compared with what other countries in this study had approved including NLEM of Thailand.

National list of essential medicine in Thailand

The first NLEM in Thailand was established and implemente in 1981 (B.E. 2524), eleven first APIs names of the antineoplastic drugs for cancer treatment were found. During 1981-2016, there were 11 versions of NLEM implemented in Thailand. The last version, announced in 2016, included thirty-eight (38) APIs accounted for 21.11 percent.

Market access

Based on table 19, in term of accessibility of antineoplastic drug by number of APIs, Thailand accessed to antineoplastic drugs nearly half of WHO items, it was approximately 42.22-48.89 percent. The accessibility was lower than the US and the UK. Among selected ASAEN countries, the accessibility of Thailand had more items than Malaysia (35-37.78%), and had a few percentages lower than Singapore (51.11%). Based on data in table 20, the cumulative API during 1983-2016 April, were divided into 5 periods for more detailed analysis on whether the change of drug registration regulation development in Thailand had any impact on market access of antineoplastic medicines.

1. Before 1983 (<=1982)

   Drug registration system in Thailand required renewal product license or marketing authorization every five years. There was no electronic record for those registered before 1983 in Thai FDA database. Thus, the products renewed their license after 1982 would be recorded as their first MAA in Thailand. However, to avoid this confounding effect, only items registered in US after 1982 were included in the analysis. Since US had the most items with MAA, the study decided to reference time lag of antineoplastic drugs in Thailand with US MAA.
2. The period 1983-1990

   The new drug classification was started in 1991, thus, only generic drug was classified for drug registration during this period. APIs that registered before 1991

was legally classified as “Generic (G)” group. New APIs registered since 1991 was legally classified as “New Drug (N)” group.

3. The period 1991- 1998

   Drug registration was classified in two types: Generic drug and New drug in this period.

4. The 1999-2006

   During this period, regulation for New generic drug (NG) registration was implemented including Biological product was coded as a separate category in drug registration by the new regulation. Therefore, during this period, drug registration regulations were separated in four types such as generic drug, new drug, biological product, and new generic.

5. The period 2007-2016 (April)

   During this period, ASEAN harmonization of drug registration was full implementation in ASEAN countries and ASEAN Common Technical Dossier (ACTD) was adopted for drug registration in Malaysia and Singapore by 31 December 2005, in Thailand by 31 December 2006, in Indonesia and Vietnam by 31 December 2007, in Brunei Darussalum, Cambodia, Lao PDR and Philippines by 31 December 2008. Moreover, during this period cancer drug and HIV drugs were classified as the priority review by Thai FDA.

In the table 20, the number of APIs represented number lag in each period of time. Before 1982, the antineoplastic drugs seemed to be highly accessed in the US market above UK, EMA including Thailand, Singapore, and Malaysia. This could partly due to good electronic record of USFDA information system comparing with other regulatory agencies. The MAA information was thus available and easy accessible.

Based on the reviewed literature, drug registration in each country, including Thailand, Malaysia, Singapore, and EMA, was started in 1983,1985,1987 and 1995 respectively, thus MAA data of these countries were not found before 1982. The total number of antineoplastic drugs was increased in every country with more items were market authorized. However, the number of MAA in each period was also increased from 1983

till 2016 except in Malaysia. The increases of APIs during each period in ASEAN countries was less than US, UK, and EMA, particularly in Malaysia of which the number of newly registered APIs seemed to be compromised during 2007-2016. Since US, UK, and EMA were research and development based and were referenced by the rest of the world, innovation products usually started their first MAA in either US, or EU before distributing to other regions.

Table 20: Number of active pharmaceutical ingredient (API) available in each country across period of drug registration regulation development in Thailand

Country or Institute	Number of Active Pharmaceutical Ingrdient (API)					
	Total	<=1982	1983-1990	1991-1998	1999-2006	2007-2016(Apr)
WHO	180					
US	130	28	5	21	30	46
EMA	75			3	26	46
UK	119	1	6	18	38	56
SG	92		14	15	18	45
MAL	68		15	14	21	18
TH	88		18	19	21	30
NLEM-TH	38	11		5	10	12
EML-WHO	34					

Table 21, revealed the respectable accessibility in each year during period 2007-2016. The accessibility in the US, UK, and EMA were mostly the same level with higher above 50 APIs in total. But it was varied in each year due to the discovery of new innovative product. The accessibility in ASEAN countries was mostly based on the first MAA in the referenced country such as US and EMA. Even though, all ASEAN countries adopted the ASEAN Common Technical Dossier (ACTD) submission template to use in their country for product registration, but the accessibility by number of antineoplastic APIs in Thailand was still lower than in Singapore by overall of 15 APIs during this period. An analysis by year illustrated that a larger gap had significantly observed after 2012. While Malaysia revealed no API found since 2013 causing the increased number of APIs during the last period seemed to lower than other

compared countries. This might due to some changes in the system of drug registration after 2012.

Overall, the accessibility by number of APIs in Singapore, even better, was shown not much difference from Thailand and Malaysia. However, for the period of 2007-2016 or to be specific since 2013, Singapore seemed to have more antineoplastic APIs approved than Thailand and Malaysia. These differences could be from the specific regulation or process of drug registration of each country that could pose as the barrier or supporting factor to the market entry and affected antineoplastic drugs.

Table 21: Number of active pharmaceutical ingredient (API) across country during 2007 – April 2016

Year	Number of Active Pharmaceutical Ingrdient (API) in each year during 2007 - 2016 April						
	US	EMA	UK	SG	MAL	TH	NLEM
2007	4	6	6	6	7	5	
2008	1	2	3	2	2	3	
2009	5	4	6	5	3	4	
2010	2	3	4	2	3	1	
2011	6	4	4	4	2	2	
2012	10	8	8	3	1	5	
2013	4	9	9	5		3	5
2014	10	8	8	9		3	
2015	8	7	7	5		2	5
2016(Apr)		1	1	4		2	2
total	**50**	**52**	**56**	**45**	**18**	**30**	**12**

Patient access

Table 19, 38 antineoplastic APIs was found on NLEM or approximately 21 % of all APIs that could be accessed by patients in Thailand with less or no financial burden. Comparison with the EML-WHO (18.89) as a priority list, NLEM had 4 more APIs above the standard listed of WHO (EML-WHO). Table 20, during five periods, the number of APIs listed on NLEM was fluctuated due to the decision maker of NLEM and frequency of revision. However, during 2007- April 2016, there were three updated versions found in 2013, 2015, and 2016. The antineoplastic drugs for cancer treatment were detailed in each version as in table 22 and figure 10. There were 11 Antineoplastic

APIs on first or 1981 version of NLEM. This first version of NLEM was before the drug registration database implemented in Thailand. These 11 APIs had been maintained for 10 years until the 4th version. The accessibility of antineoplastic for Thai patients was improved since then as seen in the figure 10.

Table 22: The chronological number of national list of essential drug in Thailand

No.	National List of Essential Medicine (NLEM)		Antineoplastic drug found in NLEM	
	Version	Implemented time of each version	Number of ATC name	ATC name
1	1981 (B.E 2524)	16 Aug 1981 (implemented in August 1981 and adjusted / revised in 1982)	11	Bleomycin, busulfan, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, fluorouracil, melphalan, mercaptopurine, methotrexate, vincristine
2	1985 (B.E 2528)	1985 (NLEM volume 1)	-	
		1986 (NLEM volume 2)	11	Same items as in 1982
3	1987 (B.E 2530)	1987	11	Same items as in 1982
4	1992 (B.E 2535)	18-Jun-92	13	Cisplatin and dactinomycin were added on the list of 1982
5	1996 (B.E 2539)	31 Oct 1996 (started to control use level as A, B, C)	17	Asparaginase, epirubicin, etoposide and paclitaxel were added on the list of 1992
6	1999 (B.E 2542)	29 Jan 1999 ((started to control use level as C, D, E(2))	28	Carboplatin, carmustine, hydroxycarbamide, idarubicin, ifosfamide, lomustine, mitomycin, mitoxantrone, tegafur & uracil (UFT), thioguanine and vinblastine were added on the list of 1996
7	2004 (B.E 2547)	27-Dec-04	26	Deleted three items (tegafur & uracil (UFT), lomustine and epirubicin) from the list of 1999, and added gemcitabine on the list of 1999
8	2008 (B.E 2551)	23-Jan-08	26	Same as the list of 2004
9	2013 (B.E 2556)	30-Sep-13	31	Docetaxel, imatinib, oxaliplatin, tegafur & uracil (UFT) and tretinoin was added on list of 2008
10	2015 (B.E. 2558)	10-Aug-15	36	Arsenic trioxide, dacarbazine, dasatinib and nilotinib were added on the list of 2013
11	2016 (B.E. 2559)	12-Apr-16	38	Carmustine and procarbazine were added on the list of 2015

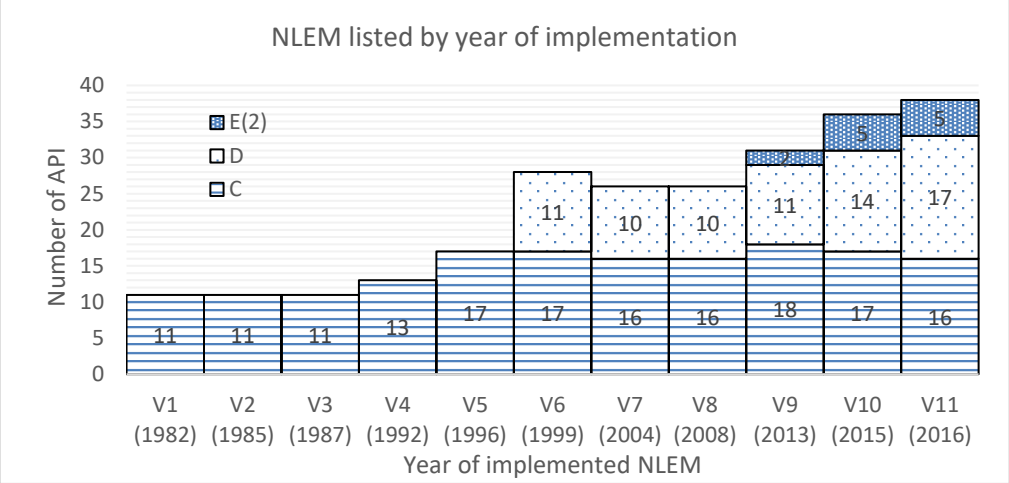


Figure 10: The chronological number of national list of essential medicine (NLEM) in Thailand

The access to anticancer drugs was developed widely to high cost drugs which were controlled by specifying prescribers for cancer treatment since 1999. However, to control utilization of high cost medicines, several measures were implemented including, clinical practice guideline, recommended cancer treatment regimens, as well as, required drug utilization evaluation for a specified class of NLEM. The NLEM had classified essential medicines into 5 major groups, A, B, C, D, and E. Anticancer medicines could fall under 3 classifications, including Groups C, D, and E (2). Those items that were classified under D and E(2) would be closely monitored via drug utilization evaluation (DUE) before the hospital could be reimbursed. Since the drug reimbursement in Thailand was based on the NLEM list, the items of antineoplastic API were expected to influence on number of patients accessing the treatment and the number of MAA of listed APIs were expected to increase.

4.2.1.1.2 Number of active pharmaceutical ingredient by ATC system

From 180 antineoplastic APIs of WHO ATC, they were grouped into 5 pharmacological groups as ACT level 3. Each pharmacological group has a number of chemical groups (ACT level-4) and has a number of APIs or chemical substances (ATC level-5) as in

table 23 and 24. Since, products which were approved under the centralized procedure by EMA, were also valid in all EU members including UK, EMA, therefore, EMA was not presented in these tables: 23 and 24.

Table 23, detailed number of pharmacological groups, number of chemical groups under each pharmacological group, as well as number of APIs or chemical substances under each chemical group.

The ratios between number of chemical groups (level-4) of antineoplastic drug in each country and WHO were 20:23(US: WHO), 21:23 (UK: WHO), 19:23(SG: WHO), 18:23 (MAL: WHO), 20:23 (TH: WHO), 18:23 (NLEM-TH: WHO), 16:23 (EML-WHO: WHO). When compared with the total number of chemical groups of WHO, the percentage (%) of chemical group of antineoplastic drug of each country was highest in UK (91.30), in US and TH (86.96), in SG (82.61), in MAL and NLEM-TH (78.26) and EML-WHO (69.57).

The detail distribution of APIs for each chemical group was presented in table 24. Each country had anticancer drugs in all pharmacological groups and most of chemical groups except a few. The WHO only recommended 2 out of 6 chemical groups for alkylating agents: nitrogen mustard and other alkylating agents on the EML list. Colchicine derivatives, other plant alkaloids, and sensitizers were among chemical groups under other pharmacological groups that were not recommended by the EML-WHO. The epoxides under alkylating agents and the colchicine derivatives under plant alkaloids had no product registered in all studied countries. Of Alkylating agents, the ethylene imines chemical group had one chemical substance registered in US and UK but none in ASEAN countries, also none was recommended by the EML-WHO. While UK did not have other plant alkaloids, Singapore did not register methylhydrazines, Malaysia did not have product for methylhydrazines and sensitizers, Thailand had product for all chemical groups that other studied countries had except ethylene imines. The NLEM also contained products from all chemical groups except sensitizers of "other antineoplastic agents" pharmacological group. Thus, both market and patient accessibility of antineoplastic chemical group should not have any problem.

Consideration on chemical substances or APIs, the percentage of number of chemical substances as compared with WHO ATC was highest in US (72.22), with 66.11% in UK, 51.11% in Singapore, 48.89% in Thailand, 37.78% in Malaysia, 21.11% in Thai NLEM and 18.89% in EML-WHO. However, when considering APIs available in each pharmacological group, for US, group X or "other antineoplastic agents" had the highest percentage of number of APIs at 80% or 82 out of 102 APIs, cytotoxic antibiotics and related substances had the second highest percentage at 69% or 11 out of 16 APIs, following with antimetabolites (68%, 15 out of 22 APIs), plant alkaloids and other natural products (57%, 8 out of 14 APIs), and alkylating agents (50% 13 out of 26 APIs). Other countries including UK, Singapore, Malaysia and Thailand had different distribution of chemical substances. The two groups with the highest percentage of APIs were antimetabolites and plant alkaloids. Only Singapore that had about the same percentage (64%) of APIs between these 2 groups, the rest had the antimetabolite group as the largest percentage of APIs, 73% for UK and Thailand and 64% for Malaysia. The pharmacological group X or "other antineoplastic agents" in UK even had the third highest percentage but still contained 70% of all items in this group. While EML-WHO recommended more percentage for plant alkaloids and antimetabolites, Thai NLEM chose the highest percentage of APIs from cytotoxic antibody group. The pharmacological group X which had the most number of APIs at 102 chemical substances could be the increasing trend in cancer treatments. Both US and UK had high proportion of APIs from this group.

As for patient access through NLEM, cytotoxic antibodies, antimetabolites, and plant alkaloids had the largest percentages of APIs with 38%, 36% and 36% respectively. Even the percentage was not the highest but the number of APIs under the pharmacological group X "other antineoplastic agents" had the most number with 12 chemical substances. To increase patient access and support the advance in anticancer treatment, 12 APIs for NLEM had been added during the last 3 revisions since 2013 (table 22).

Table 23: Summary of chemical groups and chemical substances

Pharmacological group (ATC code Level 3)	Chemical group (ATC code Level 4)								Chemical substance (ATC code Level 5)							
Items/country	WHO	US	UK	SG	MAL	TH	NLEM	WHO-EML	WHO	US	UK	SG	MAL	TH	NLEM	WHO-EML
A: Alkylating Agents	6	5	5	4	4	4	4	2	26	13	12	9	9 (8)*	9 (8)*	7	5
B: Anitimetabolites	3	3	3	3	3	3	3	3	22	15	16	14	14	16 (14)*	8	8
C: Plant alkaloids and other natural Product	5	3	4	4	4	4	3	3	14	8	10	9	8	9 (7)*	5	6
D : Cyctotoxic antibiotics and related substance	3	3	3	3	3 (2)*	3	3	3	16	11	9	9	8 (7)*	10 (8)*	6	4
X: Other antineoplastic agents	6	6	6	5	4	6 (5)*	5	5	102	83 (82)*	72	51	29 (26)*	44 (39)*	12	11
Total	23	20	21	19	18 (17)*	20 (19)*	18	16	180	130 (129)*	119	92	68 (63)*	88 (76)*	38	34
%	100	86.96	91.30	82.61	78.26 (73.91)*	86.96 (82.61)*	78.26	69.57	100	72.22 (71.67)*	66.11	51.11	37.78 (35)*	48.89 (42.22)*	21.11	18.89

( )*number of chemical substances which were still available at April 30, 2016
NLEM: National list of Essential Medicines EML-WHO: Essential Medicines List of WHO ATC: Anatomical Therapeutic Classification UK: United Kingdom TH: Thailand US: The United States SG: Singapore MAL: Malaysia WHO: World Health Organization ATC-L4: ATC code level 4

Table 24: Comparison of each country, number of chemical substance (or API) under chemical group (ATC-code level 4) of antineoplastic agents

Pharmacological group (ATC code level 3): chemical group (ATC-code Level 4)			Number of chemical substance or API (ATC-code level 5)							
			WHO	US	UK	SG	MAL	TH	NLEM	EML-WHO
A: Alkylating Agents	ATC - L4	A: Nitrogen mustard analogues	8	5	5	5	4	4	4	4
		B: Alkyl sulfonates	3	1	2	1	1	1	1	-
		C:Ethylene imines	3	1	1	-	-	-	-	-
		D:Nitrosoureas	7	3	2	1	2 (1)*	2 (1)*	1	-
		G:Epoxides	1	-	-	-	-	-	-	-
		X:Other alkylating agents	4	3	2	2	2	2	1	1
	Total		26	13	12	9	9 (8)*	9 (8)*	7	5
	%		100	50	46.154	34.62	34.62 (30.77)*	34.62 (30.77)*	26.92	19.23
B: Antimetabolites	ATC - L4	A :Folic acid analogues	4	3	3	4	2	2	1	1
		B:Purine analogues	6	6	6	3	4	5 (4)*	2	3
		C:Pyrimidine analogues	12	6	7	7	8	9 (8)*	5	4
	Total		22	15	16	14	14	16 (14)*	8	8
	%		100	68.18	72.73	63.64	63.64	72.73 (63.64)*	36.36	38.36
C: Plant alkaloids and other natural Product	ATC-L4	A: Vinca alkaloids and analogues	6	3	5	4	3	4 (2)*	2	3
		B: Podophyllotoxin derivatives	2	2	1	1	1	1	1	1
		C: Colchicine derivatives	1	-	-	-	-	-	-	-
		D: Taxanes	4	3	3	3	3	3	2	2
		X: Other plant alkaloids	1	-	1	1	1	1	-	-
	Total		14	8	10	9	8	9 (7)*	5	6
	%		100	57.14	71.43	64.29	57.14	64.29 (50)*	35.71	42.86
D: Cytotoxic antibiotics and related substance	ATC-L4	A: Actinomycines	1	1	1	1	1	1	1	1
		B: Anthracyclines and related substances	11	6	6	5	5	6 (4)*	3	2
		C: Other cytotoxic antibiotics	4	4	2	3	2	3	2	1
	Total		16	11	9	9	8 (7)*	10 (8)*	6	4
	%		100	68.75	56.25	56.25	50 (43.75)*	62.5 (50)*	37.5	25
X: Other antineoplastic agents	ATC-L4	A: Platinum compounds	5	3	3	3	3	3	3	3
		B: Methylhydrazines	1	1	1	-	-	1	1	1
		C: Monoclonal antibodies	21	18 (17)*	17	13	4	8 (7)*	1	2
		D: Sensitizers used in photodynamic /Radia.-T	5	3	4	1	-	1(0)*	-	-
		E: Protein kinase inhibitors	33	28	28	23	11 (10)*	16	3	1
		X: Other antineoplastic agents	37	30	19	11	11 (9)*	15 (12)*	4	4
	Total		102	83 (82)*	72	51	29 (26)*	44 (39)*	12	11
	%		100	81.37 (80.39)*	70.59	50	28.43 (25.49)*	43.14 (38.24)*	11.76	10.78
Total: Chemical substances			**180**	**130 (129)***	**119**	**92**	**68 (63)***	**88 (76)***	**38**	**34**
%			**100**	**72.22 (71.67)***	**66.11**	**51.11**	**37.78 (35)***	**48.89 (42.22)***	**21.11**	**18.89**

Note: ( ) * number of Chemical substance which was still available at April 30, 2016
NLEM: National list of Essential Medicine, EML-WHO: Essential Medicines List of WHO, ATC: Anatomical Therapeutic Classification UK: United Kingdom, TH: Thailand US: The United States SG: Singapore, MAL: Malaysia, WHO: World Health Organization ATC-L4: ATC code level 4

4.2.1.1.3 Number of marketing authorization approval in Thailand

From 88 APIs, the total of 935 marketing authorization approvals (MAAs) were found accounted for 10.63 MAAs per API. However, in April 2016, only 76 APIs had drug products registered with Thai FDA with 402 MAAs accounted for 5.29 MAAs per API as shown in Table 25. The rest of MAAs or 533 MAAs were withdrawn or cancelled for some reasons.

Table 25 explained the accessibility of antineoplastic drugs in each pharmacological group in term of ratio as MAA per API. Each API having an average of 5.29 MAAs or drug products available in the market reflected that each chemical substance carried products authorized with different strengths and/or dosage forms or had products authorized by more than one traders. The chemical group of platinum compounds under the "other antineoplastic agents" pharmacological group held the highest MAAs per API at 16.67 and folic analogue chemical group of "antimetabolites" at 15.00 MAAs per API. The highest average MAAs per API was found in the group of plant alkaloids with average 8.71 MAAs per API. Plant alkaloids had 2 chemical groups, taxanes and podophyllotoxin derivatives, with more than 12 MAAs per API. With the largest number of APIs (39 APIs) and MAAs (152 MAAs), the pharmacological group of "other antineoplastic agents" had the lowest average MAAs per API at 3.90. The lowest average MAAs per API might not reflect low level of access but only showed few competitive products or few varieties on strengths and/or dosage forms.

Consideration in term of patient access, 38 APIs of NLEM held a cumulative 714 MAAs since 1981 with only 285 MAAs available in April 2016, shown in table 26. The ratio of MAAs per API for NLEM was consistent with overall market registration. Platinum compounds group carried the largest MAAs per API at 16.67 since all registered items were listed in NLEM. The pharmacological group of "plant alkaloids" had the highest MAAs per API at 8.71. When compared between overall market registration (table 25) and NLEM (table 26), all pharmacological groups except alkylating agents had higher ratio of MAAs per API. This evidenced that items listed NLEM were more attractive for pharmaceutical companies to enter the market due to

accessibility by larger group of population as well as reimbursement by three major health schemes of Thailand including civil servant medical benefit scheme (CSMBS), social security scheme (SSS), and universal coverage scheme (UC).

Table 25: Total number of MAA available in Thailand classified pharmacological and chemical group (ATC-code level 3 and 4)

Pharmacological group(ATC-Code Level 3) and Chemical group (ATC-Code Level 3)			Chemical substance (ATC-code level 5)					
			Cumulative number since 1983 till April 2016			Available number at April 2016		
			API	MAA	MAA per API	API	MAA	MAA per API
A: Alkylating Agents	ATC L4	A: Nitrogen mustard analogues	4	47	11.75	4	17	4.25
		B: Alkyl sulfonates	1	7	7.00	1	1	1.00
		C: Ethylene imines						
		D: Nitrosoureas	2	5	2.50	1	3	3.00
		G: Epoxides						
		X: Other alkylating agents	2	32	16.00	2	17	8.50
	Total		**9**	**91**	**10.11**	**8**	**38**	**4.75**
B: Antimetabolites	ATC L4	A :Folic acid analogues	2	84	42.00	2	30	15.00
		B:Purine analogues	5	31	6.20	4	8	2.00
		C:Pyrimidine analogues	9	146	16.22	8	70	8.75
	Total		**16**	**261**	**16.31**	**14**	**108**	**7.71**
C: Plant alkaloids and other natural products	ATC L4	A: Vinca alkaloids and analogues	4	61	15.25	2	11	5.50
		B: Podophyllotoxin derivatives	1	34	34.00	1	12	12.00
		C: Colchicine derivatives						
		D: Taxanes	3	76	25.33	3	37	12.33
		X: Other plant alkaloids	1	1	1.00	1	1	1.00
	Total		**9**	**172**	**19.11**	**7**	**61**	**8.71**
D: Cytotoxic antibiotics and related substances	ATC L4	A: Actinomycines	1	5	5.00	1	1	1.00
		B: Anthracyclines and related substances	6	87	14.50	4	30	7.50
		C: Other cytotoxic antibiotics	3	25	8.33	3	12	4.00
	Total		**10**	**117**	**11.70**	**8**	**43**	**5.38**
X: Other antineoplastic agents	ATC L4	A: Platinum compounds	3	139	46.33	3	50	16.67
		B: Methylhydrazines	1	2	2.00	1	1	1.00
		C: Monoclonal antibodies	8	24	3.00	7	18	2.57
		D: Sensitizers used in photodynamic /Radia.-T	1	1	1.00			
		E: Protein kinase inhibitors	16	64	4.00	16	50	3.13
		X: Other antineoplastic agents	15	64	4.27	12	33	2.75
	Total		**44**	**294**	**6.68**	**39**	**152**	**3.90**
Total			**88**	**935**	**10.63**	**76**	**402**	**5.29**

Table 26: Total number of MAA available in NLEM classified pharmacological and chemical group (ATC-code level 3 and 4)

Pharmacological group(ATC-Code Level 3) and Chemical group (ATC-Code Level 3)			Chemical substance (ATC-code level 5)				
			NLEM	Cumulative number since 1981		Available number at April 2016	
				MAA	MAA per API	MAA	MAA per API
A: Alkylating Agents	ATC L4	A: Nitrogen mustard analogues	4	47	11.75	17	4.25
		B: Alkyl sulfonates	1	7	7.00	1	1.00
		C:Ethylene imines					
		D:Nitrosoureas	1	4	4.00	3	3.00
		G:Epoxides					
		X:Other alkylating agents	1	5	5.00	4	4.00
	Total		**7**	**63**	**9.00**	**25**	**3.57**
B: Antimetabolites	ATC L4	A :Folic acid analogues	1	79	79.00	25	25.00
		B:Purine analogues	2	13	6.50	4	2.00
		C:Pyrimidine analogues	5	136	27.20	63	12.60
	Total		**8**	**228**	**28.50**	**92**	**11.50**
C: Plant alkaloids and other natural products	ATC L4	A: Vinca alkaloids and analogues	2 (1)*	48	24.00	6	6.00
		B: Podophyllotoxin derivatives	1	34	34.00	12	12.00
		C: Colchicine derivatives					
		D: Taxanes	2	74	37.00	35	17.50
		X: Other plant alkaloids					
	Total		**5 (4)***	**156**	**31.10**	**53**	**13.25**
D: Cytotoxic antibiotics and related substances	ATC L4	A: Actinomycines	1	5	5.00	1	1.00
		B: Anthracyclines and related substances	3	68	22.67	28	9.33
		C: Other cytotoxic antibiotics	2	23	11.50	10	5.00
	Total		**6**	**96**	**16.00**	**39**	**6.50**
X: Other antineoplastic agents	ATC L4	A: Platinum compounds	3	139	46.33	50	16.67
		B: Methylhydrazines	1	2	2.00	1	1.00
		C: Monoclonal antibodies	1	8	8.00	8	8.00
		D: Sensitizers used in photodynamic /Radia.-T					
		E: Protein kinase inhibitors	3	14	4.67	12	4.00
		X: Other antineoplastic agents	4	8	2.00	5	1.25
	Total		**12**	**171**	**14.25**	**76**	**6.33**
Total			**38 (37)***	**714**	**18.79**	**285**	**7.70**

* : the last MAA of vinblastine was found cancelation in 2015 (acessed dated April 2016)

Marketing authorization approval classified by drug registration classification

Based on registration system in Thailand, registered drug products would be assigned one of the three statuses: new drug (N or NC for drug products that were during safety monitoring period), new generic drug (NG), and generic (G). With the fast increase of biologic drug products, the new drug status was further specified as new chemical drug (N or NC) or new biological drug (NB or NBC). From 88 APIs, there were 45 APIs classified as New Drugs, 29 APIs as Generic Drugs and 14 APIs as New Generic Drug (NG) as shown in figure 11. Two APIs used to be generic drugs (doxorubicin, melphalan) were later registered as new drug under its "secondary dosage form". Nine new drugs were also classified as new biological products (NBC) because its biologic nature.

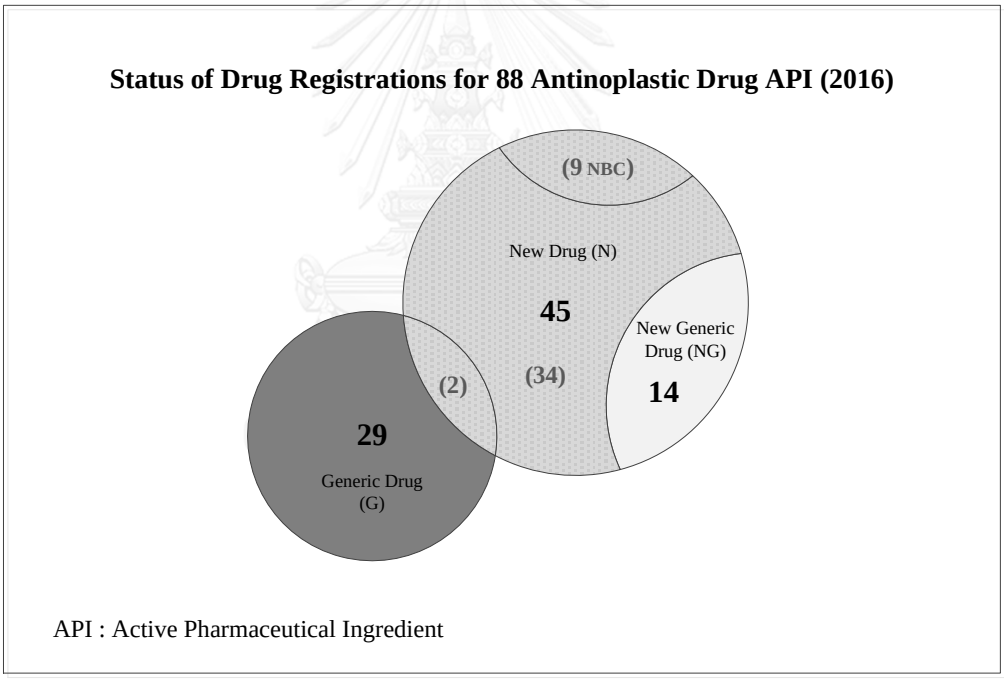


Figure 11: Number of API based on the last status of drug registration classification

In term of market access, new drugs composed majority at 51.14% of antineoplastic APIs and ratio MAA/API was approximately 2.33 while 29 generic drug APIs (32.95%) had 6.18 MAA/API, and new generic (NG), accounted for 15.91% of items, had 12.36 MAA/API. New drug (N) items were normally innovative drugs of which owners were

multinational companies. Most or all of new drug items had no competitor when they were first launched into the market and it took several years before the first new generic drug item got an MAA. The MAAs of new drug were thus based on the different strengths, dosage forms, and different sources of drug manufacturers. The ratio MAA/API of N was generally low compared with G and NG. The accessibility of antineoplastic drugs was expanded when more NG products were approved evidenced by high MAA/API ratio of NG above N and G items.

Table 27: Number of MAA of active pharmaceutical ingredient (API) across the drug registration classification in Thailand

Type of drug registration classification	Cumulative approval since 1983 till April 2016			Available approval in April 2016		
	API	MAA	MAA/API	API	MAA	MAA/API
Generic Drug (G)	29	458	15.79	22	136	6.18
New Drug (N)	45	138	3.07	40	93	2.33
New Generic Drug (NG)	14	339	24.21	14	173	12.36
Antineoplastic drug for all classification	88	935	10.63	76	402	5.29

Table 28 revealed the accessibility in term of patient access. Out of 38 APIs listed by NLEM, 21 new APIs still composed 55.26% of all NLEM items with 6.56 MAA/API ratio, while 9 generic APIs was accounted for 23.68% and 2.56 MAA/API, and 8 NG APIs represented 21.05% with16.13 MAA/API. Same as market access, the ratio MAA/API of NG was found high among three drug classifications. NLEM items also had more MAA/API except for generic drugs.

Table 28: Number of MAA of active pharmaceutical ingredient (API) across the drug registration classification on the NLEM

Type of drug registration classification	Cumulative approval since 1981 till April 2016 (NLEM)			Available approval in April 2016 (NLEM)		
	API	MAA	MAA/API	API	MAA	MAA/API
Generic Drug (G)	9	37	4.11	9	23	2.56
New Drug (N)	21	433	20.62	20*	133	6.65
New Generic Drug (NG)	8	244	30.50	8	129	16.13
Antineoplastic drug for all classification	38	714	18.79	37*	285	7.70

* MAA of vinblastine was canceled in 2015,

Marketing authorization approval classified by biological product

Twenty-three items of Antineoplastic APIs were biological drugs, which were classified according to USFDA (21 APIs) and Thai FDA (10 APIs). There were two APIs, nimotuzumab and temsirolimus, classified as new biological drugs by Thai FDA but not by USFDA. Temsirolimus was a new chemical entity in US and nimotuzumab was not available in US. The total biological list was in the appendix 1. One biologic API, asparaginase, was classified as generic drug registration and nine other APIs were classified as new biological drugs, including nimotuzumab and temsirolimus. Thus there were total of 10 biologic items out of 88 APIs in Thailand. The average number of MAA/APIs was 2.9 (29/10) and active only 2.2 (22/10) in April 2016 as in table 29. Of these 10 APIs, 2 were listed in NLEM for widely accessed by patients. These 2 items had an average number of MAA/API of 6 (12/2) and active only 5 (10/2) MAA/API in April 2016 as shown in table 29

Table 29: Number of marketing authorization approval (MAA) by biological registration classification in Thailand.

Type of drug registration classification	Cumulative approval since 1983 till April 2016			Available in April 2016		
	API	MAA	MAA/API	API	MAA	MAA/API
Biological product classified by both USFDA and Thai FDA	10*	29	2.90	10*	22	2.20
*one API, asparaginase was classified by Thai FDA as a generic drug (G)						

In term patient access, 2 items of biological APIs were found on NLEM. The total number of MAA of Antineoplastic API was 12/10 (6) in term of ratio MAA/API (a cumulative number since 1983) and only 10/2 (5) of ratio MAA/API were available at April 2016 as shown in table 30

Table 30: Number of marketing authorization approval (MAA) by biological registration classification on NLEM

Type of drug registration classification	Cumulative approval since 1981 till April 2016 (NLEM)			Available in April 2016 (NLEM)		
	API	MAA	MAA/API	API	MAA	MAA/API
Biological product classified by both USFDA and Thai FDA	2*	12	6	2*	10	5
*one API, asparaginase was classified by Thai FDA as a generic drug (G)						

Marketing authorization approval classified by targeted cell therapy

According to standard list of the targeted cell therapies for cancer classified by Abramson, R. (Abramson, 2016), there were 25 of 88 API items as targeted cell therapy in Thailand. The WHO list composed 52 items and US had the most targeted cell therapy at 51APIs and Malaysia had the least number of this group at 16 APIs.

Table 31: Number of API classified as a targeted cell therapies across the countries

Country or item listed	Number of API		% TGC
	Total	Targeted cell therapies (TGC)	
WHO	180	52	100
US	130	51	98.08
UK	119	45	86.54
EMA	75	45	86.54
SG	92	35	67.31
MAL	68	16	30.77
TH	88	25	48.08
New generic drug (NG)	14	1	1.92
NLEM	38	4	7.69
EML-WHO	34	3	5.77

In term of market access, the accessibility of the new trend of treatment “Targeted cell therapy” was found in Thailand 48.08% of WHO, meanwhile in Singapore 67.31% as seen in table 31. The ratio MAA/API of “Target cell therapy” was 3.44 (86/25) as a cumulative number since 1983 and only 2.84 (71/25) MAA/API were available in April 2016 as in table 32. The ratio 2.84 of MAA/API reflected very few product items on the market because the targeted cell therapy was classified as a new drug. During the period of this study, there was only one of 25 targeted cell therapy APIs, imatinib, that had a new generic drug available in Thai market. The number of MAAs for targeted cell therapy drugs was mostly from innovative companies and registered in different strengths.

In term of patient access, four targeted cell therapies, including dasatinib, imatinib, nilotinib and trastuzumab, were found on NLEM of 2016 under the category E (2). Meanwhile, only three targeted cell therapies, imatinib, rituximab and trastuzumab, were found in EML-WHO. The ratio of 5.5 MAA/API of “Target cell therapy” on NLEM, was cumulated since 1983 and only 5 MAA/API was available in April 2016 as in the table 33.

Table 32: Number of marketing authorization approval (MAA) by targeted cell therapies

Type of drug registration classification	Number of API or MAA					
	Cumulative approval since 1983 till April 2016			Available in April 2016		
	API	MAA	MAA/API	API	MAA	MAA/API
Targeted cell therapies in Thailand	25	86	3.44	25	71	2.84

Table 33: Number of marketing authorization approval (MAA) by targeted cell therapies on NLEM

Type of drug registration classification	Number of API or MAA					
	Cumulative approval since 1981 till April 2016 (NLEM)			Available in April 2016 (NLEM)		
	API	MAA	MAA/API	API	MAA	MAA/API
Targeted cell therapies in Thailand	4	22	5.50	4	20	5.00

Marketing authorization approval classified by country of headquarter

The country of headquarter was defined as the country where headquarter (HQ) of product owner (product license holder in Thailand or drug manufacturer) was located. The data was collected through the search for product owner of the first brand of antineoplastic API in Thailand. Then, the country of HQ of product owner was identified and classified by country zone

Eight APIs was unknown for their company HQ. For the unknown HQ, the search for the local imported company in Thailand and country or origin of APIs were conducted. It was found that production of these unknown HQ items was under many sources such as manufacturer from India, South Korea, China, Japan, Israel, Australia, Taiwan, USA, Cuba. However, they are recorded as unknown HQ items.

The market accessibility of antineoplastic drugs reflected by MAA/API showed that antineoplastic drugs imported to Thailand mostly from EU with MAA/API of 6.34 and down to 3.79 in 2016. When compared items from the US, EU, and Asia, MAA/API was highest among items imported from US with active MAA/API at 6 as in the table 34. Another interesting evidence was those unknown, it was found having 33.50 MAA/API with all product registration but only 13 active MAA/API. Even active MAA/API was much reduced from total registered, it was still substantial different from those imported from US. Since there was not much information about the origin of these products, not much further analysis could be conducted.

Table 34: Number of marketing authorization approval (MAA) by country zone based on the country of origin which the headquarter is located.

Zone of country of origin	Number of API and MAA					
	Cumulative data since 1983 till April 2016			Available in April 2016		
	API	MAA	MAA/API	API	MAA	MAA/API
US	31	352	11.35	27	162	6.00
EU*	38	241	6.34	34	129	3.79
Asia**	11	74	6.73	9	33	3.67
Unknown	8	268	33.50	6	78	13.00
Total	88	935	10.63	76	402	5.29

EU*: France, German, Ireland, Swiss, UK, Hungary. Asia** : Japan, Taiwan, SG for Cuba manufaturer

Similar pattern of MAA/API was found for items list on NLEM. The items imported from US held the most MAA/API at 8.92, followed with EU and Asia at 5.36, 5.00 MAA/API respectively. The unknown HQ also had considerable MAA/API at 15.60. Items listed under NLEM had drawn more market approval as reflected by higher MAA/API across all origins as in the table 35

Table 35: Number of marketing authorization approval (MAA) by country zone based on the country of origin which the headquarter is located for NLEM

Zone of country of origin	Number of API and MAA					
	Cumulative data since 1981 till April 2016 (NLEM)			Available in April 2016 (NLEM)		
	API	MAA	MAA/API	API	MAA	MAA/API
US	12	232	19.33	12	107	8.92
EU**	15	154	10.27	14*	75	5.36
Asia***	5	62	12.40	5	25	5.00
Unknown	6	266	44.33	5	78	15.60
Total	38	714	18.79	37	285	7.70

* : MAA of vinblastine was cancel by company. EU**: France, German, Ireland, Swiss, UK, Hungary. Asia*** : Japan, Taiwan, SG for Cuba manufaturer

4.2.1.2 Time lag

Regarding to the market time lag, or another term of launch delay of drug; the market time lag was measured by time difference between the first Marketing Authorization Approval (MAA) available in the world and the first MAA available in Thailand. Meanwhile, among the selected ASEAN countries, the market time lag of the first MAA available in Thailand compared with Malaysia and Singapore were also presented. The pathway of drug access was presented in term of time delay to the market as a market access; including the delay to patient as a patient access. The calculate time lag of docetaxel was shown as an example in the Figure 12

To standardize for comparison purpose, the study selected the US as the main comparator country as a first country of MAA. The time difference between the first MAA of US and the first MAA of other countries, UK, Singapore (SG), Thailand (TH), Malaysia (MAL), European Medicines Agency (EMA) were calculated. It was confirmed with all positive time lag. Then, the US was selected as the main comparator country as a first country of MAA

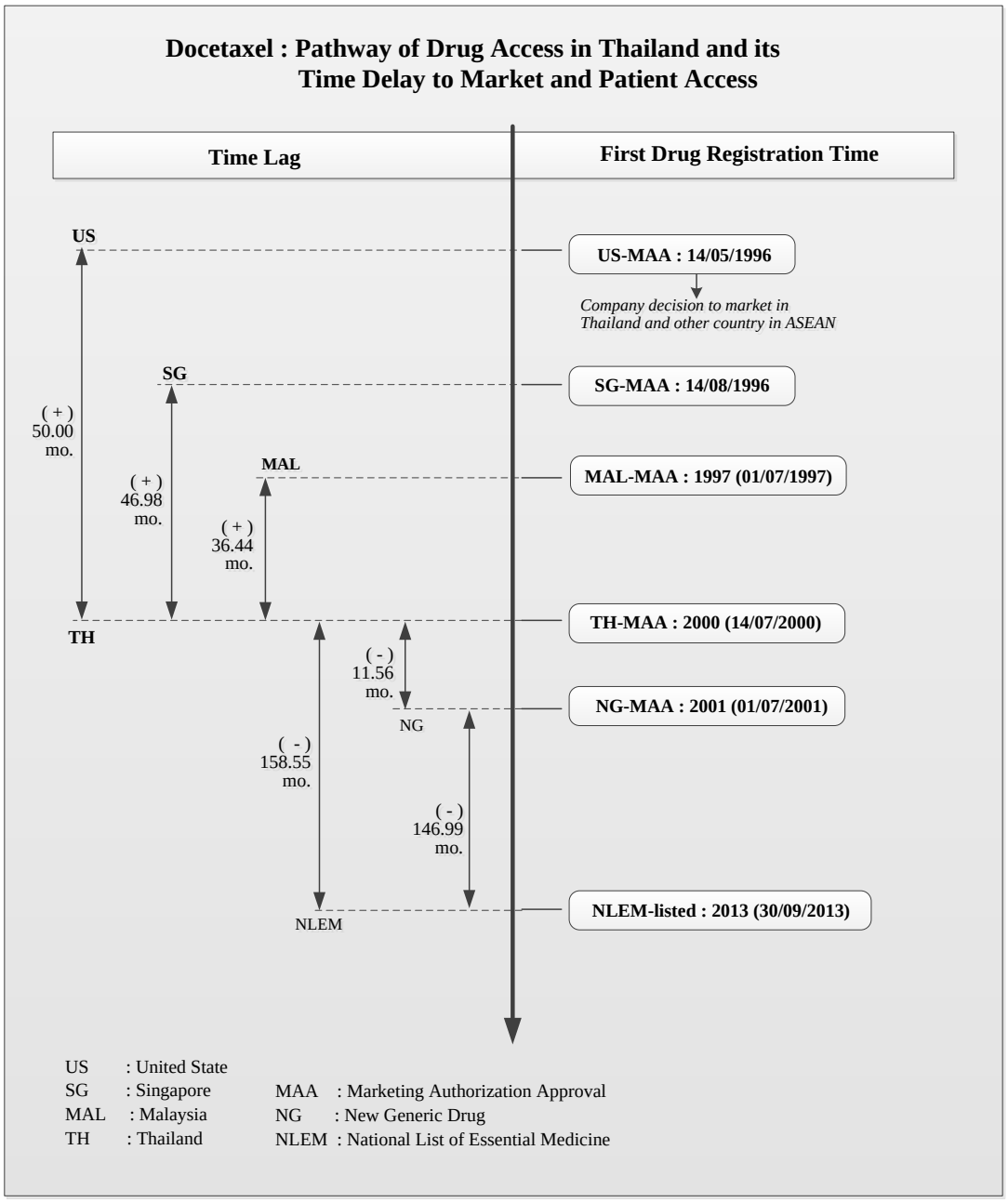


Figure 12**:** Pathway drug registration of docetaxel and calculation time lag between Thailand (TH) and other countries

Market access

From the reviewing of literature and history of drug law and regulation of Thailand, it was revealed that that some drugs had accessed the market before the 1982. the initial year of new regulation implementation. The database of drugs registration of Thai FDA was started the initiate record in 1983 in Thailand. Most of ASEAN countries had started their registration database about the same period, 1985 in Malaysia and 1987 in Singapore. For example, the first Singapore registration number SIN00001P was issued on 16/10/1987. Therefore, in order to prevent having an error in time lag calculation, the drug registrations, which was approved in US before 1983, were excluded from the time lag calculation of this study.

The comparison of time lags between first MAA in Thailand and first MAA in US, UK, EMA, SG and MAL including the first MAA of NG and first time drug listed in NLEM were described in Table 36. The average market time lags of Thailand were shown with some delay from US, UK, EMA, SG and MAL. Thailand had delayed launch of antineoplastic products on an average of 37.16 months, after MA of product approved in USA. The average time lag or delay from UK 4.52 months, EMA 11.75 months, Singapore 10.28 months, and Malaysia 6.44 months as shown in table 36. The time lag pathway of drug access in Thailand was shown in the figure 13

Calculation of time lag between Thailand and other countries, the study used the first approval time (date/month/year) in Thailand deducted with the first approval time in other countries for each individual chemical substance, such as TH – US, TH – UK, TH – EMA, TH – SG, TH – MAL. The number of negative and positive time lags (months) were shown in the table 36. It revealed that antineoplastic drugs were mostly imported from the US after MAA. Same APIs (50 items) were registered in both Thailand and Singapore. Compare with Singapore, Thailand had the average time delay of 10.73 months. Thailand had positive time delay of 35 APIs and negative time delay of 15 APIs meaning that 15 products were launched in Thailand before Singapore and vice versa for 35 substances. The similar situation was evidenced when compared with Malaysia, the time lag was 6.51 months. About one third or 14 APIs were launched in

Thailand before Malaysia and two-third or 27 APIs were market approved in Malaysia before Thailand. The time lag from EMA was about 1 year or 12.22 months and only 4.52 months from UK. The considerable delay was found when compared with US. The accessibility of antineoplastic APIs in Thai market was delayed approximately 3 years or 37.16 months after MAA in US was granted. There were only 4 out of 57 APIs that were registered in Thailand before US.

In term of patient access in Thailand, after MAA of drug was granted, antineoplastic drug was found approximately 88.05 months (7.33 years) delay to be listed on the NLEM. To support new drug (innovative drug) to be on NLEM, the MA approval of new generic drug (copied of innovative drug) must be fast granted as soon as possible after product was free from patent protection. Table 38, MAA of new generic drug was found delay 84.81 months from the approval date of its' innovative product. Figure 13 presented pathway of drug access in Thailand.

Table 36**:** Time lag between the first MAA in Thailand and the first MAA in other country including NG and NLEM

	TH-US	**TH-UK**	**TH-EMA**	**TH-SG**	**TH-MAL**	**NLEM-TH**	**NG -TH**
Number of APIs used in computation between two countries (N)	57	54	40	50	41	17	13
Average time lag (months)	37.16	4.52	12.22	10.73	6.51	88.05	84.81
Std. Deviation	44.42	45.50	29.05	39.27	41.52	65.42	60.57
Minimum of time lag (months)	-103.06	-180.63	-59.76	-90.02	-132.01	-29.17	11.56
Maximum of time lag (months)	150.01	78.92	78.92	156.75	144.00	171.01	192.07
Number of negative time lag (-)	4	17	9	15	14	2	-
Number of positive time lag (+)	53	37	31	35	27	15	13
EMA: European medicine Agency, US: United States of America, UK: United Kingdom, TH: Thailand , SG: Singapore , MAL: Malaysia							

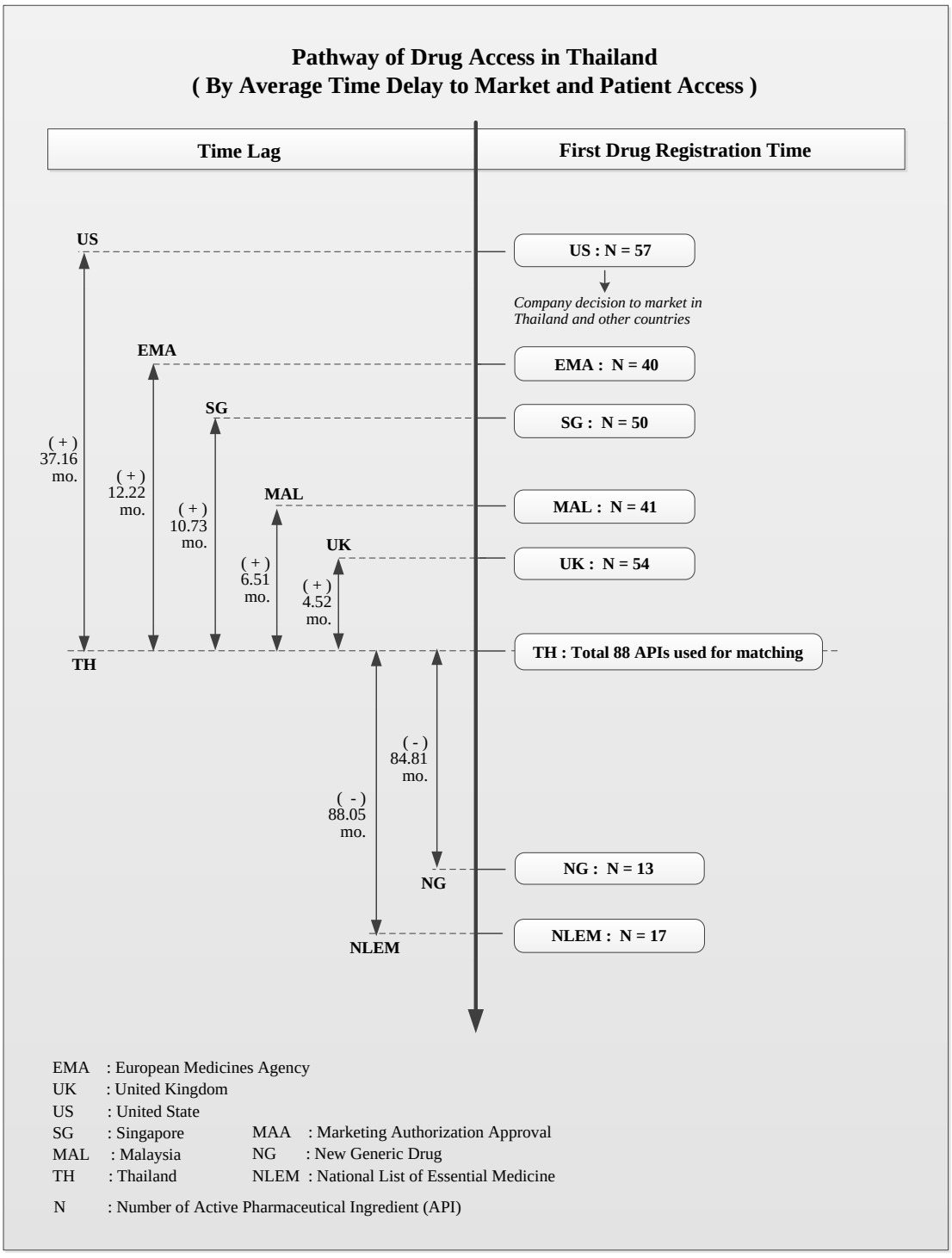


Figure 13: Time lag between the first MAA in Thailand and the first MAA in other country including NG and NLEM

Table 37 was created to present time lag across 5 periods of time. It was aimed to explore the development of time lag during each period according to regulation of Thai FDA changes. There were twenty-two (22) APIs having MAA in Thailand and found registered in the US before 1983, 22 APIs in UK, zero (0) items of EMA, 20 items in Singapore and 21 items in Malaysia as shown in Table 37 below. These were items that would be excluded from the time lag analysis since Thailand had no record of these data before 1983. All of these items, if any existed in current market, were renewed their licenses after 1983 and were mistakenly recorded as the first MAA in Thailand.

During 1983-1990 period, the drug registrations in Thailand had cancelled the 5-year renew of license requirement and started the no-renewal system of the drug registration. Until late 1989, the type of classification for drug registration was separated in two groups, Generic Drug (G) and New Drug (N). However, there was a transition period was between 1989 and 1991. During this period, the average time lag was 87.59 months when compared with 5 API items of USA, (-57.25) months when compared with 4 API items of UK, 15.36 months when compared with 4 API items of Singapore, and 14.19 months when compared with 4 API items of Malaysia.

After that period, the regulation of drug registration had been changed enormously. The period during 1991-1998, the average time lag delay between Thailand and the US was reduced to 45.69 months with 15 matched APIs. It was 12.75 months with 15 matched APIs between Thailand and UK, and was 8.45 months with 7 matched APIs between Thailand and EMA, 35.17 months with 14 matched APIs between Thailand and Singapore, and 15.26 months with 14 matched APIs between Thailand and Malaysia.

During 1999-2006, New generic drug (NG) regulation was established, after the MAA of NCE was introduced into Thai Market. The transition period to establish and to implement the new generic drug regulation was during 1999-2002. However, the fast track channel of drug registration for cancer drugs was implemented in 2004 in Thailand. The average time lag delay between Thailand and the US was reduced to 29.97 months with 19 matched APIs. It was 2.35 months with 18 matched APIs between Thailand and UK, and was 11.89 months with 16 matched APIs between Thailand and

EMA. It was (-4.70) months with 15 matched APIs between Thailand and Singapore, and was (-1.66) months with 17 matched APIs between Thailand and Malaysia.

After ASEAN Harmonization had fully been implemented in Thailand by the end of year 2006, the time lag between Thai FDA and the US was still reduced continuously when it was compared with the previous period. After the year 2006, the average time delay was 23.62 months with 18 matched APIs between Thailand and the US and was 14.09 months with 16 matched APIs between Thailand and UK including EMA. The time delay was less for ASEAN countries, 3.11 months with 17 matched APIs between Thailand and Singapore, and 4.08 months with 6 matched APIs between Thailand and Malaysia.

Table 37: Average time lag between first MAA in Thailand and in compared countries during the 1982-2016 Apr in Thailand

Lag time between Thailand and other countries	Before 1982		1983-1990		1991-1998		1999-2006		2007-2016 April	
	N	time lag	N	time lag	N	time lag	N	time lag	N	time lag
TH - US	22	293.41	5	87.59	15	45.69	19	29.97	18	23.62
TH - UK	22	-66.65	4	-57.25	15	12.75	18	2.35	17	14.09
TH - EMA	0	-	0	-	7	8.45	16	11.89	17	14.09
TH - SG	20	-26.92	4	15.36	14	35.17	15	-4.70	17	3.11
TH - MAL	21	-18.95	4	14.19	14	15.26	17	-1.66	6	4.08
EMA : European medicine Agency, N: number of API which was matched between Thailand (TH) and compared countries										

The market access of antineoplastic drugs in Thailand was continuously improved across time and according to the evolution of drug registration regulation and its process in each period described above. The drug lag in terms of time delay to access antineoplastic drugs was reduced from more than 7 years (87.59 months) during 1980s to about 2 years (23.62 months) during early 2010s. Before 1990, UK seemed to experience delayed access compared with Thailand but enormously improved when EMA was set up in 1995 and with centralized marketing authorization system established in 2007. The drug lag situation in UK was improved to approximately 1

year faster than Thailand. During 2007-2016 period when centralized procedure was implemented for cancer drugs, UK and EMA had the same time lag. However, when compared with US, UK was still behind in terms of time lag.

Compared with Malaysia and Singapore, Thailand had time lag more than 1 year during the period before 2000 but situation became more comparable after 2000 when ASEAN Harmonization started implementation. After ASEAN harmonization implementation, during 2007-2016, the antineoplastic drug access in Thailand delayed approximately 3 months from Singapore and only 1 months from Malaysia. The number of APIs registered increased quite significantly and time delay was also improved in Singapore during the period of this study.

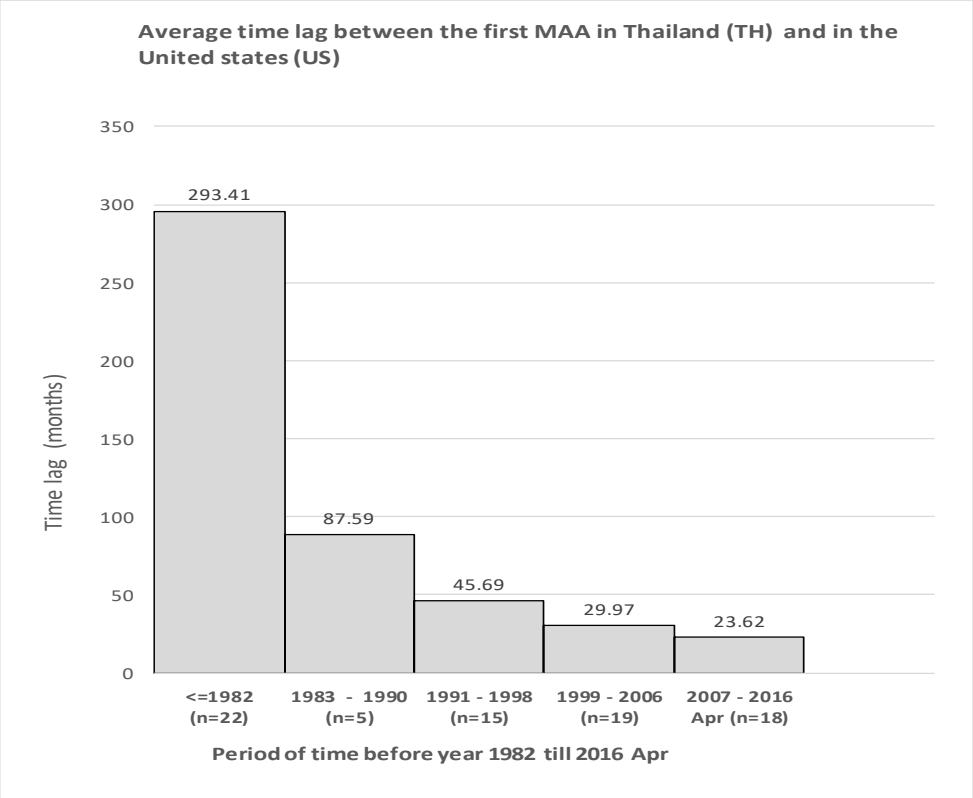


Figure 14 : Average time lag between first MAA in Thailand and in the United States (US)

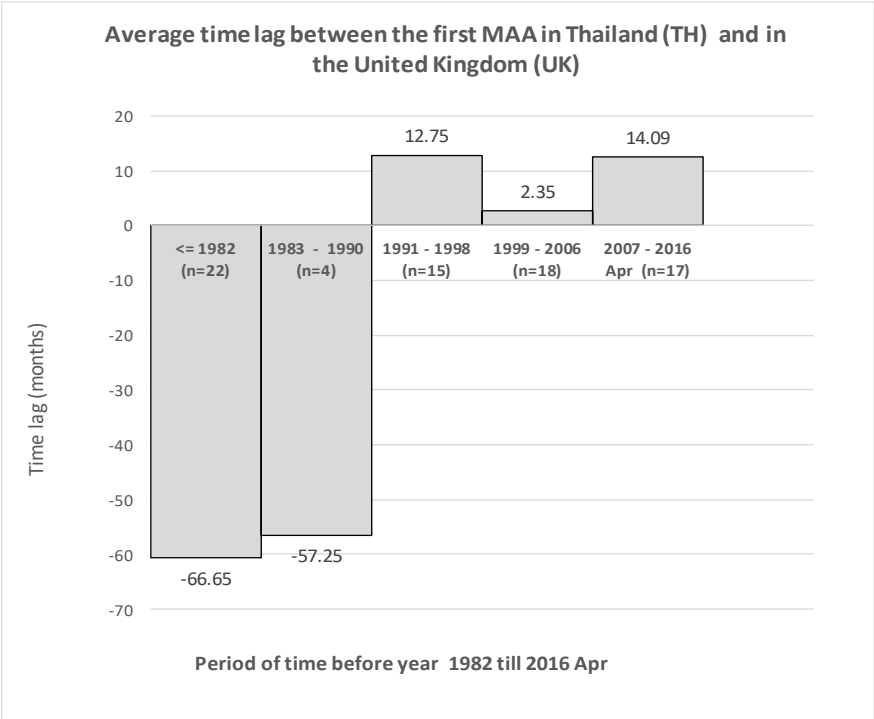


Figure 15: Average time lag between the first MAA in Thailand and in the UK

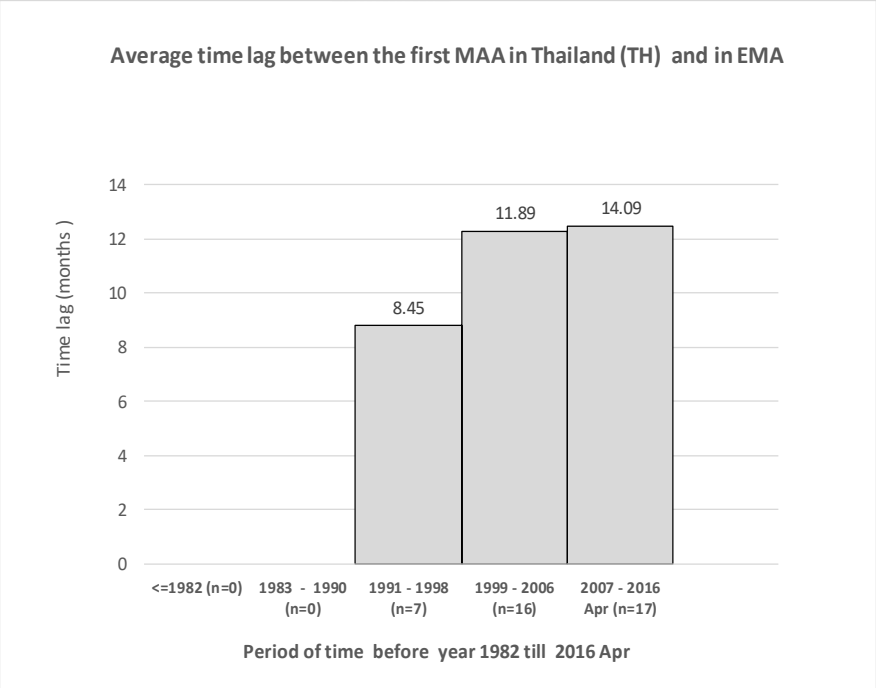


Figure 16: Average time lag between the first MAA in Thailand and in the EMA

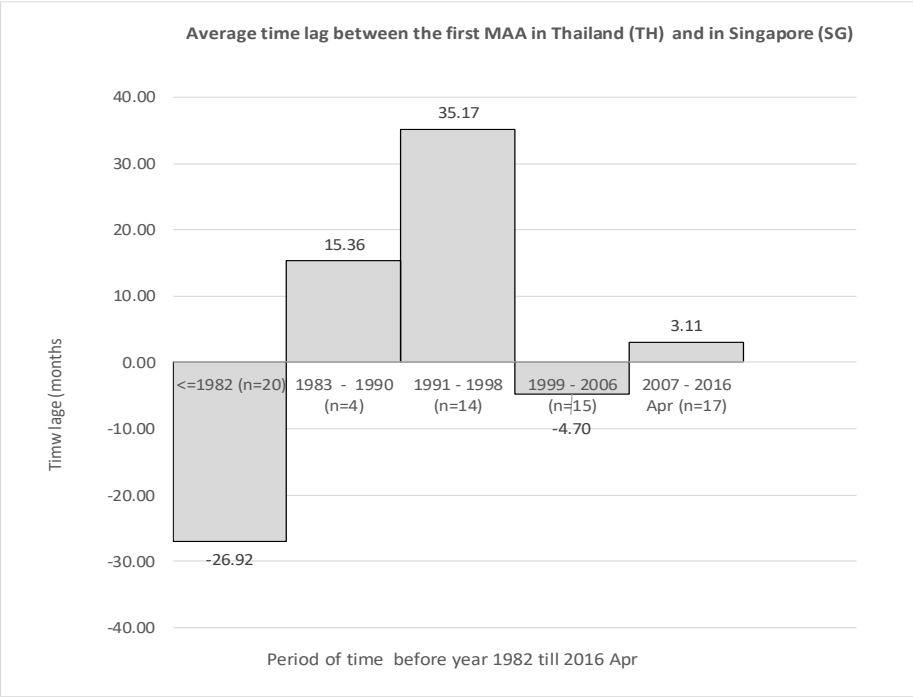


Figure 17: Average time lag between first MAA in Thailand and in SG

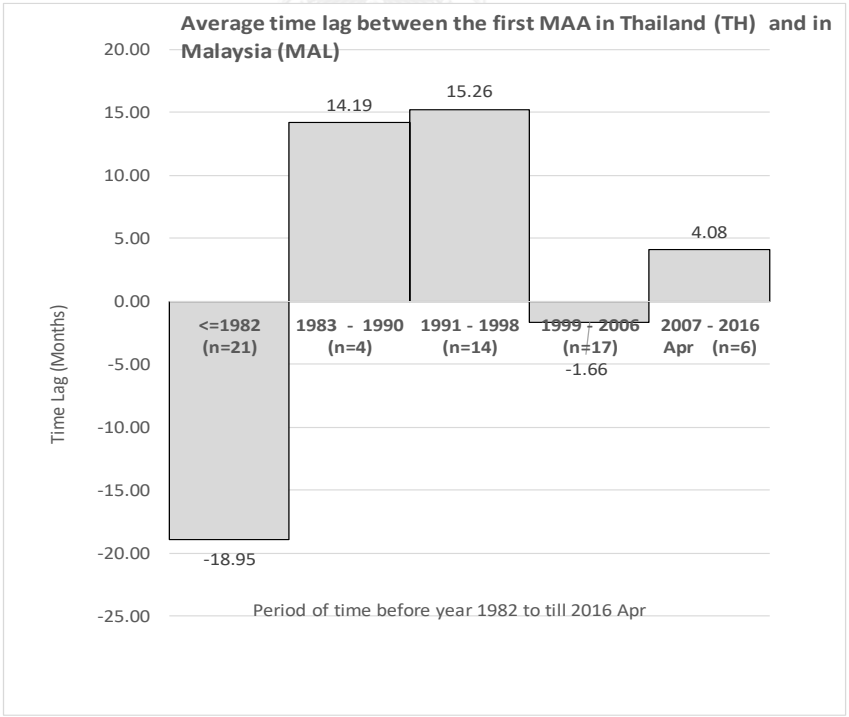


Figure 18: Average time lag between first MAA in Thailand and in MAL

Patient access

There were fourteen (14) New Generic (NG) drugs, including Capecitabine, Docetaxel, Doxorubicin, Fludarabine, Gemcitabine, Idarubicin, Imatinib, Irinotecan, oxaliplatin, Paclitaxel, Pemetrexed, Temozolomide, Topotecan, and Vinorelbine, found in the list of MAA in Thailand. However, one new generic drug 'doxorubicin' (approved in 2003) was excluded from the calculation of the average time lag because this product had the secondary dosage form (considered as a new drug). In the table below, only 13 APIs of NG were analyzed for time lag. Only 37 APIs of NLEM were calculated for time lag since the combination of tegafur (UFT) was not available in USFDA database.

Table 38: Average time lag between first MAA in Thailand and first new generic during the 1982-2016 April in Thailand

Lag time between Thailand and other countries	Before 1982		1983-1990		1991-1998		1999-2006		2007-2016 April	
	N	time lag	N	time lag	N	time lag	N	time lag	N	time lag
NLEM - TH	20	-9.14	4	52.02	8	90.05	4	122.20	1	80.82
NG - TH	-	-	1	75.20	8	78.87	4	99.10	0	-
NG: New Generic Drug, NLEM: National list of essential medicine, N: number of API										

The patient access to antineoplastic drugs in Thailand was seriously delayed from the time of market authorization approval. The time delay from the first approval in Thailand and first on NLEM were fluctuated in each period based on the Thai FDA plan to update NLEM as the information of table 22. Since the information on registration for the period before 1983 was not reliably recorded, some antineoplastic drugs were found to be listed on NLEM before APIs got the MAA in Thailand. There were 2 updated versions during 1983-1990 and 1991-1998, 2 updated versions during 1999-2006, 4 updated versions during 2007-2016 Apr. However, time delay for patient access to antineoplastic drugs was overall approximately 88 months.

The time delay to have new generic drugs in the market during each period took 75 to 99 months. The approval process of Thai FDA on NG drugs was not linked with the

patent. The market authorization holder was responsible to examine the patent status before submission of application to Thai FDA. The long delay of new generic (NG) drugs in entering the market was related to patent life of new drugs as well as the product development process which required bioequivalence study. Even though, the available of NG would help reducing the cost of treatment but not much influence the listing of drug on NLEM. From 14 new drugs listed on NLEM, 7 APIs had NG (as copied innovative drug), 5 APIs (Paclitaxel, idarubicin, capecitabine, gemcitabine, imatinib) of these NGs were listed on NLEM before drug registration of NG was approval. Only 2 of 7 APIs of NG, docetaxel and oxaliplatin, were listed on NLEM after approval of drug registration. The NLEM list was considered based on the necessity of medication with health technology assessment as one of several criteria. The treatment would have to follow the recommended treatment regimen. The cancer treatment cost was covered by the health universal coverage scheme under the vertical program which had a separate fund and reimbursement process. The civil servant medical benefit scheme (CSMBS) was still under the fee-for-service reimbursement with some cost containment mechanisms while the social security scheme (SSS) set up a reimbursement criteria using diagnosis-related group (DRG) for cancer treatment.

Overall picture of antineoplastic drug access in Thailand, drug lag was measured in terms of number and time also from the market and patient perspectives. The study found that Thai market had adequate number of APIs available covering all pharmacological groups and most of chemical groups with approximately 50% of all WHO ATC items. Patient access through the national list of essential medicine, even the number of APIs comprised about 20% of items listed by WHO, covered all pharmacological groups and almost all chemical groups available in Thai market except 2 groups, other plant alkaloids and sensitizers used in photodynamic/radiation therapy. More items had been added in the NLEM list during last three revisions. To increase the opportunity and treatment choices for patients, new and expensive items were included but placed in the category required Drug Use Evaluation (DUE) for close monitoring. In terms of time lag, the delay of cancer treatment in entering Thai market had been improved over time. Incidences, such as the international coalition and/or

harmonization leading to internal regulatory modification and adjustment, had been observed and might directly or indirectly influenced these improvements. Current time lag was about one year delayed from UK and EMA, only a few months delayed from Singapore and Malaysia. The significant delay was found when compared with US where most of drug products got their first market approval. However, patient access had to wait for more than 7 years on average before items were listed on NLEM. The redesigned NLEM selection process, which required more information and careful consideration, was called for to shorten the time delay for patient access to the needed medication. Since Thailand still relied on importation of all antineoplastic drug products, time delay of product entering market would be the first indicator of patient access to potential treatment options.

4.2.2 Factor or determinants related to accessibility

4.2.2.1 Price

As known for the chemotherapy, price of antineoplastic drugs was normally high, especially for new innovative products or breakthrough drugs. The treatment of cancer disease was based on type and stage of cancer. In this study, price was calculated as cost of treatment per month. Two sources of price of each product were explored including the 2014 price from the IMS Health database (IMS-price) and "Reference price" during January to June 2014 from Drug and Medical Supply Information Center, Ministry of Public Health (DMSIC). The cost treatment in term of "cost per month" was calculated. From the data obtained from the Ref-Price and the IMS-price, the items of API from IMS-price (70 items) revealed more items than Ref-Price (56 items). The IMS-price of 2014 was perceptibly selected for calculation cost per month of each API item for 2 reasons. The IMS-price was more consistent across products since price list was recorded and IMS had price information for more products than Ref-price. Another reason was the cost per month would be used to calculate the utilization as a representative of market size. The study also obtained sales volume data from IMS database. It was thus more reliable using the data of price and sales from the same source.

Cost per month

In this study, cost per month was defined as an average cost of treatment for one month using dosage regimen for an average size of Thai patient. The cost of a particular API was calculated from dosage regimen to treat main cancer indication for 12-week course divided by 2.77 to obtain cost per month of that API. The fixed dose combination drug such as “tegafur, uracil (UFT)” and “tegafur/ gimeracil / oteracil” are excluded from this calculation.

Table 39: Parameters for calculation the cost per month of product

Parameters for calculation "cost per month"	
Average weight adult*	63.115 mg
Average height adult*	163.23 cm
Body surface area (Calculated by Mosteller formula**)	1.69 square meters
12 weeks	2.77 months

Note*: "SizeThai" is form the website: http://www.sizethailand.org/region_all.html,
**: http://www.nejm.org/doi/full/10.1056/NEJM198710223171717

Cost per month for each API was compared across drug registration classifications. Ten APIs with new generic products had two different price levels (one for NG price and the other for new drug (N) price). One API (doxorubicin) had three price items (NG, N and G).

Table 40: Cost per month of each chemical substance across drug registration classifications

Drug classification	Number of API	Cost per month by average price (THB)*			
		Minimum	Maximum	Mean	Std. Deviation
Generic drug (G)	21	254.20	117,003.95	15,314.37	26,760.04
New Drug (N)	48	2,845.93	1,094,534.30	143,523.09	170,055.38
New generic drug (NG)	11	15,965.45	146,517.93	54,428.60	34,844.93

* Price from IMS database 2014, API: active pharmaceutical ingredient

Table 40 illustrated the new drug (N) had the average cost per month of 143, 523 THB which was considerably above generic drug (G) at 15,314 THB and new generic drug (NG) at 54,428.60 THB. Drug expenditure for treatment cancer in Thailand revealed high in cost per month. It was shown that many items of new drugs were monopoly sold since only 14 new generic drugs were available in Thai market with 11 APIs having price information.

4.2.2.2 Market size

Market size could be measured by annual total sales in monetary value or by utilization through the patient-months which was calculated from dividing sales by cost per month. Here both measures would be presented.

Sale value of antineoplastic drug

From IMS database during 2011-2014, the total sales of antineoplastic drugs were increased from 5.61 to 7.79 billons THB. The percentage of compound annual growth rate (CAGR) was shown that antineoplastic market had annual growth at 11.52 % during 2011-2014.

Table 41: Summary for the total sale during 2011-2014

Annual sale by year	Number of API		Sale Value* (THB)		
	TH	IMS	Minimum	Maximum	Total sale
2011	73	59	200,872	639,031,080	5,613,476,103
2012	78	64	71,390	736,426,958	6,500,551,150
2013	81	65	131,500	998,776,369	7,242,856,368
2014	84	67	113,325	1,004,525,812	7,785,703,047
* Sale value from the IMS database during 2011-2014					
CARG(%) of sale value = 11.52 , CARG(%) of number of API in Thailand = 4.79					
CARG(%) of number of API of IMS database = 4.33					

During 2011-2014, Thai FDA had registered 73, 78, 81 and 84 APIs respectively accounted for 4.79 percentages of CAGR as shown in the Table 41. However, not all registered products were put on the market, IMS Health database had recorded only 70 items of APIs with price information available during the same period. Some APIs were faded in and faded out of the market and some APIs were new additional items. According to the IMS market data, there were 59, 64, 65 and 67 of APIs sold from year 2011 to 2014 in the hospitals respectively. As seen in Table 42, some products have never been launched since MAA were granted and/or were fade out from the market. The percentage of non-marketed products was on average of 19.28% during 2011 - 2014.

Table 42: Not available antineoplastic API in the market after marketing authorization was approved during year 2011 to 2014

Annual sale by year	Number of API		Difference	% Difference
	TH*	IMS**		
2011	73	59	14	19.18
2012	78	64	14	17.95
2013	81	65	16	19.75
2014	84	67	17	20.24
Average				19.28

* Thai FDA databse , ** IMS database

The actual usage of antineoplastic chemotherapy was based on the basic principles of cancer biology, cancer sites, and drug mechanism of actions including their toxicity. Chemotherapy was used as an adjuvant to surgery or radiation. Antineoplastic drugs, therefore, were used after or before the primary of cancer treatment. The variety pharmacological groups of antineoplastic drugs made the incremental difference of usage based on the new trend and/or new technology of cancer treatments. In the Table 43, the sale values (Thai Baht) was summarized by ATC classification system level-3 (pharmacological group) and level-4 (chemical group). It was seen that the market size

by sale values of pharmacological Group-X had highest growth at 15.29 % following with 10.06 % of Group-C (plant alkaloids and natural product), 8.20 % of group-A (Alkylating agents), 3.03 % of Group-B (Antimetabolites) and the last, 0.68 % of Group-D (cytotoxic antibiotic and related substance).

Within the highest growth and highest sales volume (3.20 billion THB) of pharmacological group X or other antineoplastic agents, the market size of protein kinase inhibitors had the highest sales volume of 1.16 billion THB and highest increase in this group at 18.63%, following with 14.65 % of platinum compound, 13.99% of monoclonal antibodies. When considering among all chemical groups, the alkyl sulfonates under alkylating agents with only one API (busulfan) had highest CAGR of 20% but the sales volume was quite small with 9.87 million THB in 2014. The three largest sales volumes were contributed by protein kinase inhibitors at 1.16 billion THB and monoclonal antibodies at 1.03 billion THB, and taxanes at 0.90 billion THB. At the chemical substance or each API level, paclitaxel under taxanes chemical group had highest sales across 4 years with 1.00 billion THB in 2014 sales. Three other chemical substances with sky rocket sales in 2014 over 500 million THB included oxaliplatin under platinum compound group with 690.43 million THB, imatinib under protein kinase inhibitors group with 661.47 million THB, and trastuzumab under monoclonal antibodies with 585,19 million THB. Another API under monoclonal antibodies group with high sales volume was rituximab at 458.31 million THB as seen in the Table 43 and Table 44.

Table 43: The Sale value in Thai baht summarized in the ATC classification system level-3 (pharmacological group) and level-4 (chemical group) during 2011-2014

Pharmacological group / Chemical subgroup			Total Value of sale in the Thailand* (THB)				CAGR (%)
			Year 2011	Year 2012	Year 2013	Year 2014	
A: Alkylating Agents	ATC - L4	A: Nitrogen mustard analogues	85,956,163	92,431,408	100,215,628	108,453,818	8.06
		B: Alkyl sulfonates	9,875,515	5,037,500	12,850,000	17,212,500	20.35
		C: Ethylene imines					
		D: Nitrosoureas		520,740	131,500		-74.75
		G: Epoxides					
		X :Other alkylating agents	92,696,211	96,721,060	122,183,940	113,173,920	6.88
	Total		188,527,889	194,710,708	235,381,068	238,840,238	8.20
B: Antimetabolites	ATC - L4	A :Folic acid analogues	190,328,956	216,106,363	246,643,260	242,381,082	8.39
		B :Purine analogues	19,555,295	20,526,651	22,370,317	21,539,814	3.27
		C :Pyrimidine analogues	715,460,840	784,285,053	760,182,667	748,208,664	1.50
	Total		925,345,090	1,020,918,067	1,029,196,244	1,012,129,560	3.03
C: Plant alkaloids and other natural Product	ATC-L4	A: Vinca alkaloids and analogues	40,076,489	45,721,211	50,330,294	40,269,745	0.16
		B: Podophyllotoxin derivatives	31,175,434	29,965,827	27,391,968	37,758,924	6.59
		C: Colchicine derivatives					
		D: Taxanes	902,315,497	1,030,736,863	1,277,474,626	1,222,667,712	10.66
		X: Other plant alkaloids	1,979,914	2,070,000			4.55
	Total		975,547,334	1,108,493,901	1,355,196,888	1,300,696,381	10.06
D: Cytotoxic antibiotics and related substance	ATC-L4	A: Actinomycines	402,613	391,380	148,720		-39.22
		B: Anthracyclines & related sub.	294,289,976	297,091,586	293,744,967	307,784,275	1.51
		C: Other cytotoxic antibiotics	30,468,932	29,761,846	29,037,280	24,070,688	-7.56
	Total		325,161,521	327,244,812	322,930,967	331,854,963	0.68
X: Other antineoplastic agents	ATC-L4	A: Platinum compounds	627,920,456	723,937,039	871,320,271	946,211,872	14.65
		B: Methylhydrazines					
		C: Monoclonal antibodies	1,033,356,800	1,257,428,817	1,455,135,558	1,530,437,481	13.99
		D: Sensitizers used in photodynamic /R-T					
		E: Protein kinase inhibitors	1,161,260,899	1,388,924,135	1,530,542,105	1,938,768,079	18.63
		X: Other antineoplastic agents	376,356,115	478,893,671	443,153,267	486,943,912	8.97
	Total		3,198,894,270	3,849,183,662	4,300,151,201	4,902,361,344	15.29
Total Sale of Antineplastic Drug			**5,613,476,103**	**6,500,551,150**	**7,242,856,368**	**7,785,882,486**	**11.52**

Note:* by IMS sale at the end of each year, CAGR: Compound Annual Growth Rate

Table 44: Sale value of each active pharmaceutical ingredient (API) or chemical substance based on ATC-code number during 2011-2014

ATC-code	API name	Total value of sale during year 2011-2014				CAGR (%)
		Year 2011	Year 2012	Year 2013	Year 2014	
L01AA01	cyclophosphamide	42,075,380.37	43,472,283	49,172,648	51,010,705	6.63
L01AA02	chlorambucil	2,543,577.70	2,491,180	2,519,060	2,855,320	3.93
L01AA03	melphalan	5,030,878.79	4,574,075	6,643,015	8,031,225	16.87
L01AA06	ifosfamide	36,306,326.37	41,893,870	41,880,905	46,556,568	8.64
L01AB01	busulfan	9,875,514.60	5,037,500	12,850,000	17,212,500	20.35
L01AD01	carmustine		520,740	131,500		-74.75
L01AX03	temozolomide	73,816,120.49	80,865,560	98,172,940	88,027,420	6.04
L01AX04	dacarbazine	18,880,090.50	15,855,500	24,011,000	25,146,500	10.02
L01BA01	methotrexate	71,707,046.18	80,426,623	97,496,500	105,019,382	13.56
L01BA04	pemetrexed	118,621,909.42	135,679,740	149,146,760	137,361,700	5.01
L01BB02	mercaptopurine	9,430,644.33	8,811,051	9,002,477	8,278,974	-4.25
L01BB03	tioguanine (thioguanine)	644,820.02	999,600	644,840	497,840	-8.26
L01BB05	fludarabine	9,479,830.15	10,716,000	7,755,000	12,027,000	8.26
L01BB06	clofarabine			4,968,000	736,000	-85.19
L01BC01	cytarabine	55,587,538.07	58,772,704	55,040,585	53,152,647	-1.48
L01BC02	fluorouracil	23,964,857.63	28,026,901	35,253,519	40,803,761	19.41
L01BC05	gemcitabine	233,057,937.41	277,614,060	298,986,538	328,400,149	12.11
L01BC06	capecitabine	347,767,852.37	374,545,977	281,072,350	224,791,237	-13.54
L01BC07	azacitidine	37,443,636.36	30,891,000	53,067,000	51,450,000	11.17
L01BC08	decitabine	8,594,265.19	6,818,690	10,938,315	16,123,363	23.33
L01BC53	tegafur, uracil (UFT)	9,044,752.66	6,289,721	15,631,860	19,794,007	29.83
L01BC53	tegafur/ gimeracil / oteracil		1,326,000	10,192,500	13,693,500	221.36
L01CA01	vinblastine	2,489,295.08	1,423,130	276,620	113,325	-64.29
L01CA02	vincristine	17,329,448.06	16,766,241	15,714,015	14,347,708	-6.10
L01CA04	vinorelbine	20,257,746.01	27,531,840	34,339,659	25,808,712	8.41
L01CB01	etoposide	31,175,433.83	29,965,827	27,391,968	37,758,924	6.59
L01CD01	paclitaxel	639,031,079.50	736,426,958	998,776,369	1,004,525,812	16.27
L01CD02	docetaxel	263,284,417.37	291,834,905	266,158,257	201,476,900	-8.53
L01CD04	Cabazitaxel		2,475,000	12,540,000	16,665,000	159.49
L01CX01	trabectedin	1,979,913.92	2,070,000			4.55
L01DA01	dactinomycin	402,612.90	391,380	148,720		-39.22
L01DB01	doxorubicin	223,067,111.15	232,578,332	233,413,111	244,335,280	3.08
L01DB03	epirubicin	19,572,755.86	13,693,100	9,889,604	7,575,491	-27.12
L01DB06	idarubicin	47,989,049.19	46,434,204	46,275,252	50,523,994	1.73
L01DB07	mitoxantrone	3,661,060.10	4,385,950	4,167,000	5,349,510	13.48
L01DC01	bleomycin	11,365,449.81	11,989,413	12,772,941	14,188,707	7.68
L01DC03	mitomycin	7,026,062.40	7,476,433	11,026,339	8,999,981	8.60
L01DC04	ixabepilone	12,077,419.35	10,296,000	5,238,000	882,000	-58.20

(Table 44: continued)

ATC-code	API name	Total value of sale during year 2011-2014				CAGR (%)
		Year 2011	Year 2012	Year 2013	Year 2014	
L01XA01	cisplatin	54,944,160.72	59,279,255	66,826,708	64,067,767	5.25
L01XA02	carboplatin	140,918,415.91	147,048,367	181,491,666	191,715,622	10.81
L01XA03	oxaliplatin	432,057,879.14	517,609,417	623,001,897	690,428,483	16.91
L01XC02	rituximab	344,053,715.45	395,868,205	424,190,568	458,307,815	10.03
L01XC03	trastuzumab	297,939,383.56	437,404,809	536,392,101	585,187,272	25.23
L01XC06	cetuximab	112,597,675.97	98,061,316	110,541,092	100,973,366	-3.57
L01XC07	bevacizumab	269,726,628.03	321,163,496	376,435,536	355,607,860	9.65
L01XC13	pertuzumab				22,939,000	
L01XC-TH	nimotuzumab	9,039,396.88	4,930,991	7,576,261	7,422,168	-6.36
L01XE01	imatinib	457,606,657.61	538,877,600	536,359,000	661,466,600	13.07
L01XE02	gefitinib	126,224,516.03	129,102,435	137,550,105	174,095,460	11.31
L01XE03	erlotinib	238,566,110.05	261,444,600	285,545,200	318,324,600	10.09
L01XE04	sunitinib	66,787,671.23	78,008,000	73,402,000	79,331,000	5.90
L01XE05	sorafenib	88,531,784.58	125,759,400	144,147,900	119,301,000	10.45
L01XE06	dasatinib	40,520,283.32	50,342,400	57,456,000	96,134,400	33.37
L01XE07	lapatinib	22,180,268.31	23,808,300	25,674,900	29,426,400	9.88
L01XE08	nilotinib	102,414,569.54	139,181,400	180,470,300	238,785,650	32.60
L01XE09	temsirolimus		3,744,000	2,952,000	2,844,000	-12.84
L01XE10	everolimus	18,429,038.66	34,372,000	69,478,800	97,677,625	74.35
L01XE11	pazopanib		4,284,000	14,529,900	29,398,950	161.96
L01XE15	vemurafenib				6,376,894	
L01XE16	crizotinib			2,976,000	30,721,000	932.29
L01XE21	regorafenib				54,884,500	
L01XX02	asparaginase	7,177,461.25	8,659,607	8,272,443	7,099,501	-0.36
L01XX05	hydroxycarbamide (HydroxyUrea)	47,615,698.97	50,615,488	58,069,088	68,464,704	12.87
L01XX14	tretinoin	5,586,938.53	7,425,600	6,621,160	2,537,080	-23.14
L01XX17	topotecan	7,072,517.87	9,484,329	8,337,312	6,633,504	-2.11
L01XX19	irinotecan	183,537,885.24	219,611,443	218,290,812	242,340,425	9.71
L01XX27	arsenic trioxide	200,872.26	71,390		204,490	0.60
L01XX32	bortezomib	104,120,383.25	164,635,150	121,698,100	114,084,400	3.09
L01XX35	anagrelide	21,044,357.48	18,390,664	17,333,352	24,649,808	5.41
L01XX41	eribulin			4,531,000	20,930,000	361.93

Number of patient –month

Since the cost per month of each API was, naturally, difference due to the price, course/protocol of treatment, the dosage regimen, therefore, the number of patient-month was obtained by the calculation of the sale value divided by the cost per month of each product. Table 45 presented the number of patient-month based on the pharmacological groups and chemical groups. The analysis showed that during 2011-2014, antineoplastic drug market measured by utilization was grown at only 8.80 % CAGR (lower than measurement by sales value). It seemed that the tendency of incremental rate for patient-month increased at the lower rate than market size in monetary value due to higher inflation rate of price of new APIs.

In the Table 46, the patient-month was summarized in ATC classification system level-3 (pharmacological group) and level-4 (chemical group). It was depicted that the utilization by patient-month of pharmacological Group-X still had highest growth 13.06 % following with 10.13 % of Group-C: Plant alkaloids and natural product, 9.04 % of Group-B: Antimetabolites, 6.70 % of Group-A: Alkylating agents, and the last, 5.47 % of Group-D: Cytotoxic antibiotic and related substances.

At the ATC level-4 or chemical group level, the alkyl sulfonates had 20% increase with one API (busulfan) in this chemical group. Protein kinase inhibitors had the highest increase at 18.55 %, following with 16.26 % of monoclonal antibodies, 14.42 % of Taxanes. Considering the utilization of each chemical substance, cyclophosphamide which had approximately 50 million THB annual sales volume had highest usage with over 200,000 patient-months. Methotrexate and 5-fluorouracil were among APIs with high utilization as seen in the Table 45 and Table 46. The utilization and sales data reflected that high price contributed more on the expenditure of antineoplastic drugs than utilization volume.

Table 45: Number of patient-month summarized in ATC classification system level-3 pharmacological group (ATC code level 3) and Chemical group (ATC code level 4) during 2011-2014

Pharmacological group / Chemical subgroup			Total number of patient - month				CAGR (%)
			Year 2011	Year 2012	Year 2013	Year 2014	
A: Alkylating Agents	ATC - L4	A: Nitrogen mustard analogues	169,729.31	175,513.86	198,264.66	206,153.03	6.70
		B: Alkyl sulfonates	40.63	20.73	52.87	70.82	20.35
		C: Ethylene imines					
		D: Nitrosoureas		162.27	40.98		-74.75
		G: Epoxides					
		X :Other alkylating agents	608.96	586.65	791.58	771.49	8.20
	Total		170,378.90	176,283.51	199,150.09	206,995.34	6.70
B: Antimetabolites	ATC - L4	A :Folic acid analogues	47,533.09	53,337.02	64,520.79	69,294.05	13.39
		B :Purine analogues	1,368.73	1,373.75	1,260.20	1,348.81	-0.49
		C :Pyrimidine analogues	85,940.35	95,297.48	99,458.34	104,195.95	6.63
	Total		134,842.17	150,008.25	165,239.33	174,838.81	9.04
C: Plant alkaloids and other natural Product	ATC-L4	A: Vinca alkaloids and analogues	5,013.56	4,684.07	4,210.65	3,708.51	-9.56
		B: Podophyllotoxin derivatives	4,929.36	4,738.10	4,331.13	5,970.32	6.59
		C: Colchicine derivatives					
		D: Taxanes	22,215.32	25,853.85	34,350.27	33,278.12	14.42
		X: Other plant alkaloids	6.01	6.28			4.49
	Total		32,164.25	35,282.30	42,892.05	42,956.95	10.13
D: Cytotoxic antibiotics and related substance	ATC-L4	A: Actinomycines	89.24	86.75	32.96		-39.23
		B: Anthracyclines & related sub.	17,335.49	18,128.86	19,348.24	19,628.25	4.23
		C: Other cytotoxic antibiotics	8,852.44	9,393.36	13,547.86	11,198.30	8.15
	Total		26,277.17	27,608.97	32,929.06	30,826.55	5.47
X: Other antineoplastic agents	ATC-L4	A: Platinum compounds	41,535.62	45,318.97	55,314.66	58,327.39	11.98
		B: Methylhydrazines					
		C: Monoclonal antibodies	7,212.38	9,112.12	10,575.45	11,333.29	16.26
		D: Sensitizers used in photodynamic /R-T					
		E: Protein kinase inhibitors	10,265.47	12,060.19	13,429.43	17,103.57	18.55
		X: Other antineoplastic agents	21,800.22	23,931.50	26,141.81	30,022.27	11.26
	Total		80,813.69	90,422.78	105,461.35	116,786.52	13.06
Total Sale of Antineplastic Drug			444,476.18	479,605.81	545,671.88	572,404.17	8.80
Note:Patient-month is sale value devided by cost per month, CAGR: Compound Annual Growth Rate							

Table 46: Patient-month of each active pharmaceutical ingredient (API) or chemical substance based on ATC-code number during 2011-2014

ATC-code	API name	Total patient -month during year 2011-2014				CAGR (%)
		Year 2011	Year 2012	Year 2013	Year 2014	
L01AA01	cyclophosphamide	165,527	171,023	193,448	200,679	6.63
L01AA02	chlorambucil	974	954	965	1,094	3.93
L01AA03	melphalan	767	697	1,013	1,224	16.87
L01AA06	ifosfamide	2,461	2,840	2,839	3,156	8.64
L01AB01	busulfan	41	21	53	71	20.35
L01AD01	carmustine	-	162	41	-	-74.75
L01AX03	temozolomide	294	322	391	352	6.19
L01AX04	dacarbazine	315	264	400	419	10.02
L01BA01	methotrexate	46,457	52,106	63,165	68,038	13.56
L01BA04	pemetrexed	1,077	1,231	1,356	1,256	5.26
L01BB02	mercaptopurine	953	890	910	837	-4.25
L01BB03	tioguanine (thioguanine)	32	50	32	25	-8.26
L01BB05	fludarabine	384	434	314	487	8.26
L01BB06	clofarabine	-	-	5	1	-85.19
L01BC01	cytarabine	36,675	38,777	36,315	35,069	-1.48
L01BC02	fluorouracil	30,634	35,827	45,065	52,159	19.41
L01BC05	gemcitabine	4,885	5,957	6,822	7,853	17.15
L01BC06	capecitabine	13,487	14,526	10,901	8,722	-13.52
L01BC07	azacitidine	186	153	263	255	11.17
L01BC08	decitabine	73	58	93	138	23.33
L01BC53	tegafur, uracil (UFT)	-	-	-	-	-
L01BC53	tegafur/ gimeracil / oteracil	-	-	-	-	-
L01CA01	vinblastine	753	431	84	34	-64.29
L01CA02	vincristine	3,924	3,797	3,558	3,249	-6.10
L01CA04	vinorelbine	336	457	569	425	8.15
L01CB01	etoposide	4,929	4,738	4,331	5,970	6.59
L01CD01	paclitaxel	18,908	22,152	30,932	30,596	17.40
L01CD02	docetaxel	3,307	3,687	3,344	2,583	-7.90
L01CD04	Cabazitaxel	-	15	74	99	159.49
L01CX01	trabectedin	6	6	-	-	4.55
L01DA01	dactinomycin	89	87	33	-	-39.22
L01DB01	doxorubicin	15,169	16,273	17,738	17,995	5.86
L01DB03	epirubicin	1,158	810	585	448	-27.12
L01DB06	idarubicin	705	682	680	742	1.73
L01DB07	mitoxantrone	303	363	345	443	13.48
L01DC01	bleomycin	511	539	574	638	7.68
L01DC03	mitomycin	8,238	8,767	12,929	10,553	8.60
L01DC04	ixabepilone	103	88	45	8	-58.20
L01XA01	cisplatin	14,848	16,020	18,059	17,314	5.25
L01XA02	carboplatin	18,330	19,128	23,608	24,938	10.81
L01XA03	oxaliplatin	8,357	10,171	13,647	16,075	24.37

(Table 46: continued)

ATC-code	API name	Total patient -month during year 2011-2014				CAGR (%)
		Year 2011	Year 2012	Year 2013	Year 2014	
L01XC02	rituximab	2,810	3,233	3,464	3,743	10.03
L01XC03	trastuzumab	2,869	4,212	5,166	5,635	25.23
L01XC06	cetuximab	415	361	407	372	-3.57
L01XC07	bevacizumab	1,078	1,284	1,504	1,421	9.65
L01XC13	Pertuzumab	-	-	-	129	-
L01XC-TH	nimotuzumab	41	22	34	33	-6.36
L01XE01	imatinib	2,195	2,585	2,573	3,173	13.07
L01XE02	gefitinib	2,034	2,080	2,216	2,805	11.31
L01XE03	erlotinib	2,598	2,847	3,110	3,467	10.09
L01XE04	sunitinib	472	551	519	561	5.90
L01XE05	sorafenib	973	1,383	1,585	1,312	10.45
L01XE06	dasatinib	767	953	1,087	1,819	33.37
L01XE07	lapatinib	465	499	538	617	9.88
L01XE08	nilotinib	643	874	1,133	1,499	32.60
L01XE09	temsirolimus	-	8	6	6	-12.84
L01XE10	everolimus	119	222	448	630	74.35
L01XE11	pazopanib	-	59	201	406	161.96
L01XE15	vemurafenib	-	-	-	377	-
L01XE16	crizotinib	-	-	14	145	932.29
L01XE21	regorafenib	-	-	-	288	
L01XX02	asparaginase	1,902	2,295	2,192	1,881	-0.36
L01XX05	hydroxycarbamide (HydroxyUrea)	16,731	17,785	20,404	24,057	12.87
L01XX14	tretinoin	273	363	324	124	-23.14
L01XX17	topotecan	109	145	126	100	-2.76
L01XX19	irinotecan	1,670	2,050	1,965	2,322	11.61
L01XX27	arsenic trioxide	3	1	-	3	0.60
L01XX32	bortezomib	455	719	531	498	3.09
L01XX35	anagrelide	657	574	541	770	5.41
L01XX41	eribulin	-	-	58	266	361.93

4.2.2.3 Patent

Patent protection of drugs was one factor that could delay generic drug launching into the market. Based on the implementation of new regulation of the Thai FDA in 1989, the innovative product registration was classified as new drug (N) in Thailand. It meant that the copy of an innovative product was classified as a new generic drug (NG) which needed to prove the bioequivalence to the innovative product. To launch a new generic drug (NG) product in the market, a product had to be free from the patent protection. According to Thai FDA database in April 2016, there were 45 APIs of antineoplastic

drugs classified as new drugs. However, only 14 APIs of these 45 new drugs were found at least one new generic drug in Thailand starting from 2001 by the MAA of paclitaxel and docetaxel.

In Thailand, patent information did not require to be declared to Thai FDA as in the US system. Whether or not a drug had a patent protection was not a part of required information to be submitted. The new generic product could get the MAA if it met the requirement of Thai FDA. The product patent information, voluntarily provided to Thai FDA in the drug registration application, was not revealed to the public by Thai FDA. Without patent linkage platform, the patent information, therefore, could not be searched via the Thai FDA database like in the US. Thus, the information on complete patent status in Thailand could not be obtained for all 88 APIs available in the market. The patent information was then obtained from the orange book of the US system and some patent extension information was from the United States Patent and Trademark Office (USPTO). The patent in this study was defined as the current patent status in the US. APIs that did not show current patent status in the orange book could be assumed as patents had been expired. It was unlikely that the product owner never applied patents for their product.

Type of patient based on USFDA

The patent information was obtained from USFDA database: orange book by last access on 14 April 2016. From 130 APIs approval by USFDA, 55 APIs were found the patented claims which could be categorized into three types of claimed information 1) 45 APIs had at least one drug product claim, 2) 46 APIs had at least one drug substance claim, and 3) 50 APIs had patent use code claim as in the table 47. On average, each API had 4.58 patents with most patents on drug product claims. On the accessed date in April 2016, there were on average 4.58 patent claims per API, 3.13 for drug patent claim, 2.70 for drug substance claim, and 2.8 for patient use code claim. Form 130 API, 55 items of API still had patent protection.

Table 47: Patient information from product USFDA database at April 2016

Items	Patent Claim	Drug Product Claim	Drug Substance Claim	Patent Use Code Claim
Number first API which is still active claimed patent	55	45	46	50
Total number of patented protection by separated claim which is still active	252	141	124	140
Average patent per API (%)	4.58	3.13	2.7	2.8

Table 48 and figure 49, among 55 APIs, 41 APIs were claimed for all three types of patent (DS claim +DP claim + patent use code (PUC) claim), 4 APIs claimed for two types (DS and DP claim). Meanwhile, one type claimed was found for DS (one API) and for PUC claim (9 APIs).

Table 48: Patent information of 55 API separated by type of claim

Items of Type	Number of API
Drug Substance (DS) Claim	1+4+41=46
Drug Product (DP) Claim	4+41=45
Patent Use Code (PUC) Claim	9+41=50
Two Claims (DS+DP)	4
All claim (DS+DP+PUC)	41
Total: API (found active patent)	**55**

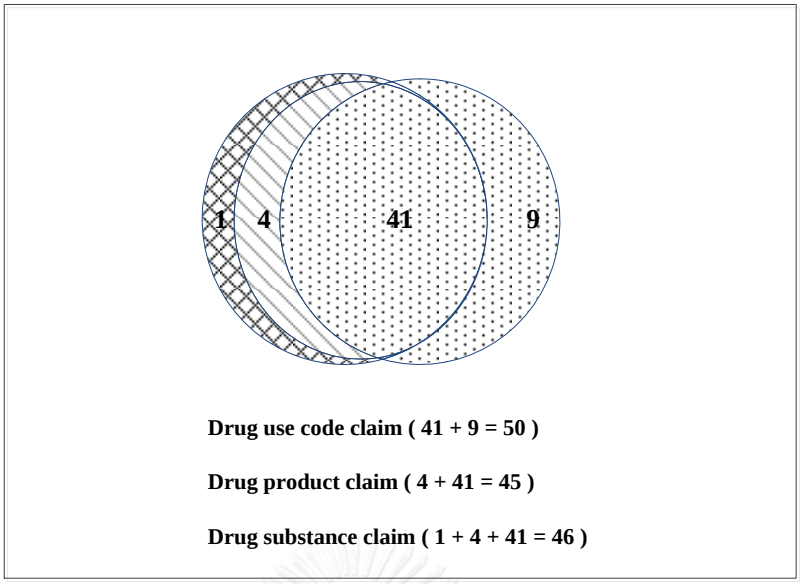


Figure 19: Patent information of 55 API separated by type of claim

The patent information from USFDA database was the current information of patent protection at the date of searching. If the patent was expired, its patent information claim was also deleted from the database. Moreover, there were no information patent protection of 21 APIs classified as biological license application (BLA) in USFDA database. The information whether patented claims of biologics were available in USA was not identified and taken into account in this study. However, there was no linkage between US patent and Thai patent, thus, patent status was active in US did not reflect patent protection status of the same API in Thailand.

Based on the 46 APIs with drug substance claims that were not yet expired in US, 27 items of APIs were found MAA in Thailand. Two from these 27 antineoplastic APIs, including imatinib and pemetrexed, were found to have new generic drugs in Thai market since 2001 and 2005 respectively. The rest or 25 from 27 antineoplastic APIs with unknown patent protection status in Thailand still had drug substance claims in the US. Two products, aminolevulinic acid and bevacizumab, were classified as biological product, the patent protection status was searched from USPTO and found protected period was still active.

Table 49: List of 25 APIs with no new generic drug in Thailand and the patent protection expiry date of API found in US

API name	Expired date of drug substance (DS) claim in the US: mm/dd/yyyy
afatinib	07/29/2018
aminolevulinic acid	09/30/2013
bevacizumab	02/26/2018
bortezomib	05/03/2017
cabazitaxel	03/26/2016
carfilzomib	04/14/2025
cetuximab	02/12/2018
clofarabine	01/14/2018
crizotinib	08/26/2025
dasatinib	06/28/2020
eribulin	06/16/2019
erlotinib	11/08/2018
everolimus	09/09/2019
gefitinib	05/05/2017
ixabepilone	05/26/2018
lapatinib	09/29/2020
lenvatinib	10/19/2021
nilotinib	07/04/2023
pazopanib	12/19/2021
regorafenib	01/12/2020
sorafenib	01/12/2020
sunitinib	02/15/2021
temsirolimus	02/15/2019
vemurafenib	06/21/2026
vismodegib	11/11/2028
Total : 25 APIs	

4.2.2.4 Novelty

Based on the ATC-code system of WHO, the last two digits was defined as "Novelty Code" in this study. This code normally initiated "01" as a breakthrough

of each chemical group and followed with 02, 03 and etc. as a me-too in the same group. The ratio of breakthrough/me-too in each country, was the index of breakthrough accessibility for treatment in that county. It was found that the breakthrough accessibility approximately 0.26 in Malaysia, 0.22 in Thailand, 0.18 in Singapore, 0.17 in UK, 0.14 by WHO and in USA, and 0.06 by EMA as presented in the table 50.

Table 50 Number of API based on novelty classification "breakthrough" and "me-too" across country, including NLEM and EML-WHO

The last two digits of ATC-code as a novelty code									
Novelty code	Number of chemical substance or API								
	WHO	USA	UK	EMA	TH	SG	MAL	NLEM - TH	EML-WHO
01 (Breakthrough)	22	16	17	4	16	14	14	14	12
%	12.22	12.31	14.29	5.33	18.18	15.22	20.59	36.84	35.29
Other (Me-too)	158	114	102	71	72	78	54	24	22
%	87.78	87.69	85.71	94.67	81.82	84.78	79.41	63.16	64.71
Total	180	130	119	75	88	92	68	38	34

As noticed that the index (breakthrough/me-too) of breakthrough accessibility for treatment for NLEM was 0.58 %. It was not different from EML-WHO. It was revealed that 87.5% (ratio: 14/16) of breakthrough APIs in Thailand was listed on NLEM for treatment. Patient, therefore, could access almost all of breakthrough APIs and 33.33% (ratio: 24/72) of me-too product in Thailand. The list of "Novelty Code" of antineoplastic API available in each country was shown in table 65.

The higher proportion of breakthrough could, to a certain extent, reflect recommended practice guideline of NLEM. However, the breakthrough, even represented the new technology, did not necessary imply the best choice or treatment of the group. Table 51 presented the novelty code of each antineoplastic API.

Table 51: Number of APT based on the last two digits of ATC-code level 5 as a novelty code

The last two digits of ATC-code as a novelty code									
Novelty code	Number of chemical substance or API								
	WHO	USA	UK	EMA	TH	SG	MAL	NLEM - TH	EML - WHO
01	22	16	17	4	16	14	14	14	12
02	16	14	12	3	10	10	11	7	9
03	17	10	11	3	11	9	8	5	3
04	12	9	7	4	8	6	5	1	2
05	12	6	6	3	6	6	4	2	3
06	9	6	6	4	6	6	6	4	2
07	8	5	5	4	4	4	4	1	
08	6	4	4	3	3	2	2	1	
09	5	4	3	2	1	2	2		1
10	4	3	2	2	2	2	1		
11	4	3	4	3	2	3	2		
12	2	2	2	2		1			
13	2	2	2	2	2	2			
14	3	3	3	2	1	2	1	1	1
15	2	2	2	2	1	2			
16	4	2	2	2	2	1			
17	3	3	3	3	1	3	1		
18	3	2	1	1		2			
19	3	2	2	1	1	1	1		1
21	2	2	2	2	1	1			
22	3	2	2	2					
23	2	1	2	2		1			
24	2	2	1	1					
25	2	2	2	2					
26	1	1	1	1					
27	2	2	2	2	1	1	1	1	
28	1	1	1	1		1			
29	2	2	1	1	1	1			
31	1	1	1	1		1			
32	2	1	1	1	1	1	1		
33	2	1							
34	1								
35	1	1	1	1	1	1	1		
36	1								
37	1								
38	1	1					1		
39	1	1							
40	1	1							
41	1	1	1	1	1	1			
42	1	1							
43	1	1	1	1	1	1			
44	1	1	1	1	1	1			
45	1	1	1	1	1				
46	1	1	1	1					
47	1	1	1	1		1			
48	1	1	1	1					
49	1	1							
50	1	1							
52	1								
53	2		1	1	2	2	2	1	
59	1								
Total	**180**	**130**	**119**	**75**	**88**	**92**	**68**	**38**	**34**

4.2.2.5 Priority list

In Principal, selection of a cancer drug for treatment was based on the relative efficacy and cost effectiveness. Based on the appropriate dosage forms, the assured quality, and at a price the individual and the community could afford, World Health Organization (WHO) recommended medicines to be on the essential medicine list for patients. The concept of essential medicines was forward-looking. It incorporated the need to regularly update medicine selections to reflect new therapeutic options and changing therapeutic needs; the need to ensure drug quality; and the need for continued development of better medicines, medicines for emerging diseases, and medicines to meet changing resistance patterns. The WHO's 'Model Lists of Essential Medicines' or 'Essential Medicines List' (EML-WHO) was initially implemented in 1977. The new version was set to be updated every two years. The existing version at the time of study was the 19th version which was implemented in 2015. More than 35 years, EML-WHO was accepted by many counties as a global concept of essential drug model to provide in the country health system. Thailand also accepted the WHO's model list of essential drug to be our model before 1980. The principle of EML-WHO was the minimal list but the NLEM concept in Thailand had been modified to the appropriate list. In other therapeutic category, the NLEM of Thailand could carry a long list of medicine if considered as appropriate for treatment of particular disease or symptom.

Then, based on the Thailand epidemiology, the first of National list of essential medicine (NLEM) of Thailand was implemented in 1981. Until now, the current version is 11th version of NLEM updated in year 2016. Correspondence of health policy, in this study, the WHO Model Lists of Essential Medicines was selected to be 'the priority list'. According to WHO policy, antineoplastic drugs were also listed in EML-WHO as essential items. Thirty-four (34) APIs of antineoplastic drugs were found in the 19th version of EML-WHO. Meanwhile, thirty-eight (38) items of APIs were presented in the current version (11th version) of NLEM of Thailand. The NLEM have 4 more APIs than EML-WHO.

Table 52: Comparison of chemical substance or API of antineoplastic drug between NLEM and EML-WHO

Pharmacological group (ATC code level 3): chemical group (ATC-code Level 4			Number of API	
			NLEM-TH (Version 2016)	EML-WHO (Version 2015)
A: Alkylating Agents	ATC - L4	A: Nitrogen mustard analogues	4	4
		B: Alkyl sulfonates	1	-
		C:Ethylene imines	-	-
		D:Nitrosoureas	1	-
		G:Epoxides	-	-
		X:Other alkylating agents	1	1
	Total		**7**	**5**
B: Antimetabolites	ATC - L4	A :Folic acid analogues	1	1
		B:Purine analogues	2	3
		C:Pyrimidine analogues	5	4
	Total		**8**	**8**
C: Plant alkaloids and other natural Product	ATC-L4	A: Vinca alkaloids and analogues	2	3
		B: Podophyllotoxin derivatives	1	1
		C: Colchicine derivatives	-	-
		D: Taxanes	2	2
		X: Other plant alkaloids	-	-
	Total		**5**	**6**
D: Cytotoxic antibiotics and related substance	ATC-L4	A: Actinomycines	1	1
		B: Anthracyclines and related substances	3	2
		C: Other cytotoxic antibiotics	2	1
	Total		**6**	**4**
X: Other antineoplastic agents	ATC-L4	A: Platinum compounds	3	3
		B: Methylhydrazines	1	1
		C: Monoclonal antibodies	1	2
		D: Sensitizers used in photodynamic /Radia.-T	-	-
		E: Protein kinase inhibitors	3	1
		X: Other antineoplastic agents	4	4
	Total		**12**	**11**
Total: Chemical substances			**38**	**34**

NLEM: National list of Essential Medicine, EML-WHO: Essential Medicines List of WHO

Based on five (5) main pharmacological groups of antineoplastic drugs, twenty-three (23) chemical groups, and three (3) pharmacological groups of NLEM have the items of chemical substance on top of EML-WHO such as A: 'Alkylating Agents' had 7 APIs in NLEM but 5 APIs in EML-WHO, 'D: Cytotoxic antibiotics' and related substance had 6 APIs in NLEM but 4 APIs in EML-WHO, 'X: Other antineoplastic agents' had 12 APIs in NLEM but 11 APIs in EML-WHO. Only 'C: Plant alkaloids' and other natural products had 5 APIs in NLEM which was less than 6 APIs in EML-WHO. The detail was presented in the table 52

4.2.2.6 Targeted cell therapies

Out of 88 APIs registered in Thailand, 25 were classified as targeted cell therapies as presented in the previous table (table 31)

(Table 31: Number of API classified as targeted cell therapies across the countries)

Country or item listed	Number of API		% TGC
	Total	Targeted cell therapies (TGC)	
WHO	180	52	100
US	130	51	98.08
UK	119	45	86.54
EMA	75	45	86.54
SG	92	35	67.31
MAL	68	16	30.77
TH	88	25	48.08
New generic drug (NG)	14	1	1.92
NLEM	38	4	7.69
EML-WHO	34	3	5.77

Targeted cell therapies were new technology and concept of cancer treatment. The objective of targeted therapies was to combat directly to cancer cells with fewer side effects to normal body cells (National Cancer Institue, 2014). It was revealed that all

targeted call therapies, 25 of 88 items of APIs, were new drug classification in Thailand. Only one API, imatinib, that had new generic (NG) drug available in the market as in table 53.

Table 53: Number of API classified as targeted cell therapies across drug registration classification

Targeted cell therapies (TGC) and number of API		Number of API		
		Generic drug (G)	New drug (N)	New Gen drug (NG)
TGC	25		24	1
Not TGC	63	29	21	13
Total	88	29	45	14

In term of market access, the accessibility of the new trend of treatment "Target cell therapy" was found in US almost 100% of WHO, UK and EMA 86.54 %, Singapore 67.31%, Thailand 48.08%, and Malaysia 30.77 % as seen in table 32. However, in term of new technology and new trend of treatment, Singapore presented the access this new technology of treatment above Thailand. Assuming innovative company decision to submission TGC product in the same time in ASEAN countries which drug registration guideline and ACTD were harmonized. It was revealed that the potential of drug registration system and its process in Singapore had well organized to speed up the access new technology of treatment.

4.2.2.7 The country of headquarter

The country of headquarter was defined as the country where headquarter (HQ) of product owner (product license holder in Thailand, drug manufacturer) was located. In this study, the first brand of antineoplastic API in Thailand was search for product owner. Then, the country of HQ of product owner was obtained and classified by country zone.

Since approximately 50% of antineoplastic drug in Thailand were new drug classification which located in EU:24 APIs, in US: 15 APIs and Asia: 6 API. One new

generic drug was doxorubicin which was the secondary dosage form in Thailand. The first registration of doxorubicin in Thailand was generic drug with unknown HQ. Since doxorubicin had three classification types in the market, the last classification was new generic drug from Taiwan (Asia zone). Table 54 and 55 revealed that new technology on TGCs were mostly from EU with 18 APIs, 6 APIs from US, and one API from Asia (lenvatinib: Japan). Similarly, the HQ from EU zone had the most number of biological products.

Table 54: Number of active pharmaceutical ingredient (API) by country zone, where the country of headquarter was located, across drug classification

Drug classification (Type and number of API)		Number of API by zone of country where HQ was located			
		US	EU	Asia	Unknown
Generic drug (G)	29	9	8	5	7
New drug (N)	45	15	24	6	
New generic drug (NG)	14	7	6		1*
Total	88	31	38	11	8

* the first registration of doxorubicin in Thailand was generic drug with unknown HQ. Doxorubicin had three classification type in the market, the last classification was NG

Table 55: Number of active pharmaceutical ingredient (API) by country zone, where the country of headquarter was located, across type of drugs (TGC and BLA)

Targeted cell therapies (TGC) and Biological license application (BLA) in TH and number of API		Number of API by zone of country where HQ was located			
		US	EU	Asia	Unknown
TGC	25	6	18	1	
BLA	10	1	7	2*	

*one BLA was classified by Thai FDA as a generic drug

4.2.3 Additional analysis

Approved indication in Thailand

According to the epidemiology of cancer in Thailand, the treatment or medical algorithm must be consistency. Therefore, the approved indication of antineoplastic drugs should correspond to the statistics of cancer diseases and patients of which registry was recorded in Thailand.

Cancer statistic in Thailand (2009-2012)

Table 56: Number of new cancer registry patient in Thailand during 2009-2011

Cancer Site	Year of Hospital Based Cancer Registry Report*				CAGR%	Cumulative Growth %
	2009	2010	2011	2012		
Breast	768	821	761	943	7.08	22.79
Colon and rectum	342	369	417	454	9.90	32.75
Trachea bronchus, lung	371	332	336	407	3.14	9.70
Cervix uteri	298	276	289	340	4.49	14.09
Liver and bile duct	236	215	336	285	6.49	20.76
Lip & Oral cavity	165	135	175	188	4.45	13.94
Non-Hodgkin lymphoma	100	98	96	109	2.91	9.00
Oesophagus	70	87	80	105	14.47	50.00
Ovary	77	69	90	87	4.15	12.99
Prostate gland	70	19	45	79	4.11	12.86
Other sites	817	715	716	920	4.04	12.61
Total all sites	**3,314**	**3,136**	**3,341**	**3,917**	**5.73**	**18.20**
Total without other sites	**2,497**	**2,421**	**2,625**	**2,997**	**6.27**	**20.02**

Note*: Number of new cancer registry patient during during year 2011-2012, data from website of National Cancer Institute (NCI),Thailand. http://www.nci.go.th/th/cancer_record/cancer_rec1.html, accessed date on Mar 23, 2016

Based on the registry cancer records by cancer site, of the National Cancer Institute (NCI) during 2009-2011, the number of breast cancer won as one of the top 10 registry

cancers in Thailand. Then, It was followed with trachea bronchus and lung, colon and rectum, cervix uteri, lip & oral cavity, Non-Hodgkin lymphoma, esophagus, ovary, and the last one, prostate gland. Consideration from top six of cancer sites for the compound annual growth rate (CAGR) of cancer sites; it was revealed that colon cancer had high CAGR at 9.90% with second most number of patients following with breast cancer, liver cancer, cervical cancer, respectively, as shown in the Table 56

Antineoplastic drug based top five of cancer site in Thailand

Based on the cancer statistic in Thailand including 88 APIs that were available in the maket in April 2016, when considering only for top five cancer sites, 23 APIs were approved for breast cancer, 9 APIs for colon cancer, 21 APIs for lung cancer, 6 APIs for cervical cancer, and 15 APIs for ovarian cencer as presented in the Table 57 below.

The National Health Security Office (NHSO) of Thailand had allocated funding through the Universal Coverage (UC) program originally known as the "30 baht program" (implemtnted in 2001 until now) to treat cancer patients. Therefore, majority of Thai patients were covered under the UC scheme for health treatment. In 2013, National Health Security Office (NHSO) has launched the cancer treatment protocol or guideline for 10 cancer treatments based on cancer sites: breast, cervix uteri, ovary , oesophagus, lung, liver and bile duct, colon and rectum, nasopharynx (lip&Oral cavity), bladder and prostate gland (NHSO, 2013). This cancer treatment protocol was, finally, implemented in public hospitals in Thailand. Antineoplatics drugs in this protocol were based on drug listed on the NLEM. Therefore, in this study, treatments for ten cancer sites were listed, based on the cancer treatment protocol 2013 of NHSO. One cancer site Non-Hodgkin lymphoma was ranked sixth of ten in the Thailand registry cancer recorded of NCI during 2009-2011 but there was no treatment on the list of cancer protocol but the list contained bladder cancer protocol instead as in table 57

From 10 cancer sites, twenty three (23) APIs were for breast cancer treatment, but only 14 APIs were listed in NLEM of 2016. All six APIs for cervical cancer treatment were in the NLEM list. Eleven of 15 APIs for ovarian cancer, six of nine for lip and oral

cavity cancers, 13 of 21 APIs for lung cancer, all 2 APIs for esophageal cancer, 4 of 10 for colon and rectal cancer, 4 of 5 for liver cancer, 4 of 5 for bladder cancer and 2 of 3 for prostate cancer were listed in NLEM. These information was shown in Table 58, 59, 60, 61, 62, 63, 64, 65, 66 and 67.

There were only 2 APIs for breast cancer, 1 for lung cancer, and 1 for prostate cancer that were listed under E(2) category of NLEM that required DUE before hospitals could get reimbursement. In general, even the list was not substantial but the NLEM had included almost all chemical groups and seemed to cover treatment for major cancer sites.

Table 57: Number of API across approved indication cancer sites

Cancer site*	Number of API of antineoplastic drugs					
	Thailand (N=88)		NLEM 2016 (N=38)			
	N	%	C	D	E(2)	Total
Breast Cancer	23	26.14	4	9	2	15
Colon and rectal cancer	10	11.36	1	3		4
Lung cancer	21	23.86	8	4	1	13
Cervical cancer	6	6.82	4	2		6
Liver cancer	5	5.68	1	3		4
Lip and oral cavity cancers	9	10.23	5	1		6
Esophageal Cancer	2	2.27	1	1		2
Ovarian cancer	15	17.05	8	3		11
Bladder cancer	5	5.68	3	1		4
Prostate cancer	3	3.41		1	1	2

* drugs of cancer treatment are based on 10 cancer sites of cancer protocol in 2013,
%: percentage was calculated based on total 88 APIs registered in Thailand

Table 58: List of API approved for breast cancer across dug classification and subgroup in NLEM

Drug classificaiton	Number of chemical substance for breast cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	cyclophosphamide	1		
	doxorubicin**	1		
	epirubicin			
	fluorouracil	1		
	ifosfamide		1	
	methotrexate	1		
	mitomycin		1	
	mitoxantrone		1	
	pirarubicin			
	tegafur, uracil (UFT)		1	
	Total = 10	4	4	-
New Drug (N)	bevacizumab			
	eribulin			
	everolimus			
	ixabepilone			
	lapatinib			
	pertuzumab			
	trastuzumab			1
	Total = 7	-	-	1
New Generic drug (NG)	capecitabine		1	
	docetaxel			1
	gemcitabine		1	
	idarubicin		1	
	paclitaxel		1	
	vinorelbine			
	Total = 6	-	5	1
Total =23		4	9	2
		15		

*: Form the Thai FDA database at April 2016, NLEM: National list of essential medicine.

** : doxorubicin on NLEM is generic drug. The secondary dosage form of doxorubicin (liposome) classified as a new drug, and it is not on NLEM

Table 59: List of API approved for colon cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for colon cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug(G)	epirubicin			
	fluorouracil	1		
	mitomycin		1	
	Total = 3	1	1	-
New drug (N)	aflibercept (ZIV)			
	bevacizumab			
	cetuximab			
	regorafenib			
	Total = 4	-	-	-
New genric drug (NG)	capecitabine		1	
	irinotecan			
	oxaliplatin		1	
	Total = 3	-	2	-
Total =10		1	3	-
		4		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

Table 60: List of API approved cervical cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for cervical cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	bleomycin	1		
	carboplatin	1		
	cisplatin	1		
	ifosfamide		1	
	Total = 4	3	1	-
New drug (N)	hydroxycarbamide (HydroxyUrea)	1		
	Total = 1	1	-	-
New generic (NG)	gemcitabine		1	
	Total = 1	-	1	-
Total = 6		4	2	-
		6		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

Table 61: List of API approved for lung cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for lung cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	bleomycin	1		
	carboplatin	1		
	cisplatin	1		
	cyclophosphamide	1		
	doxorubicin**	1		
	epirubicin			
	etoposide	1		
	ifosfamide		1	
	methotrexate	1		
	mitomycin		1	
	Total = 10	7	2	-
New drug (N)	afatinib			
	bevacizumab			
	crizotinib			
	erlotinib			
	gefitinib			
	Total = 5	-	-	-
New generic drug (NG)	docetaxel			1
	gemcitabine		1	
	paclitaxel	1	1	
	pemetrexed			
	topotecan			
	vinorelbine			
	Total = 6	1	2	1
Total = 21		8	4	1
		13		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

** : doxorubicin on NLEM is generic drug. The secondary dosage form of doxorubicin (liposome) classified as a new drug, and it is not on NLEM

Table 62: List of API approved liver cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for liver cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	fluorouracil	1		
	mitoxantrone		1	
	Total = 2	1	1	-
New drug (N)	sorafenib			
	Total = 1	-	-	-
New generic drug (NG)	gemcitabine		1	
	oxaliplatin		1	
	Total = 2	-	2	-
Total = 5		1	3	-
		4		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

Table 63 : List of API approved for lip and oral cavity cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for lip and oral carvity cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	bleomycin	1		
	carboplatin	1		
	cisplatin	1		
	methotrexate	1		
	mitomycin		1	
	pirarubicin			
	Total = 6	4	1	-
New drug (N)	cetuximab			
	hydroxycarbamide	1		
	nimotuzumab			
	Total =3	1	-	-
Total = 9		5	1	-
		6		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

Table 64: List of API approved for esophageal cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for esophageal cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (GD)	fluorouracil	1		
	Total = 1	1	-	-
New generic drug (NG)	capecitabine		1	
	Total = 1	-	1	-
Total = 2		1	1	-
		2		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

Table 65: List of API approved for ovarian cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for ovarian cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	carboplatin	1		
	chlorambucil	1		
	cisplatin	1		
	cyclophosphamide	1		
	doxorubicin**	1		
	epirubicin			
	fluorouracil	1		
	ifosfamide		1	
	melphalan**	1		
	pirarubicin			
	Total = 10	7	1	-
New drug (N)	altretamine			
	hydroxycarbamide	1		
	Total = 2	1	-	-
New generic drug (NG)	gemcitabine		1	
	paclitaxel		1	
	topotecan			
	Total =3	-	2	-
Total = 15		8	3	-
		11		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

** doxorubicin and melphalan on NLEM are generic drug. The secondary dosage form of doxorubicin (liposome) and melphalan (inj) classified as new drug, and they are not on NLEM

Table 66: List of API approved for bladder cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for bladder cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug (G)	carboplatin	1		
	cisplatin	1		
	doxorubicin**	1		
	pirarubicin			
	Total = 3	3	-	-
New generic drug (NG)	gemcitabine		1	
	Total = 1	-	1	-
Total		3	1	-
		4		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

** : doxorubicin on NLEM is generic drug. The secondary dosage form of doxorubicin (liposome) classified as a new drug, and it is not on NLEM

Table 67: List of API approved for prostate cancer across dug classification and subgroup in NLEM

Drug classification	Number of chemical substance for prostate cancer*			
	Chemical substance	NLEM		
		C	D	E(2)
Generic drug(G)	mitoxantrone		1	
	Total = 1	-	1	-
New drug (N)	cabazitaxel			
	Total = 1	-	-	-
New generic drug (NG)	docetaxel			1
	Total = 1	-	-	1
Total = 3		-	1	1
		2		

* Form the Thai FDA database at April 2016, NLEM: National list of essential medicine

4.3. Bivariate Relationship

4.3.1 Relation between time lag (between match TH – US) and each variable

The dependent variables were time lags. The first lag was measured by differences between first MAA in Thailand and first MAA in US for each API. The second dependent variable measured the time lag between the time API was listed on NLEM and time when it was first approved by Thai FDA. The independent variables included all concepts in the conceptual framework, i.e., patent, drug classification, novelty code, EML-WHO, cost per month, market size or patient-month, country of headquarter, and targeted cell therapy.

Patent status in the US

Market access

The relation between "time delay of antineoplastic drug to Thai market" and "patent status in the US", the result was shown in the table below.

Table 68: Independent t-test table of relation between "time delay of antineoplastic drug to Thai market" and "patent in US"

Time lag	Patent in US	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
TH - US	Yes	29	29.18	32.80	6.09	-16.25	-1.38	44.62	.174
	No	28	45.43	53.27	10.07				

There was no statistically significant difference of time lag between the patent status in US. "Yes" referred to active current status of patent, while "No" referred to no patent protection in the US. Even the statistics did not show significant difference between patented and not patented group, the not patented group had an average of 45.43 months of time lag while patented group had 29.18 months delayed representing longer than 1 year different between 2 groups. The non-significant statistics could be resulted from small sample sizes or large standard deviation of both groups.

As discussed in the patent section, APIs with patents referred to those that patents were not yet expired, while no patented APIs more likely to refer to those with patent already expired. So, the shorter time lag possibly reflected APIs that were first registered more recently than the longer time lag. According to time lag across period, the most current period tended to have a shorter time lag. The shorter time delay could have represented that current patented products in US accessed Thai market faster than those not patented product.

Patient access

Table 69: Independent-sample t-test table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "patent in the US"

Time lag	Patent in US	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
NLEM - TH	Yes	4	99.66	33.14	16.57	15.08	.392	15	.700
	No	13	84.58	73.31	20.33				

The time lag of being listed on NLEM between patented and not patented products were not significantly different. Both groups needed to wait 7- 8 years before an API could be listed on NLEM.

EML-WHO

Market access

EML-WHO was defined as priority list for cancer treatment recommended by WHO. The relationship between "time delay of antineoplastic drug to Thai market" and "EML-WHO as shown in the table below. There was no statistically significant difference of time lag between items on the priority list and not on the list of EML-WHO.

Table 70: Independent t-test table of relation between “time delay of antineoplastic drug to Thai market” and “availability of essential medicine list of WHO (EML-WHO)”

Time lag	EML-WHO	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
TH - US	Yes	16	35.54	58.39	14.60	-2.25	-0.17	55	.865
	No	41	37.79	38.51	6.01				

Patient access

The relation between “time delay of antineoplastic drug to be listed on NLEM” and availability on essential medicine list of WHO (EML-WHO) was shown in table below. There was no statistically significant difference between 2 groups, those listed and not on the list on EML-WHO. However, for this analysis, the EML-WHO had 12 items on the list and 5 items not on the list. The sample size was too small to analyze the difference between both groups.

Table 71: Independent-sample t-test table of relation between “time delay of antineoplastic drug to be listed on NLEM” and “availability of essential medicine list of WHO”

Time lag	EML-WHO	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
NLEM - TH	Yes	12	102.45	69.41	20.04	-48.70	-1.45	15	.169
	No	5	53.75	42.19	18.87				

Targeted cell therapy

Market access

The relation between “time delay of antineoplastic drug to Thai market” and targeted cell therapy API was shown in the table below. There was significantly different (p=0.014) between targeted cell therapy items and non-targeted cell therapy items on the time lag. Those TGC items had average time lag of 22.19 months while non-targeted cell therapy took approximately 4 years delayed entering Thai market. Since

TGCs were new trend of cancer treatment. The need of new treatment showed some influences on the time lag. This could also have related to the more current groups of cancer therapy of TGCs.

Table 72: Independent t-test table of relation between "time delay of antineoplastic drug to Thai market" and "targeted cell therapy (TGC) classification"

Time lag	TGC	N	Mean	SD	SE.mean	Mean Diff	t	df	Sig. (2-tailed)
TH - US	yes	25	22.19	21.41	4.28	-26.66	-2.56	42.60	.014
	no	32	48.85	53.74	9.50				

Patient access

The relation between "time delay of antineoplastic drug to be list on NLEM" and targeted cell therapy API was shown in the table below. To list on NLEM still took a very long waiting time, however, the NLEM items on this analysis had too small sample size to meaningfully interpret the result of the real difference.

Table 73: Independent-sample t-test table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "targeted cell therapy (TGC) classification"

Time lag	TGC	N	Mean	SD	SE.Mean	Mean Diff	t	df	Sig. (2-tailed)
NLEM - TH	yes	4	117.60	47.79	23.90	38.54	1.03	15	.318
	no	13	79.06	68.97	19.13				

The country of headquarter

Market access

The relation between "time delay of antineoplastic drug to Thai market" and the country of origin was shown in the table below. Since the country of headquarter was classified into 3 regions plus some items with unknown location of headquarter, only 2 regions, US and EU was selected for the analysis. The Asian countries and unknown had small

sample sizes and they were not major research and development countries, thus only US and UK were selected for the analysis. The result showed that no significant difference was found on time lag between 2 groups. However, the time lag showed that items having headquarter in US had approximately 4 years delayed while those in EU had a few months over 2 years of time lag. Even it did not show statistical different, items from EU tended to enter Thai market after registered in US with shorter waiting period than those from US.

Table 74: Independent t-test table of relation between "time delay of antineoplastic drug to Thai market" and "country of HQ"

Time lag	Country of HQ	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
TH - US	US	24	48.32	42.03	8.58	20.87	1.95	49	.057
	EU	27	27.45	34.41	6.62				

Patient access

The relation between "time delay of antineoplastic drug to be list on NLEM" and the country of origin was shown in the table below. There was a significant difference found between items with country of origin USA and EU ($p = 0.002$). However, small sample sizes should be noted. The findings depicted opposite picture from the market time lag that items from EU entered Thai market faster than those from US. The time lag to be listed on Thai NLEM was taken 135.94 months for items from EU, while items from US took approximately 3 years. This posed a substantial difference of time lag between items from 2 different sources and needed further exploration.

Table 75: Independent-sample t-test table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "country of HQ"

Time lag	Country of HQ	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
NLEM - TH	US	7	32.15	55.78	21.08	-103.79	-4.01	12	.002
	EU	7	135.94	39.80	15.04				

Novelty

Market access

The relation between "time delay of antineoplastic drug to Thai market" and novelty of antineoplastic drug was shown in the table below.

Table 76: Descriptive table of one-way ANOVA test between time delay of antineoplastic drug to Thai market" and three novelty groups.

Time lag	Novelty code	N	Mean	SD	SE
TH - US	01	3	48.21	40.45	23.35
	02 and 03	11	12.14	58.61	17.67
	> 03	43	42.79	39.12	5.97
	Total	57	37.16	44.42	5.88

All novelty codes were recoded into 3 groups, including 01or first in the chemical group, 02 and 03 or the first 2 me-too APIs, and >03 or later me-too items. Since the "01" group had only 3 items, this group was dropped from the analysis and the comparison of time lag across 2 novelty groups was conducted.

The finding of t-test in table 76 showed significant difference of time lag between "02 and 03" group and ">03" group (p-value=0.042). While "02 and 03" took about 1 year, ">03" group took about 3.5 years different between Thai first registration and US first registration. Evidence showed that the accessibility of me-too level 02 and 03 of antineoplastic drugs needed a shorter time than me-too level ">03". Since breakthrough (01) was the newness in the chemical group, time delay before entering the Thai market was found longest when compared with me-too products. This 01 group also needed further analysis since the sample size was only a few items. However, among me-too products, novelty level 02 and 03 had shorter time delayed when compared to other me-too beyond >03.

Table 77: Independent-sample t-test table of relation between time delay of antineoplastic drug to Thai market" and "two novelty groups"

Time lag	Novelty code	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
TH - US	02 and 03	11	12.14	58.61	17.67	-30.65	-2.08	52	.042
	> 03	43	42.79	39.12	5.97				

Patient access

Table 78 showed statistically significant difference of time lag listed on NLEM between 2 novelty groups of me-too level "02 and 03" and me-too level ">03" (p-value = 0.07). The patient access to me-too level "02 and 03" of antineoplastic drugs needed to wait longer than me-too ">03". The same pattern found among other independent variables including targeted cell therapy, country of headquarter, and novelty code.

It could be estimated that the NLEM decision, particularly early versions, was not revised on a regular schedule, thus, items with shorter market time lag and items with longer market time lag would be reviewed for NLEM listing during the same revision version. Those were already in the market had to wait for the decision at the same time with the new market entry items. The "02 and 03" group which entered the market before the ">03" group had shorter market time lag but would have longer patient time lag.

Table 78: Independent-sample t-test table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "two novelty groups"

Time lag	Novelty code	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
NLEM - TH	02 and 03	5	147.57	28.57	12.78	85.96	3.23	12	.007
	> 03	9	61.61	54.77	18.26				

Price of antineoplastic drug

Market access and patient access

For standardization, price was calculated in term of "cost per month". The relationship between "time delay of antineoplastic drug to Thai market" and cost per month was shown in the table below. The pearson correlation did not show significant relationship between time lag and cost per month. The relationship was also not existed across different drug registration classification. No relationship was confirmed with the patient time lag as well.

Table 79: Correlation table of relation between time delay of antineoplastic drug to Thai market" and "cost per month across the drug classification"

Time lag	Statistic parameter	Cost per month		
		Generic drug	New drug	New generic drug
TH - US	Pearson Correlation	.026	.180	.015
	Sig. (2-tailed)	.956	.267	.967
	N	7	40	10

Table 80: Correlation table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "cost per month across the drug classification"

Time lag	Statistic parameter	Cost per month		
		Generic drug	New drug	New generic drug
NLEM - TH	Pearson Correlation	- .980**	.259	.397
	Sig. (2-tailed)	.003	.417	.508
	N	5	12	5

**. Correlation is significant at the 0.01 level (2-tailed).

There was a correlation between the two variables: time lag and cost per month: generic drug [r = 0.980, n = 5, p = 0.003]. Therefore, in term of patient access by time lag, there are relationship with generic drug price of antineoplastic drug.

Market size

Market access and patient access

The pearson correlation between "time delay of antineoplastic drug to Thai market" and market size, measured by sale value and by patient-month across 4 years during 2011-2014 showed no significant relationship. The consistent result was found in patient time lag on NLEM as well. The findings pointed that market sizes, both sales volume in monetary measure and utilization by patient-months, did not significantly explain both market and patient time lag.

Table 81: Correlation table of relation between time delay of antineoplastic drug to Thai market" and "sale value year 2011 -2014"

Time lag	Statistic parameter	Sale value by year			
		2011	2012	2013	2014
TH - US	Pearson Correlation	-.183	-.189	-.156	-.179
	Sig. (2-tailed)	.271	.237	.319	.229
	N	38	41	43	47

Table 82: Correlation table of relation between time delay of antineoplastic drug to Thai market" and "patient – month across year 2011 -2014"

Time lag	Statistic parameter	Patient - month across year			
		2011	2012	2013	2014
TH - US	Pearson Correlation	-.069	-.075	-.049	-.057
	Sig. (2-tailed)	.680	.641	.754	.703
	N	38	41	43	47

Table 83: Correlation table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "sale value across year 2011 -2014".

Time lag	Statistic parameter	Sale value by year			
		2011	2012	2013	2014
NLEM - TH	Pearson Correlation	.100	.137	.072	.091
	Sig. (2-tailed)	.703	.599	.791	.729
	N	17	17	16	17

Table 84: Correlation table of relation between "time delay of antineoplastic drug to be listed on NLEM" and "patient - month across year 2011 - 2014".

Time lag	Statistic parameter	Patient - month across year			
		2011	2012	2013	2014
NLEM - TH	Pearson Correlation	-.165	-.162	-.187	-.165
	Sig. (2-tailed)	.528	.533	.487	.528
	N	17	17	16	17

4.3.2 Additional Analysis

Trip agreement distress

Since Thailand could not manufacture antineoplastic drugs domestically, therefore, antineoplastic products were mainly imported as a finished product from the other countries. The source of antineoplastic drug especial "new generic drug" was mostly imported from India that was the main production of generic drug imitated or copied from the innovative product. Since India was forced to accept the Trade-Related Intellectual Property Rights (TRIPS) agreement in 1995. TRIPS which was in effect

starting January 1, 1995, provided a transition period of 10 years for developing countries. The Indian pharmaceuticals was affected by the new patent laws that was enforced since January 1, 2005 as part of the (TRIPS) agreement.

Table 85 showed how TRIPS had an impact on access to antineoplastic in Thailand. The statistics explained that time lag for a new generic (NG) product to enter Thai market was about 8 years longer after TRIPS was fully enacted in 2005 (136.30 vs 40.68 months). The NG which was much less cost than the original branded product could not be marketed until the patent was expired. Thus, India could not export the NG product unless the patent was expired. Thailand, even did not manufacture, could import a less costly product if TRIPS was not enforced in India.

Table 85: Independent-sample t-test table of relation between "time delay of new generic drug of antineoplastic drug to Thai market" and year of MAA before or after 2005

Time lag	Year of MAA	N	Mean	SD	SE.Mean	Mean Diff.	t	df	Sig. (2-tailed)
NG - TH	after 2005	6	136.30	46.07	18.81	95.62	4.74	11	.001
	before 2005	7	40.68	25.43	9.61				

4.4 Multi linear regression.

The multiple linear regression was conducted to explore and explain the relationship "time lag between the first MAA in Thailand and it's in US" by seven independent variables according to the conceptual framework of the study.

Seven predictors included targeted cell therapy, novelty, country of origin or HQ, market size, patent available in US, price calculated as a cost per month, and EML-WHO as priority list. The categorical variables in the model, composed of targeted cell therapy, novelty code, patented in US, country of HQ, EML-WHO list, were dummy coded. Two groups of dummy coding included Whether or not an API was targeted cell therapy, patented in US, EML-WHO. The three groups dummy variables were

novelty code and country of HQ. The novelty code variable contained 3 attributes, API with code 01, API with code 02&03 and API with code >03. Two dummy variables were group 01 and group 02&03 with group>03 as a reference group, thus, the dummy variables entered the regression equation were novelty code 01 and novelty code 02&03. The country of HQ variable had 4 attributes including US, EU, Asia, unknown HQ. The EU group was used as the reference group while Asia and unknown were grouped together. Thus, there were 2 dummy variables for US and Asia &Unknown, entering the regression equation.

The model was shown acceptable VIF (not more than 2) for all variables in the model. The analysis shows that 35,0% of variance of market time lag was explained by 9 variables in the model with p-value = 0.043. Even the overall model was statistically significant, regression coefficient of all variables included in the model except novelty code 02&03 were not statistically significant. The dummy variable on novelty code 02 & 03 significantly explained the variance of market time lag with beta coefficient = (-44.095), standardized beta coefficient of (-0.417) and p-value = 0.012. This could be explained that APIs with novelty code of 02 and 03 had market time lag 44.095 months less than other codes.

The detail of regression model and statistics was presented in tables 86-88.

Table 86: Model summary table of multiple linear regression between time delay of antineoplastic drug to Thai market" and variables

Model	R	R Square	Adjusted R Square	SE. estimate
1	.592[a]	.350	.192	39.340

Model 1: a. Predictor: Novelty code 02 & 03, Novelty code 01, HQ from US, HQ from Asia & unknown , Patent available in US, MZ: Patient - month 2014, Price: Cost per month, EML-WHO, Targeted cell therapies

Table 87: ANOVA table of multiple linear regression between time delay of antineoplastic drug to Thai market" and variables

	Sum of Squares	df	Mean Square	F	Sig.
Regression	30817.870	9	3424.208	2.213	.043a
Residual	57261.176	37	1547.599		
Total	88079.046	46			

a. Predictor: Novelty code 02 & 03, Novelty code 01, HQ from US, HQ from Asia & unknown , Patent available in US, MZ: Patient - month 2014, Price: Cost per month, EML-WHO, Targeted cell therapies

Table 88: Coefficient table of Multiple linear regression of time delay "antineoplastic drug to Thai market" and variables

Variables	B	Std. Error	Beta	t	p	VIF
(Constant)	18.731	27.236		.688	.496	
Novelty code 02 & 03	-44.095	16.591	-.417	-2.658	.012	1.400
Novelty code 01	16.562	30.644	.094	.540	.592	1.704
HQ from US	7.706	13.751	.087	.560	.579	1.383
HQ from Asia & unknown	-23.787	24.915	-.153	-.955	.346	1.468
Patent available in US	-22.450	14.841	-.259	-1.513	.139	1.672
MZ: Patient - month 2014	-.001	.001	-.126	-.692	.493	1.875
Price: Cost per month	2.862E-05	.000	.111	.778	.442	1.163
EML-WHO	2.848	17.149	.031	.166	.869	2.005
Targeted cell therapies	19.362	15.270	.219	1.268	.213	1.705

Summary of the regression model was as followed:

Time lag (Y) = 18.731 -44.095 ATCN23 + 16.652 ATCN1 + 7.706 HQUS – 23.787 HQAsia - 22.450 Patent - 0.001 Pt-month + 0.000028 cost/month + 2.848 EML + 19.362 TGC

Where

ATCN23: Dummy variable of ATC-Level 5 with novelty code 02 & 03

ATCN1: Dummy variable of ATC-Level 5 with novelty code =01

HQUS: Dummy variable with HQ located in US country

HQAsia: Dummy variable with HQ located in Asia and Unknown country

Patent: Dummy variable whether API had patent with active status in US

Pt-month: Patient-month

Cost/month: Cost per month

EML-WHO: Dummy variable whether API was listed on EML-WHO

TGC: Dummy variable whether API was targeted cell therapies

The regression model of patient time lag could not be analyzed because of small sample size. The overall regression model and analysis reflected that market time lag, even was significantly explained by variables included in the model, only novelty code 02&03 could differentiate between group differences. The attempt to explain the time lag should be further studied with different set of variables. From periodical analysis of time lag, the study found meaningful reduction of time lag across time which represented period of regulatory changes. Further studies could be conducted choosing variables related to regulatory framework.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

Summary and conclusion

Access of antineoplastic medicines referred to availability of antineoplastic drugs for patients in an affordable way. Access to medicines could be delayed causing drug lag in Thailand during 2 steps of regulatory approval for a drug to be launched in the market, and of NLEM drug selection for broader access by patients. Antineoplastic drug lag in Thailand had been a critical public health concern. This study thus aimed at exploring the drug lag situation in Thailand for antineoplastic drugs with reference to US, UK, EU, Singapore, and Malaysia, and examined the factors that influenced the antineoplastic drug access. Seven determinants, including price, market site, patent, novelty, targeted cell therapies, WHO essential medicine list, and country of headquarter, were identified and analyzed to explain drug access in Thailand.

The study was conducted using secondary data on drug registration information from the regulatory agency website of studied countries. The 180 chemical names listed by WHO ATC was used as the reference for antineoplastic active pharmaceutical ingredients (APIs). Antineoplastic drug access was studied from the perspectives of both market access and patient access. The delayed access to antineoplastic medicines was measured by drug lag in terms of time and number of APIs registered in the market for market access and listed under the National List of Essential Medicines (NLEM) for patient access.

Market access

Time lag for market access was defined as the gap of time between date of MAA of drug in the US and date of MAA of same drug in Thailand. Market access time lag then represented “fast” and “slow” of the drug products available in Thailand. The study revealed that antineoplastic drugs from US had an average of 37.16 months or approximately 3 years before being launched in the Thai market. It was shown as

"marketing time lag" as in the figure 20. Compared with ASEAN countries, anticancer drugs entered Thai market 10.73 months after Singapore market and 6.51 months after Malaysia market. When analyzed across periods of regulatory changes, time lag of antineoplastic drugs was found to be reduced from 88.23 months during the period 1983-1990 to 23.62 months during the period 2007-2016. This reflected that the delay of market access to antineoplastic drugs had been improved or the changes overtime had positive impacts on time lag for antineoplastic medicines.

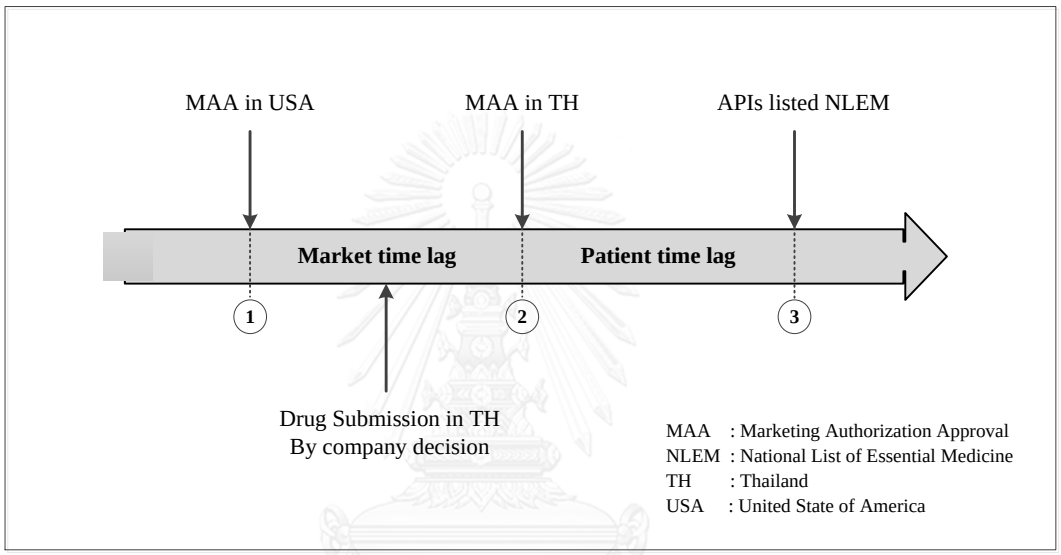


Figure 20: Calculation of market time lag VS patient time lag

In terms of availability of antineoplastic APIs, out of 5 pharmacological groups, 23 chemical groups and 180 APIs classified by WHO ATC, 88 APIs (or 48.89% of WHO items) were market authorization approved by Thai FDA, meanwhile 130 APIs (72.22%) were found in USA, 92 APIs (51.11%) in Singapore and 68 APIs (37.78%) in Malaysia. These 88 APIs, accounted for 67.69 % of items available in US, comprised all chemical groups except 3, and all of 5 pharmacological groups. However, if exploring detail into pharmacological and chemical groups, Thailand, USA, and Singapore had APIs distributed in all pharmacological groups and had equal number of chemical groups. It reflected that Thailand should have adequate number of APIs like other country.

Patient Access

Time lag for patient access was defined as the gap of time between implemented date of drug in the NLEM and first date of MAA of same drug in Thailand. This time lag could explain how soon a drug could be accessed by patients after it was available in the country. It was revealed that the implemented date of the first version of NLEM was since 1981. The current version was 11th version and announced in 2016. The product had average time lag 88.05 (about 7.5 years) to be listed on the NLEM as patient time lag as in figure 20. It seemed that patients had to wait for longer than 7 years before they could use an antineoplastic drug. New generic drugs (NG) as a copied version of innovative product was another factor influencing the NLEM selection since new generic product would be more cost-effective and imposed less budget burden on the health benefit payers. However, the average time lag from the first MAA of innovative drug and first MAA of new generic drug was 84.81 months or approximately 7 years. NG time lag took about the same length of time as NLEM. Cancer patients thus had to wait for over 7 years before they could access an antineoplastic medicine or expect a less expensive generic drug.

In terms of number of APIs available for patients, the 38 APIs were listed on NLEM while 34 APIs were recommended by Essential Medicine List of WHO (EML-WHO). While only 38 APIs were listed on NLEM for patient access, these APIs were distributed across all 5 pharmacological groups as well as all except 2 of chemical groups available in Thailand. Only 14 of 88 APIs were found new generic products.

Since the study focused on the MAA authorization approval date of country to calculation time lag, therefore, time lag was also accounted for or included the period during Thai FDA reviewed the product registration application. The registration period was contributed only a part not all of time lag.

Drug lag situation in Thailand from the market perspectives, even the number of APIs was not as many as Singapore, US, UK, or EU, the antineoplastic drugs in Thailand had covered all pharmacological groups and most of chemical groups, also it had taken a

shorter time for a drug product to enter into the market overtime. From patient perspective, which needed to take into account the price and budget, with limited number of APIs, the NLEM could at least cover every pharmacological groups and almost all of chemical groups. However, major concern was pointed at 7 years waiting period before the drug products was available on the list.

Determinants influencing time lag

Seven determinants, including price, market size, patent, novelty code, EML-WHO list, targeted cell therapy, and country of headquarter, were reviewed and identified in this study.

Price represented by cost per month for each API showed that the new drug (N) had the average cost per month of 143, 523 THB which was considerably above generic drug (G) at 15,314 THB and new generic drug (NG) at 54,428.60 THB. Most of items of new drugs were monopoly sold and only 14 new generic drugs were available in Thai market.

Market size was measured by 2 variables, sales volume and utilization by patient-month. While sales had the percentage of compound annual growth rate (CAGR) of antineoplastic market was 11.52 % during 2011-2014, utilization or patient-month growing at 8.80% CAGR of the same period. The pharmacological group X, with 3.2 billion THB in sales, had highest growth at 15.29 % following with 10.06 % of Group-C (plant alkaloids and natural product), 8.20 % of group-A (Alkylating agents), 3.03 % of Group-B (Antimetabolites) and the last, 0.68 % of Group-D (cytotoxic antibiotic and related substance). The utilization by patient-month of pharmacological Group-X also had highest growth 13.06 % following with 10.13 % of Group-C: Plant alkaloids and natural product, 9.04 % of Group-B: Antimetabolites, 6.70 % of Group-A: Alkylating agents, and the last, 5.47 % of Group-D: Cytotoxic antibiotic and related substances.

The patent information was obtained from USFDA database. From 130 APIs approval by USFDA, 55 APIs were found the patented claims. During the study period, there were on average 4.58 patent claims per API, 3.13 for drug patent claim, 2.70 for drug

substance claim, and 2.8 for patient use code claim. Form 130 API, 55 items of API still had patent protection.

Novelty code represented the newness of an API in each chemical group. It was found that the breakthrough accessibility approximately 0.26 in Malaysia, 0.22 in Thailand, 0.18 in Singapore, 0.17 in UK, 0.14 by WHO and in USA, and 0.06 by EMA.

The principle of EML-WHO was the recommended minimal list. According to WHO policy, antineoplastic drugs were also listed in EML-WHO as essential items. Thirty-four (34) APIs of antineoplastic drugs were found in the 19th version of EML-WHO. Meanwhile, thirty-eight (38) items of APIs were presented in the current version (11th version) of NLEM of Thailand.

Targeted cell therapies were new technology and concept of cancer treatment. All targeted call therapies, 25 of 88 items of APIs, were new drug classification in Thailand. In term of market access, the accessibility of the new trend of treatment "Target cell therapy" was found in US almost 100% of WHO, UK and EMA 86.54%, Singapore 67.31%, Thailand 48.08%, and Malaysia 30.77%.

The country of headquarter was defined as the country where headquarter (HQ) of product owner (product license holder in Thailand, drug manufacturer) was located. Approximately 50% of antineoplastic drug in Thailand were new drug (N) classification with 24 APIs had their HQ in EU, 15 APIs in US, and 6 APIs in Asia.

From bivariate relationship analysis, only targeted cell therapy and novelty code illustrated statistically significant relationship with market time lag. APIs classified as targeted cell therapy tended to have shorter time lag than those that were not targeted cell therapy. Me-too APIs coded 02 or 03 was associated with shorter time to enter Thai market than other coded. However, multiple linear regression resulted that only one factor, "novelty code" showed statistically significant relationship with market time lag, dummy variable of novelty code 02 and 03 having standardized beta of (-0.417) with p-value = 0.012. The result explained that APIs with ATC level 5 coded 02 or 03 was associated with shorter time lag than other codes of APIs. The regression analysis

showed that 35.0% of the variance (p-value=0.043) of market time lag was explained by seven pre-determined factors including price, market size, patent, priority list, novelty, targeted cell therapy, and country of headquarter.

Policy recommendation

1. The result of the study strongly convinced that the NLEM took approximately 7 years for an antineoplastic API to be listed. This long waiting period could take away patients' treatment opportunity. Since the three major health benefit schemes, including CSMBS, SSS, and UC are relied on the NLEM as the reimbursement list, thus, the list represents the opportunity of treatment for cancer patients. The average time lag of 7 years reflects the management process of NLEM. The selection process needs to be revised so the patient access could be enhanced.

2. Even the market access represented by market time lag was decreased from longer than 7 years during the period before 1990 to about 2 years during the period after 2007, this length of time is still considered longer than other referenced countries. Comparing with Singapore and Malaysia, Thailand seems not too much different in terms of time and number of drug lag, but improvement on both dimensions would also enhance market access and, in turn, would also influence patient access to antineoplastic. The market time lag included 2 major steps, company decision to enter Thai market as well as registration process by Thai FDA. The efficient registration management of Thai FDA is thus a significant process that would shorten the market time lag. The good governance situation would then influence company decision to enter Thai market and bring in other opportunities for the country as well.

Recommendation for future research

1. The study focused on the difference between the first MAA in referenced country, i.e., US, UK, EU, Singapore, and Malaysia. The result showed the delayed in accessing market and listing on NLEM. The major gateway in entering the market is the registration application by Thai FDA. The future study could focus on the situation analysis and how to improve the management of product registration of Thai FDA.

2. The detail on cancer treatment in Thailand and patient access to needed cancer treatments would provide more input for more effective policy decision particularly on the catastrophic health expenditures.

3. The regression analysis of this study showed that most of hypothesized variables did not significantly explain the variance of market time lag. However, market time lag was illustrated to decrease across different period of regulatory changes. Further study on variables related to regulatory changes should thus be explored.

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APPENDIX

Appendix 1: Biological product classified by drug registration type of USFDA and by drug classification in Thailand

API name	ATC-code	Status of drug registration in each country	
		US	TH
aflibercept (ZIV)	L01XX44	BLA	NBC
asparaginase	L01XX02	BLA	GD*
bevacizumab	L01XC07	BLA	NBC
blinatumomab	L01XC19	BLA	not available
brentuximab vedotin	L01XC12	BLA	not available
cetuximab	L01XC06	BLA	NBC
denileukin diftitox	L01XX29	BLA	not available
dinutuximab	L01XC16	BLA	not available
ipilimumab	L01XC11	BLA	not available
necitumumab	L01XC22	BLA	not available
nimotuzumab	L01XC	not available	NBC
nivolumab	L01XC17	BLA	not available
obinutuzumab	L01XC15	BLA	not available
ofatumumab	L01XC10	BLA	NBC
panitumumab	L01XC08	BLA	not available
pegaspargase	L01XX24	BLA	not available
pembrolizumab	L01XC18	BLA	not available
Pertuzumab	L01XC13	BLA	NBC
ramucirumab	L01XC21	BLA	not available
rituximab	L01XC02	BLA	NBC
temsirolimus	L01XE09	(NDA)	NBC
trastuzumab	L01XC03	BLA	NBC
trastuzumab emtansine	L01XC14	BLA	not available
Total		**21(2)***	**9(1)***

*: number of product which was not classifyed as biological product in Thailand, G: Generic drug, NBC: New Biological drug with SMP condition, BLA: Biolobical license application, NDA: New drug application

Appendix 2: Time lag (months) between the first MAA in Thailand and in other countries: US, UK, EMA, SG and MAL

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01DB04	aclarubicin					
L01XE13	afatinib	15.05	12.58	12.58	9.86	
L01XX44	aflibercept (ZIV)	44.42	38.44	38.44	19.84	
L01XX22	alitretinoin					
L01XX03	altretamine	138.15				
L01XD04	aminolevulinic acid	137.07	43.93	43.93		
L01DB10	amrubicin					
L01XX01	amsacrine					
L01XX35	anagrelide	99.58	7.46	7.46	15.41	0
L01XX27	arsenic trioxide	80.95	63.67	63.67		-0.2
L01XX02	asparaginase	-103.06	-0.59		-35.75	-36.01
L01XE17	axitinib					
L01BC07	azacitidine	37.39	-17.58	-17.58	-34.56	-36.01
L01XX49	belinostat					
L01AA09	bendamustine					
L01XC07	bevacizumab	16.13	5.59	5.59	3.52	0
L01XX25	bexarotene					
L01DC01	bleomycin	287.01	-108.06		109.63	107.99
L01XC19	blinatumomab					
L01XX32	bortezomib	21.72	10.25	10.25	-0.36	-3.91
L01XE14	bosutinib					
L01XC12	Brentuximab vedotin					
L01AB01	busulfan	528.16	149.55		-11.93	-24.02
L01CD04	cabazitaxel	25.03	16.07	16.07	8.51	12.58
L01XE26	cabozantinib					
L01BC06	capecitabine	2.04	-31.11	-31.11	-6.67	-24.02
L01XA02	carboplatin	15.93	-180.63		22.47	-24.02
L01AC03	carboquone					
L01XX45	carfilzomib	35.35	-4.63	-4.63		
L01BC04	carmofur					
L01AD01	carmustine	351.8	85.13		-14	-11.99
L01XC09	catumaxomab					
L01XE32	cediranib					

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01XX33	celecoxib					
L01XE28	ceritinib					
L01XC06	cetuximab	39	34.46	34.46	-23.03	22.41
L01AA02	chlorambucil	495.44	-95.7		-39.36	-77.54
L01AA05	chlormethine					
L01XA01	cisplatin	66.4	-146.2		-46.09	-35.98
L01BB04	cladribine	40.11	16.89			
L01BB06	clofarabine	95.9	78.92	78.92	14.65	17.84
L01XE16	crizotinib	25.99	8.05	8.05	8.44	
L01AA01	cyclophosphamide	307.48	-213.98		-34.27	-36.01
L01BC01	cytarabine	180.47	-179.06		-74.55	-23.98
L01XE23	dabrafenib					
L01AX04	dacarbazine	397.17	127.08		203.79	192
L01DA01	dactinomycin	246.67	-75.73		-167.79	-11.99
L01XE06	dasatinib	36.11	31.34	31.34	21.55	24.02
L01DB02	daunorubicin	210.4	34.83		109.86	132.01
L01BC08	decitabine	33.58	-43.07	-43.07		7.59
L01CC01	demecolcine					
L01XX29	denileukin diftitox					
L01XC16	dinutuximab					
L01CD02	docetaxel	50	55.56	55.56	46.98	36.44
L01DB01	doxorubicin	202.78	-59.7		-22.6	-12.02
L01XC01	edrecolomab					
L01XD06	efaproxiral					
L01DB03	epirubicin	-14.49	-70.44		-2.83	-11.99
L01XX41	eribulin	19.52	15.34	15.34	16.69	
L01XE03	erlotinib	7.39	-14.62	-14.62	-7.36	-23.98
L01XX11	estramustine	54.21	-190.78		-133.42	-155.99
L01AG01	etoglucid					
L01CB01	etoposide	67.68	74.09		0.92	0
L01XE10	everolimus	-53.91	-58.05	-58.05	-90.02	-56.97
L01BB05	fludarabine	86.44	46.65		-15.15	-11.99
L01BC02	fluorouracil	266.22	-13.63		-74.18	-48
L01BC52	fluorouracil, combination					
L01AD05	fotemustine					
L01XE02	gefitinib	13.9	-59.76	-59.76	13.34	12.02

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01BC05	gemcitabine	13.54	20.17		-0.72	-132.01
L01XC05	gemtuzumab	25.46				
L01XX05	hydroxycarbamide (HydroxyUrea)	366.78	145.08		-13.8	-11.99
L01XE27	ibrutinib					
L01DB06	idarubicin	89.92	-47.97		75.53	56.8
L01XX47	idelalisib					
L01AA06	ifosfamide	150.01	-29.47		156.75	144
L01XE01	imatinib	1.71	-4.24	-4.24	-70.64	-11.99
L01XC11	ipilimumab					
L01XX19	irinotecan	48.56	-51.52		35.02	36.01
L01DC04	ixabepilone	20.5			4.37	
L01XX50	ixazomib					
L01XE07	lapatinib	15.64	0.69	0.69	8.21	12.02
L01XE29	lenvatinib	14.06	10.64	10.64	0.3	
L01AD02	lomustine					
L01XX07	lonidamine					
L01AB03	mannosulfan					
L01XE22	masitinib					
L01XX10	masoprocol					
L01AA03	melphalan	413.44	-52.37		-43.89	11.99
L01BB02	mercaptopurine	525.63	-109.93		-20.5	-71.98
L01BA01	methotrexate	354.76	-131.22		-57.17	-48
L01XD03	methyl aminolevulinate					
L01XX09	miltefosine					
L01AX01	mitobronitol					
L01XX16	mitoguazone					
L01DC03	mitomycin	132.01	-88.87		-35.25	-36.01
L01XX23	mitotane					
L01DB07	mitoxantrone	126.26	-74.48		-37.49	23.98
L01XC22	necitumumab					
L01BB07	nelarabine					
L01XE08	nilotinib	12.55	11.86	11.86	3.94	4.47
L01XC-TH	nimotuzumab					
L01AD06	nimustine					
L01XE31	nintedanib					

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01XC17	nivolumab					
L01XC15	obinutuzumab					
L01XX36	oblimersen					
L01XC10	ofatumumab	56.15	50.4	50.4	0.95	
L01XX46	olaparib					
L01XX40	omacetaxine mepesuccinate					
L01XA03	oxaliplatin	-37.29	-77.5		12.62	0
L01CD01	paclitaxel	75.24	-3.38	-3.38	62.49	57.2
L01CD03	paclitaxel poliglumex					
L01XE33	palbociclib					
L01XC08	panitumumab					
L01XX42	panobinostat					
L01XE11	pazopanib	32.33	24.51	24.51	9.2	23.95
L01XX24	pegaspargase					
L01XC18	pembrolizumab					
L01BA04	pemetrexed	16.85	9.33	9.33	6.05	0
L01XX08	pentostatin					
L01XC13	Pertuzumab	24.74	15.9	15.9	4.8	
L01AX02	pipobroman					
L01DB08	pirarubicin					
L01DB11	Pixantrone					
L01DC02	plicamycin					
L01XA05	polyplatillen					
L01XE24	ponatinib					
L01XD01	porfimer sodium					
L01BA05	pralatrexate					
L01AA08	prednimustine					
L01XB01	procarbazine	203.3	-241.97			
L01BA03	raltitrexed					
L01XC21	ramucirumab					
L01AD07	ranimustine					
L01XE21	regorafenib	14.95	4.01	4.01	6.64	
L01XE19	ridaforolimus					
L01XC02	rituximab	7.13	0.95	0.95	-1.71	-11.99
L01XX39	romidepsin					

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01XE18	ruxolitinib					
L01XA04	satraplatin					
L01AD03	semustine					
L01XX37	sitimagene ceradenovec					
L01XX48	sonidegib					
L01XE05	sorafenib	18.33	11.4	11.4	-1.77	0
L01AD04	streptozocin					
L01XE04	sunitinib	17.12	11.4	11.4	2.4	0
L01BC03	tegafur					
L01BC53	tegafur, uracil (UFT)				-38.74	-48
L01BC53	tegafur/ gimeracil / oteracil		20.14	20.14	40.15	4.04
L01XD05	temoporfin					
L01AX03	temozolomide	22.67	29.14	29.14	-4.04	-23.98
L01XE09	temsirolimus	53.52	47.84	47.84	24.02	28.45
L01CB02	teniposide					
L01AC01	thiotepa					
L01XX18	tiazofurine					
L01BB03	tioguanine (thioguanine)	389.39	8.05			-80.49
L01XE34	tivozanib					
L01XX17	topotecan	25.1	19.58	19.58	11.27	11.99
L01CX01	trabectedin		26.35	26.35	5.29	4.9
L01XE25	trametinib					
L01XC03	trastuzumab	33.18	10.09	10.09	23.43	0
L01XC14	trastuzumab emtansine					
L01AB02	treosulfan					
L01XX14	tretinoin	67.29	56.28		75.76	59.99
L01AC02	triaziquone					
L01BC59	trifluridine, combinations					
L01AA07	trofosfamide					
L01DB09	valrubicin					
L01XE12	vandetanib					
L01XE15	vemurafenib	28.35	22.31	22.31	10.71	

ATC code	Chemical substance	TH-US	TH-UK	TH-EMA	TH-SG	TH-MAL
L01CA01	vinblastine	223.84	-68.47		-125.27	-119.98
L01CA02	vincristine	251.73	-240.39		-47.7	-35.98
L01CA03	vindesine		-272.53			
L01CA05	vinflunine					
L01CA04	vinorelbine	90.25	73.69		125.31	84.01
L01CA06	vintafolide					
L01XX43	vismodegib	41	23.62	23.62	6.47	
L01XX38	vorinostat					
L01DB05	zorubicin					

VITA

Ms. Pornsroung Saerekul was born in southern part of Thailand. She received her Bachelor's Degree in Pharmacy from Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand in 1984. She worked as a hospital pharmacist in Songklanagarind Hospital, Prince of Songkla University for 6 years. She got a Master's Degree of Pharmacy (Clinical Pharmacy and Hospital), Faculty of Pharmaceutical Sciences, Chulalongkorn University in 1991. She worked in the Bumrungrad International Hospital for 6 years; before she changed her part of career to be a regulatory affairs pharmacist. To pursue the expertise in this career, she had worked with the local manufacturer, Siam Pharmaceutical Co., Ltd., and a multinational pharmaceutical company, Servier (Thailand) Ltd. Moreover, she also worked with the law firm: Tilleke & Gibbins International Ltd. as a regulatory affairs consultant. She, currently, still works as a regulatory affair professional. She enrolled in this International Ph.D. program in Social and Administrative Pharmacy, Chulalongkorn University in 2010.