Drug Regulation and Incentives for Innovation: The Case of ASEAN

Sauwakon Ratanawijitrasin, Ph.D.

EXECUTIVE SUMMARY

Background

Drug regulation imposes standards on the products of health-related research and development intended to protect patients by ensuring the quality, efficacy and safety of new pharmaceuticals and biologicals. While regulatory standards in developed countries have been progressively tighten, issues are raised related to the influence on the increased cost of meeting regulatory requirements on the incentives for pharmaceutical firms to invest in R&D. Are the debates in countries where new drugs are developed also of policy significance in developing countries, where R&D capabilities are generally much poorer? How does drug regulation affect incentives for research and development in the context of developing countries?

This paper is prepared for the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) to address the issue of the impacts of drug regulation on incentives for research and development of new drugs and vaccines, and to make relevant recommendations.

Methods of study

The focus of this paper is to examine the ways in which regulatory frameworks affect the incentives for pharmaceutical innovations in developing countries, using member countries of the Association of South-east Asian Nations (ASEAN) as case study. The paper employs a two-level focus approach: a wide-angle view of drug regulation in the region whose members posses varying levels of research and development capacities, supplemented by a zoomed view using data from Thailand where more detailed data are available to the author. Data collection relied mainly on review of documents from various sources. Interviews and personal communication were carried out for added information and deeper understanding.

Experiences of ASEAN on Issues Related to Drug Regulation and Research

ASEAN member countries share a number of common characteristics with regards to their pharmaceutical sector and regulation. Some of these characteristics can be said to reflect what found in developing countries in general. Key relevant characteristics are:

- Drug regulatory frameworks in ASEAN member countries do not appear to discourage research and development of drugs and vaccines.
- Drug regulatory capacities in the majority of ASEAN members are constrained by limited human and financial resources.
- Gaps exist between written regulation and actual enforcement in a number of ASEAN member countries.
- Among the member countries, only Singapore—which has the most advanced R&D and regulatory capability in the group—adopts a

registration system that relies on product assessment and approval of other competent DRAs.

- All ASEAN countries are net importers of pharmaceuticals. All except Singapore do not have capability for new drug development.
- Evidence from some ASEAN members shows that R&D capability is a result of a country's investment and research environment, not a result of a compromised and weak drug regulation system.
- The process of development and implementation of ASEAN harmonized registration standards follows the traditional ASEAN culture of consensus building and flexibility.
- Levels of health insurance coverage among the populations of ASEAN members vary. In many countries, the majority of the population pays out-of-pocket for drugs. Consequently, even when drugs are available, affordability is a significant issue for access to necessary drugs. For countries with health insurance systems, high drug price affects system sustainability and service quality.

Reframing Policy Questions and Recommendations

Societies aim to protect consumers from the harms that unsafe and inefficacious drugs might bring, and to promote R&D for the discovery of new drugs that will help prevent and solve health problems at the same time. Therefore, public policies must strike balance among competing goals without compromising them.

Since the majority of developing countries lack adequate capabilities in both drug regulation and research and development, key policy questions, then, are 1) how to improve these capabilities? and 2) how to do better given existing limitations? A number of measures can be considered to improve capabilities in developing countries:

1. Recommendations for improving drug regulatory capability
    - Risk management
    - Make use of "trusted" DRAs
    - Continuous improvement
    - Human resource development
    - Reduce enforcement gaps
    - Get rid of unnecessary bureaucracy
2. Recommendations for improving R&D capability
    - Government commitment and investment
    - International collaborations
3. Recommendations for improving knowledge management

    A great number of new ideas and new developments has taken place worldwide which will evolve into different policy models. It is important for the international community to be able to learn from these models lessons of success and failure, to identify with what features and under what conditions one model works while another does not.

Drug Regulation and Incentives for Innovation: The Case of ASEAN

Sauwakon Ratanawijitrasin, Ph.D.

- Pharmaceutical System Research & Intelligence Center
- Faculty of Pharmaceutical Sciences

Chulalongkorn University
Thailand

I. Introduction

Public policies represent government's intention and action put forth to achieve collective goals. Oftentimes, a public policy produces impacts beyond its stated objectives. In addition, it may also interact with other public policies in ways that enhance or hinder the effects—both intended and unintended effects—of one another. These phenomena, or the possibility of them, raise further policy issues for debate. Pharmaceutical sector is an area where such issues arise at both national and international levels.

Consumer protection and promotion of pharmaceutical research and development are the two societal goals towards which public policies regularly generate extensive debates. While a lot of new medications discovered have given great benefits to humanity, many of them have caused serious harms to those who use them. Consequently, while society needs continuous development of new medicines to combat diseases and improve health, society also demands protection from potential damage that the use of drugs might bring.

Drug regulation is the totality of all measures—legal, administrative, and technical—which governments take to ensure the safety, efficacy and quality of drugs, as well as the relevance and accuracy of product information. It is a public policy that restricts private-sector activities in order to attain social goals set by the State. To ensure that drugs are efficacious, safe and of good quality, drug regulation imposes standards on the pharmaceutical products, as well as the ways these products are discovered, made, distributed, and dispensed. Through legislation, administrative rules, and technical requirements, drug regulation exerts controls on how clinical trials, product assessment, manufacturing and importation process, quality control, promotion and advertising, and dispensing are to be carried out.[1]

With reports of a number of tragic adverse events caused by use of drugs, especially in the latter half of the last century, more stringent controls have been imposed upon the procedures for market authorization of drugs. These controls inevitably entail increased costs on the part of pharmaceutical businesses. Among the various activities that have to meet regulatory requirements, research and development (R&D) of new drugs is the most costly. Although estimates on how much pharmaceutical industry actually spends on R&D of new drugs vary, and what proportion of the costs are borne by pharmaceutical firms vis-à-vis by the taxpayers

[1] Ratanawijitrasin & Wondemagegnehu (2002)

through government research agencies and funds is an issue being debated,[2] the notion that regulation adds to the costs of drug development both in terms of money and time continues. These costs, it has been argued, constitute disincentives for pharmaceutical firms to invest in R&D. In fact, arguments positing that drug regulation unnecessarily delays the development and introduction of valuable new drugs and deprives patients of life-saving drugs have been around for decades.[3]

Meanwhile, patent laws have been adopted in more and more countries, especially following the TRIPS Agreement, with the aim of rewarding innovations. Another set of debates between the merit of intellectual property protection and the problem of access to drugs and vaccines high prices bring also has persisted.

These debates between providing adequate consumer protection and facilitating development of new drugs and vaccines, and between protection of intellectual property rights and access to necessary drugs are manifestations of the many expectations society places on public policies.

Are these debates, which mainly take place in countries where new drugs are developed, also of policy significance in developing countries where R&D capabilities are generally much poorer? How does drug regulation affect incentives for research and development in the context of developing countries?

This paper is prepared for the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) to address the issue of the impacts of drug regulation on incentives for research and development of new drugs and vaccines.

II. Focus and Scope

This paper aims to examine the ways in which regulatory frameworks affect the incentives pharmaceutical innovations in developing countries, using ASEAN members, and Thailand in particular, as case study.

Specifically, it seeks to do the followings:

- Review drug regulatory frameworks in ASEAN countries
- Identify key issues involved in the regulatory requirements for the approval of pharmaceutical products, and examine how they affect the cost of R&D, and the incentives for investment in R&D
- Review regional and international standards and requirements which have relevance for the approval of new drugs and of generics.
- Draw from experiences in ASEAN and Thailand to address whether the policy problems occur in developed countries are also problems for developing countries
- Discuss options for balancing consumer protection and access to necessary drugs, and R&D promotion
- Propose possible policy changes, at both national and international levels, which could contribute to effective drug regulation as well as facilitate the introduction of new and generic products.

As a multi-country study based mainly on review of published data, access to data describing regulatory system structure and functions, access and related issues in details for all the countries under study will not be feasible. Nor do data from public

[2] See, for example, Angell (2004), Kettler (1999), Engel (1998) and OTA (1993) for varying cost estimates and views.
[3] See reviews in Quirk (1980) and Dukes (1985), for example.

information sources in English alone sufficient for reflecting the intricate system functions and the relationship between regulation and its environment. This problem is particularly acute for developing countries where scarcity of data is a problem in most areas and where the language used is not English. This study, therefore, employs a two-level focus approach. Its first focus is on addressing the issues for each of the ten ASEAN members from available data. This will be a wide-angle view of drug regulation in the region whose members posses varying levels of research and development capacities. It then zooms on to Thailand where more detailed data, especially in the local language, are available to the author to allow for description and analysis based on more detailed data and highlight using concrete examples. This country-level focus will supplement the wide-angle regional focus for the study.

III. Methods of study

This study relied mainly on review of documents from various sources. Interviews were carried out to supplement the archival research, especially where there were important gaps in the literature and where views and information on actual practice of related players were needed for the analysis.

Since this was a desk-based study, the review inevitably limited mainly to available public information sources in English and Thai. Although a few unpublished documents were obtained by the author, some were classified and could not be quoted. Internet and published sources and informants were consulted in data collection process.

1. Data Collection
   1) Archival study: review of relevant literature and documents from various sources:
      - Studies related to drug regulation in ASEAN member countries, including laws, rules and standards,
      - Information on ASEAN harmonization, including guidelines for drug registration under the ASEAN Harmonization scheme,
      - Information on ICH,
      - Laws, rules and standards related to drug regulation in Thailand, including Drug Act, Patent Act, Trade Secret Act, registration manuals,
      - Published studies and reviews on the Thai drug system and intellectual property rights.
   2) Key informant interviews
      - Thai FDA officers responsible to the areas addressed in this paper
      - Representatives of pharmaceutical industry associations, both the importers (PREMA) and the local manufacturers (Thai pharmaceutical Manufacturers Association, TPMA)
      - Personal communications—face-to-face, via e-mail, and phone calls—were made primarily for collecting information on ASEAN.

2. Analysis

The analysis will focus first on addressing the key question posed by CIPIH, i.e. “how does drug regulation affect incentives for research and development in the context of developing countries?” using data from the review. Specifically data on drug regulation technical requirements, fees, and processing time will be analyzed. The paper will then examine other points related to the key theme, as well as identifying important issues from the findings. Policy recommendations related to

improving regulation and capacity for research and development in developing countries will be made.

IV. ASEAN: Drug Regulation, Research, and Environment

This is the first of the two main sections in this paper. It focuses on drug regulation and research and development in ASEAN countries. Information on ASEAN as a regional group and other relevant to the environment of drug regulation and research is also described.

1. ASEAN Overview

The Association of South-east Asian Nations (ASEAN) is a regional organization consisting of ten member states, namely, Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam

ASEAN was established in 1967 by the governments of five countries--Indonesia, Malaysia, Philippines, Singapore, and Thailand. In 1984, Brunei Darussalam joined its neighbors in the Association. As a group, these early participants are dubbed the ASEAN 6. Vietnam has become member since 1995, Laos and Myanmar since 1997, and Cambodia since 1999. These four new members are usually referred to as the CLMV group.

The ASEAN region has a population of about 500 million, a total area of 4.5 million square kilometers, a combined gross domestic product of US$737 billion, and a total trade of US$ 720 billion.[4] (Population and GDP figures are shown in the appendix.)

Since the past decade, the CLMV have transformed themselves from centrally planned economies into more market-oriented economies. The liberalization has led to significant changes in these countries and the region as a whole.

As was envisioned by the "founding fathers," by forming a regional bloc, the members, the majority of which are small countries, would gain increased political and economic clouts in the world stage. ASEAN members collaborate in many different areas—economic, social, security, cultural, among others. Over time, the members developed what is now called the "ASEAN way" of collaborating and arriving at agreement for the group by forging consensus. The evolution has also generated strong tradition that all members participate in all endeavors that come under the umbrella of the Association, even including those areas that might not relate to the central interests of the country. For example, Brunei has participated in the effort to harmonize drug registration for ASEAN even though it does not yet have drug registration system in the country.

2. AFTA and CEPT

In 1992, the governments of ASEAN Member States agreed to create the ASEAN Free Trade Area (AFTA) and to set common tariff scheme. Since that was before the accession of the CLMV into the Association, the original signatories of AFTA agreement were the ASEAN 6. The Agreement on Common Effective Preferential Tariff Scheme (CEPT) has been effective since 2003.

The newer members have a different schedule to reach the 0-5% tariff for intra-ASEAN trade. Eventually, the year when the tariffs will come down to 0% under

[4] http://www.aseansec.org/64.htm

CEPT is 2010 for the ASEAN 6, and 2015 for the rest, with flexibility for some sensitive products until 2018.[5]

Pharmaceutical trade among the members now enjoys import duties of 0-5% under CEPT, provided that the products has no less than 40% local content. The creation of a single market has significant implications on pharmaceutical trade in the region. For example, industry people who previously saw insufficient demands for new drugs and pharmaceutical raw materials within a country boundary can now look to a bigger regional market in their investment consideration. This is especially significant for country which is technologically advanced, but which has small population like Singapore.

3. R&D Investments

The level of investment in research and development in ASEAN is low, compared to North America, Western Europe and Japan. Worse, data on these investments are usually difficult to obtain, and data definitions might differ. From available data, Singapore stands out as the only country in this region with significant R&D investment in science and technology as shown below.

Table 9: Selected Science and technology creation indicators

Country	GDP/ capita 2003*	R&D expenditure (%GDP)	Patents granted (per million people)	Researchers in R&D (per million people)
Year		1996-2002	2000	1990-2001
Brunei	12,971	-	-	-
Cambodia	310	-	-	-
Indonesia	973	-	0	130
Lao, PDR	362	-	-	-
Malaysia	4,198	0.4	-	160
Myanmar	179	-	-	-
Philippines	973	-	-	156
Singapore	20,987	2.1	27	4052
Thailand	2,291	0.1	3	74
Viet Nam	481	-	-	274
ASEAN*	1,266			

Source: ASEAN statistics yearbook 2004 and
*ASEAN Secretariat http://www.aseansec.org/macroeconomic/aq_gdp22.htm

4. Health Services and Health Insurance

Since health sector is the immediate environment of pharmaceutical sector, major changes in the health sector will inevitably affect the pharmaceutical sector.

Coverage of health insurance increases affordability and hence effective demand for pharmaceuticals on the part of consumers. The way pharmaceuticals are paid under health insurance poses positive or negative incentives on the demand in terms of the amount and types of drug utilization.

In the majority of developed countries where universal health insurance system is in place, a pharmaceutical product generally passes through two approval processes before it is made available to the patient. They are evaluation for registration to make the drug available to the market in that country, and evaluation

[5] Janjaroen et al (1999) and ASEAN annual report 2002-2003.

for reimbursement under the health insurance system(s). Therefore, health insurance coverage of drugs greatly determines the demand by the population. In many developing countries, coverage of health insurance is less extensive; most patients pay out-of-pocket for their medications. Evaluation of drugs to be made available in these countries generally relies on market authorization process at the drug regulatory authority.

Unlike many developed countries with universal health insurance where the insurance authority play roles in price control, many developing countries, including some ASEAN members, drug price control lies with the DRAs or other government agencies.[6]

Health services in all ASEAN countries are offered by a mixture of public and private facilities, although the public-private mix differs among the countries. The larger proportion of health service delivery in this region remains with the public sector. For Malaysia—the only country in the group that has a federal system of government, the tasks of providing health services are divided between the federal and state governments. In terms of changes, rates of growth in the private health service sector in Vietnam and Cambodia in recent years are high, because of the general liberalization trend in these two countries.

Funding for health services in almost all ASEAN Member States relies on taxes. Health insurance is still a new development in the region. And even for countries that have substantial health insurance, many schemes are financed by general taxes, instead of contributions by beneficiaries.

ASEAN presents a mixture of different systems of health insurance among its member countries.

Singapore, the Philippines and Thailand are the only three countries in this region which employ universal health insurance approach for managing health service coverage for their populations. The rest operate based on a public assistance model in which governments' health service facilities provide affordable, subsidized care to the general public, as well as act as the last resort for those who cannot pay by providing services as welfare.

Singapore has a tiered system of health insurance.[7] Medisave, through the use of saving account, is the basic program covering the entire population, and is funded by compulsory saving scheme. A unique feature is the inclusion of Asian value in the program design, by allowing a family member to draw payment from the account of another family member if needed. Medishield provides additional protection when Medisave is inadequate. These two programs are financed by contributions from the beneficiaries. Medifund is the government-funded support for health service payments for those who cannot pay on their own. Recently, insurance programs for the elderly have been added to increase the readiness for guaranteeing insurance coverage of an aging population.[8]

In the Philippines, the National Health Insurance Program (NHIP) was established in 1995, by virtue of the National Health Insurance Act, and is managed by the Philippines National Health Insurance Corporation. NHIP replaced the old Medicare program and initially covered the poor and the non-formal sector.

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[6] Ratanawijitrasin & Wondemagegnehu (2002)

[7] The term 'health insurance' here is used in a broad sense as program providing health service coverage through financial arrangements. Strictly speaking, Medisave is not an 'insurance' because there is no risk pooling mechanisms outside the sphere of family. Medifund is a government assistant program.

[8] Lim (2004), Ratanawijitrasin (2001)

Expansion to be a program providing universal coverage is a mandate for the NHIP. The program now covers employees in the government and private sectors, individuals who pay for coverage, retirees and pensioners under certain programs, and the indigent population. [9]

Thailand has three major public health insurance schemes covering different groups of population as will be described later.

Malaysia employs a combination of health insurance and public assistant models. It has large-scale insurance programs covering certain groups of the population. One large insurance scheme is the Employees' Provident Fund which provides coverage to employees after retirement. Another program is managed by Social Security Organization, which cover employees with income under certain level. Both are compulsory and are funded by contributions of employees and employers. Private health insurance is also popular. Services provided by government's health facilities are subsidized. These subsidized services help prevent affordability problem for those who are not covered under health insurance programs.[10]

Cambodia does not yet have social health insurance program and almost no private health insurance at present, although some employers assist their employees with medical expenses. The Cambodian government has begun to plan for experiment in health insurance through the use of pilot projects in some provinces with the aim of expansion on a nation-wide basis. [11]

In terms of payment for pharmaceuticals, except for the 30-Baht and the Social Security Schemes in Thailand, costs of drugs are paid on a per item basis in all insurance and non-insurance services throughout the region.

4. Pharmaceutical Sector

All ASEAN member countries are net importers of pharmaceutical. With the exception of Brunei and Singapore, most have a pharmaceutical industry that remains at a "formulation" stage. This means that these countries import most raw materials to produce finished drug preparations locally. All countries also import finished products to fill domestic demand. In addition, some member countries manufacture finished drug products for export as well.

ASEAN's main sources of pharmaceutical imports are Europe, US, Japan, and India. Imports of pharmaceuticals ranks as one of the top 10 commodities between ASEAN and Europe, and the share has grown continuously, as shown in table 10. Pharmaceutical trade with India is also substantial, and ranked among the top 20 commodities in terms of ASEAN 6 imports from India. India is a key source of raw materials for the generic industry in the region.

Table 10: Imports of pharmaceuticals from EU by ASEAN 6

Year	2000	2001	2002	2003
Value (US$ in million)	647.5	716.1	829.8	1,013.5
Share of total imports (%)	1.7	1.8	2.1	2.4

Source: ASEAN Statistical Yearbook, 200412

[9] http://www.philhealth.gov.ph/faq.htm and personal communication
[10] Ratanawijitrasin (2001)
[11] Cambodia Ministry of Commerce (2004) and personal communication
[12] ASEAN Statistical Yearbook, 2004

Per capita consumption of pharmaceuticals among ASEAN members vary greatly. Among the ASEAN 6 where data are available, the consumption ranged from US$ 3 in Indonesia to US$ 42 for Brunei.[13]

5. Drug Regulation

A brief overview of pharmaceutical sector and regulatory system in each of the ASEAN member countries is presented below, in alphabetical order of country name. [14] Description for Thailand is not included in this section, but will be presented in detail as specific country focus later.

5.1. Brunei Darussalam[15]

The oil-rich Brunei Darussalam is the only country in ASEAN which currently does not manufacture drugs locally. It imports from EU, the US, Japan, other ASEAN countries, and elsewhere. It is also the only country in ASEAN which currently does not require registration of medicines sold in the country.

The current legislation on pharmaceutical, the Poisons Act of 1984 and Misuse of Drugs Act of 1984 do not include provisions for the registration of medicines. Department of Pharmaceutical Services which is responsible for pharmaceutical matters is under the Ministry of Health.

Brunei participates in the work of ASEAN Consultative Committee on Standard and Quality (ACCSQ) and the Pharmaceutical Product Working Group (PPWG) to harmonize drug regulatory requirements including the ASEAN Common Technical Dossier (ACTD) and its administrative and technical requirements for licensing of medicines. Consequently, it now plans to introduce a system of pharmaceutical registration in the country for the first time. A new Medicines Order is being drafted which will include legislation for medicine registration, licensing of pharmaceutical establishments, and control of promotion and advertisements of medicines, among others.

5.2. Cambodia

After decades of war, Cambodia started to rebuild all economic sectors at the end of 1970s and the beginning of 1980s.

Cambodia produces only 5 to 10% of the needs in medicines for the whole population. Except for some crude indigenous natural raw materials for traditional medicines, all input raw materials—active and inactive ingredients, and packaging materials for pharmaceuticals production are imported with an estimated annual cost of US$12 million. It has one government pharmaceutical manufacturing facility which is a joint-venture with China and six private pharmaceutical companies, which produce oral dosage forms. None of these manufacturers are GMP certified.

Cambodia does not yet have any clinical lab test, laboratories, and/or research and development facilities capable of developing new medicines.

As of October 2000, there were 892 licensed pharmacies around the country, which sell western and oriental medicines. Illegal drug outlets, estimated to be over 2800 also sell both western and oriental medicines. In the public sector, drug distribution has been done through the Central Medical Store of the Ministry of

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[13] Lim (1997)

[14] This section draws extensively from a number of multi-country study reports on regulation-related topics—USP (2004), Ratanawijitrasin & Wondegegnehu (2002), and Wondegegnehu (1999), and is supplemented by other data sources plus personal communications. The data provided are not necessarily from the same year. As systems evolve over time, there is a possibility that some of the details depicted here might not in exact accordance with the current figures or practice.

[15] WEPRO (2004)

Health. It distributes the drugs to all 73 referral hospitals and more than 700 health centers throughout the country.[16]

The system of drug registration started in 1994. The Department of Drugs and Food (DDF) is the regulatory agency under the Ministry of Health responsible for ensuring the safety, efficacy, quality of drugs and devices, and safety and quality of food and cosmetics. Only products registered by the DDF are authorized to be imported, manufactured, sold by retail pharmacy, displayed, and dispensed. Registration is mandated for all products, both imported and manufactured domestically, as well as those from both private and public sectors. The National Quality Control Laboratory conducts tests on drugs from all sources that are submitted to the Ministry of Health for registration.

Under the law, licensing is required for manufacturing, importation, export, and distribution of pharmaceutical products.

Unlicensed drug outlets exist, and counterfeit drugs and substandard drugs are in circulation despite the pharmaceutical laws and regulations. The laws enacted are weakly enforced due to a number of complicating factors including inadequate budget to implement regular inspections.

5.3 Indonesia

Indonesia is the largest country in ASEAN in terms of population. The size of the Indonesian pharmaceutical market is about $350 million in 1998. Similar to most other ASEAN countries, Indonesian pharmaceutical industry produce drugs under license from foreign drug firms or more commonly manufacture generic products. These manufacturers generally lack the financial resources and the technical expertise to carry out original research and create new compounds.

The Indonesian Drug and Food Control Agency (BPOM) is the pharmaceutical regulatory body. Applications for pharmaceutical product registration can only be submitted by a local company. Therefore, a drug company must establish manufacturing in the country to be allowed to sell products. Foreign drug companies without facilities in Indonesia must partner with Indonesian firms and let the local firm be the entity to apply for product registration.

Patent law in Indonesia provides legal protection only if a pharmaceutical is manufactured in the country. Imported drugs that have been registered with the Ministry of Health are not covered by patent law. Thus, if a foreign company, through a local partner, registers, imports and distributes a proprietary drug, an Indonesian company can legally manufacture the same drug and sell it as a generic product under a different trade name. [17]

Indonesia shares the same problems as its fellow ASEAN members in its weak enforcement of the law, which led to reports that the problem of counterfeit drugs circulating in the country.

5.4 Laos

Laos is one of the countries in this region which is undergoing liberalization of its economy. The introduction of the New Economics Mechanism of 1985-86 has led

[16] Cambodian Ministry of Commerce (2004)
[17] Gross (2001)

to the rapid growth of private pharmaceutical businesses. Regulation of private pharmacies was introduced in 1988 and a National Drug Policy was adopted in 1993.

Prior to 1990, the Ministry of Public Health was directly in charge of pharmaceutical matters through the Department of Pharmacy. When the Food and Drug Administration Committee was established in 1990, some of its functions overlapped those of the Department of Pharmacy. Consequently, the two bodies merged in 1994 to form the new Food and Drug Department (FDD), which is now the overall authority for pharmaceutical regulation. Tests are performed by the Drug Quality Control Center (DQCC).

Drug manufacturers, importers and distributors need to obtain a license from the FDD before starting their operation. Registration of pharmaceutical products is also required by the law.

About 70% of the 3000 pharmaceutical products in Laos were imported by 30 licensed pharmaceutical import companies; the remainder was locally produced. These pharmaceutical products are dispersed into more than 2000 licensed private pharmacies. Because of inadequate law enforcement, approximately 60% of drug sellers have also bought drugs from illegal sources.[18]

5.5 Malaysia

The Malaysian pharmaceutical sector is mainly made up of the generic pharmaceutical (including branded generics) manufacturers engaged in the formulation and packaging, and a very limited extent the production of pharmaceutical active ingredients. Malaysia is heavily reliant on imports of both raw materials and finished products. About 65% of its pharmaceutical market are accounted for by imports.

The manufacturing sector remains with the private sector. There is no nationally owned pharmaceutical industry. Out of the total number of about 100 licensed pharmaceutical houses, about 60 percent are local based industry mainly involved in production of pharmaceutical active ingredients, formulation and packing or otherwise packaging of finished products only. Only one of them is research-based.[19]

Regulation of pharmaceutical comes under the Drug Control Authority (DCA) with National Pharmaceutical Control Bureau (NPCB) as its Secretariat. Regulatory controls over the pharmaceutical sector covers the general handling of pharmaceuticals, including poisons and narcotics, with respect to importation, manufacture, compounding, storage, distribution, and transportation. It also covers advertisements, sales, record-keeping and use of pharmaceuticals.

Licensing of facilities that produce, import, and distribute pharmaceuticals is mandated by laws. GMP compliance is made a requirement for manufacturing licensing, both for western and traditional medicines. For the importation of each consignment of registered products, an import permit is required, so too for investigational products.[20]

[18] USP (2004)
[19] Abdul Razak (1999)
[20] http://www.bpfk.gov.my/default1.asp

At the end of 2001, there were 72 licensed pharmaceutical manufacturers, 364 licensed importers and 795 licensed wholesalers. A total of 8,993 scheduled poisons and 6,696 OTC products registered.[21]

All human pharmaceutical products, whether locally manufactured or imported, must be registered with the Drug Control Authority prior to being manufactured, imported, sold or supplied, unless the product is exempt under specific provisions of the regulations—for example, drugs for individual patient use in specified quantities. Both western and traditional drugs have to be registered. Current registration categories include: scheduled poisons, non-scheduled poisons (over the counter products), traditional medicines, cosmetics, contract manufactured, export only, repacked, and second source. [22]

Registration applications must include product particulars, data and supporting documentation sufficient to establish safety, efficacy and quality. Other documents which must accompany the application include applicant's company incorporation or registration certificate, letter of authorization from the manufacturer (if applicant is not the manufacturer), Certificate of Free Sale in the country of manufacture and GMP certificate in the country of origin for imported products. If the product is being packed by different company, the GMP certificate of that company is required. The certificate must be issued by the authority recognized by the DCA, that is, listed in the WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Fees are charged for registration. The rates for pharmaceutical product registration are shown in table 10.

Table 10: Fees scheme for pharmaceutical product registration at NPCB

Drug Category	Fee (RM)	US$
New Chemical Entities	250	65.79
Poison	250	65.79
OTC	250	65.79
Traditional medicines	100	26.32

Note: exchange rate at 1 US$ = 3.8 Malaysian Ringgit

Source: Dzul, with new exchange rate calculation

Quality control is handled by the Drug Analysis Division based at NPCB. Its main responsibility is to determine quality, efficacy and safety of drugs and cosmetics to support the drug registration process.

The regulatory agency is also responsible for controlling clinical trials of pharmaceutical products carried out in the country. This is done through the issuance of the Clinical Trial Import license by the Drug Evaluation and Safety Division when the application of the license is approved by DCA. The applicant is required to follow guidelines set by the Research Committee of the Ministry of Health, apart from adhering to the Helsinki Declaration and also WHO Good Clinical Practice (GCP) Guidelines. It is expected that the harmonized ASEAN guideline will be implemented when available.

[21] http://www/pharmacy.gov.my
[22] Gross (2001)

There is to date no specific regulatory control in matters of price regulation.

5.6 Myanmar

A 1999 WHO study shows that Myanmar had 1 state-owned pharmaceutical firm, about 60 private small scale pharmaceutical plants, 20 importers, and 275 wholesalers. The public sector offered 144 drug outlets and the private pharmacies numbered about 8500. The total public sector drug expenditure was US$ 6.5 million. The total value of drug imports during the same period was US$ 0.9 million.[23]

The production, trade and use of pharmaceutical come under the jurisdiction of three Ministries—Health, Trade and Commerce, and Industry. The Central Medical Stores Depot (CSMD) of Ministry of Health (MOH) imports drugs and distributes them to government hospitals and health care facilities. Most of the drug supplies from CSMD are purchased from the sole state-owned pharmaceutical company--the Myanmar Pharmaceutical Factory, which is under the Ministry of Industry. The Medicines and Medical Equipment Trading (MMET), under the Ministry of Trade and Commerce, imports drugs and distributes them to the public and to private clinics.

In 1992, the National Drug Law was enacted; regulations for enforcement were issued by the MOH in the following year. The drug law and regulations cover importation, manufacture, distribution, drug registration, inspection, and quality control of drugs. Under the new law, the central and state governments are given authority in the different activities of regulation. The central body is the Myanmar Food and Drug Board Authority (MFDBA), within the MOH, which overseas the enforcement of laws as well as the implementation of the national drug policy. Licensing of drug manufacturers and approval of import certificates are the responsibility of the Central Food and Drug Supervisory Committee, while the State/Division Food and Drug Supervisory Committees license drug wholesalers and retailers located in the area under their jurisdiction.

Registration is required for imported and locally manufactured products for both the public and the private sectors. The evaluation is carried out by Drug Advisory Committee. According to the law, for a product to be registered, clinical trials have to be conducted in Myanmar. A fee system was also instituted, with the rates as shown in table . Registration is valid for a period of five years. Once a drug is registered, it can be imported into the country by anyone who has a license to import pharmaceuticals. As of 1995, there were a total of 1600 registered products. However, it was also found that more than 50% of the drugs in the market, including those domestically produced, were not registered by the authority.

Table 11: Fees scheme for pharmaceutical product registration at MFDBA

Fee type	Fee (US$)
assessment fee	100
registration fee	200
renewal fee	200
variation fee	100

Source: Wondemagegnehu (1999)

[23] Wondemagegnehu (1999)

The regulation mandates GMP inspection of pharmaceutical manufacturing plants. Companies owned by Myanmar nationals are expected to meet only part of the requirements, as opposed to foreign companies who are obliged to meet all of them. There were no standard procedures for inspectors to follow.[24]

5.7 Philippines

As with most other ASEAN countries, the Philippines has little pharmaceutical R&D, and the activities are mainly associated with the academic sector rather than with the production sector. It has a formulation pharmaceutical industry, and depends on imports of raw materials for production and finished products for part of the domestic consumption.

System of drug regulation in the Philippines has been in place for decades. The Food, Drug and Cosmetic Act provides the legal framework for drug regulation. The Bureau of Food and Drugs (BFAD), within the Philippine Department of Health, is the agency responsible to carry out activities stipulated in the Act.

Licensing of pharmaceutical facilities is required by law. Manufacturers have to comply with GMP standards.

Under the Food, Drug and Cosmetic Act, all pharmaceutical products can be distributed and sold only after having been registered with the Bureau of Food and Drugs. There are exemptions granted to Sera vaccine and bacteriological preparation manufactured by government institution or laboratory. The Act also requires licensing of manufacturers, importers, and distributors. And only those licensed entities can submit applications for pharmaceutical product registration.

As with many other countries, the level of technical information required for registration application differ according to whether the application is for a new drug or a generic. Reports on the pharmacological, clinical and other medical testing performed to show efficacy and safety of use of the drug are required for registration of new chemical entity. There is a set of requirements for registration of vaccine and biologic products. In addition, a new Guidelines on the Registration of Traditionally-Used Herbal Products was issued by BFAD in December 2004.

Registration fees, as shown in table 12, vary depending on whether the product is a new drug, a branded generic, or an unbranded generic. Renewal fees also apply.

Table 12: Fees scheme for pharmaceutical product registration at BFAD

Drug Classification	Initial (1-Year validity)	US$	Renewal (5-Year validity)	US$
New Drug/Monitored Release	20,000 /3 years	365.50		
Unbranded	2,000	36.55	7,500	137.06
Branded	3,000	54.82	10,000	182.75

Note: exchange rate at 1 US$ = 54.72 pesos

Source: http://www.bfad.gov.ph

5.8 Singapore

1) Drug regulation

[24] Wondemagegnehu (1999)

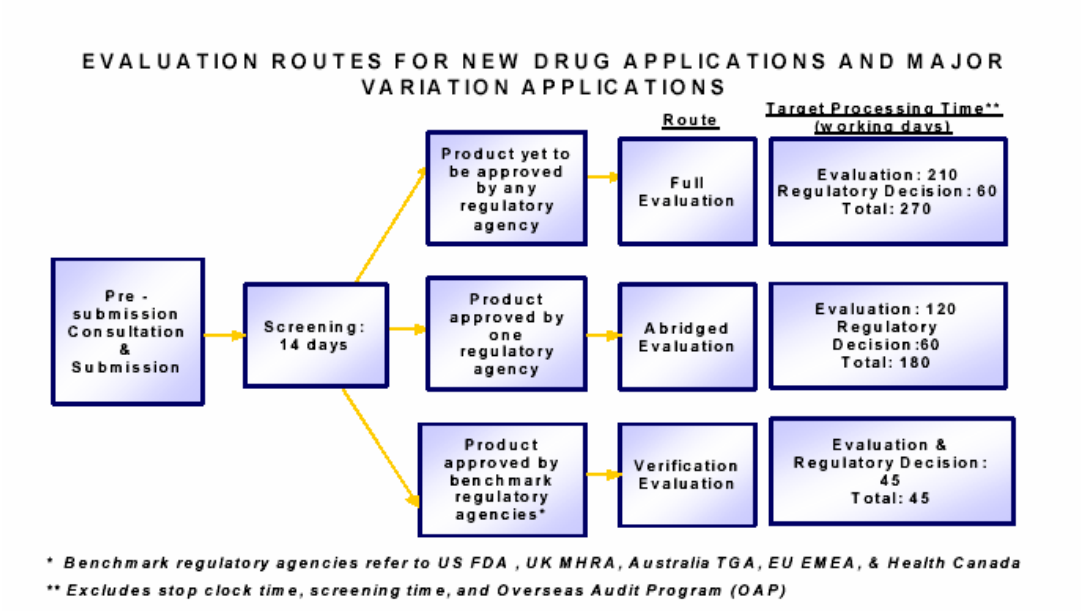
The Medicines Act requires all medicinal products sold in Singapore and manufactured locally for export to be licensed with the Centre for Drug Administration (CDA), which is the responsible agency under the Health Sciences Authority (HSA). CDA is responsible for the administration of legislation, formulation of drug regulatory policies and guidelines, evaluation of medicinal product applications and the issuance of final regulatory decisions and product licenses.

Within CDA, the Drug Registration Branch (DRB) and Innovative Therapeutics Group (ITG) of the Product Evaluation and Registration (PER) Division are responsible for the registration of medicines and the continual review of approved medicinal products.

For pharmaceutical product registration, there are four application types: New Drug Application (NDA), Generic Drug Application (GDA), Major Variation (MAV), Minor Variation (MIV).

A new drug application or a major variation application goes through one of the three evaluation routes as shown in figure 3. The level of technical data required from each application vary according to whether the product being applied has been approved by competent regulatory agency elsewhere.

Figure 3: CDA's new drug evaluation routes, including target processing time for each route



The product assessment process employs a confidence-based approach leverages on selected overseas agencies' regulatory and evaluation expertise.

- Verification evaluation route is for an application for a product that has been evaluated and approved by at least two of the HSA's benchmark regulatory agencies (BAs) for drug registration. The sponsor submits verification dossier. The

benchmark agencies identified by HAS are Australian TGA, Health Canada, the European Medicines Agency (EMEA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), and US Food & Drug Administration (FDA).[25]

This evaluation route can be chosen only if the product intended for sale in Singapore is the same as the one approved for registration by the BA (which issues the assessment report) with regards to Quality, Product composition, Site of manufacture, and Product labeling including package insert. Where there are differences in the indications approved by the BAs, only those indications that have been approved by all the concerned BAs will be considered for approval.

However, verification evaluation is not applicable to 1) first in class product, 2) biological derived from a new technology, 3) product rejected or withdrawn in part or in whole by a BA, and 4) product which needs to be assessed more stringently as a result of differences in local disease patterns or medical practices e.g. some anti-infectives, blood products and vaccines.

- Abridged evaluation is for an application for a product that has been evaluated and approved by at least one competent drug regulatory agency, as defined by the World Health Organization. The documentation required in an abridged dossier includes proof of approval by another drug regulatory agency, complete quality documentation, non-clinical overview, clinical overview, and summaries and selected study reports.
- Full evaluation is for a new product which has not yet been approved by any competent drug regulatory agency prior to its submission for registration in Singapore, and applies to an innovator product containing a new chemical/biological entity, new combination of chemical/biological entities or an innovative use of a registered product. Complete information on chemical/biological & pharmaceutical/genetic development data, toxicological and pharmacological data and clinical documentation needs to be submitted.

The time required for product assessment range from 45 working days in the verification evaluation to 270 working days in the full evaluation, as indicated in figure 3.

A generic drug application is for a product that is essentially similar to a currently registered product in Singapore (known as the “reference product”). Generic drug applications and other variation applications, there is no differentiation of evaluation routes at present. For all new generic Prescription Only Medicines (POM) in solid oral dosage forms, applicants are required to submit bioequivalence study data. It is required that the proposed use of the product and other essential information stated in the package insert and/or packaging materials of the product must be similar to the corresponding information approved for the reference product registered in Singapore.

Dossiers submitted for product registration can be either in the ASEAN CTD format or the ICH CTD format.

Once approved, a product license is valid for 1 year. Fees are charged for product registration and for annual license as indicated in table 13.

[25] CDA (2004)

Table 13: The Fees and Validity of Medicinal Product License are as follows:

Type of Fee	Fee (in S$)	Fee (in US$)
Application Fee ($) (valid for 1 year)	240	147.24
Annual License Fee ($) (valid for 1 year)	60	36.81
Amendment Fee ($)	20	12.27

Note: at 1 US$ = 1.63 S$
Source: http://www.hsa.gov.sg/html/business/cda_itg_faq.html

Traditional medicines are also regulated. Since a large number of Singaporeans use Chinese medicines, the CDA has taken steps to regulate products and practices in this area. The Centre's Chinese Proprietary Medicines Unit was set up in 1996 to regulate Chinese Proprietary Medicines (CPM). Dealers of CPM must obtain relevant licenses prior to the import, wholesale, manufacture or assembly of CPM. As licenses are only issued to locally registered companies, local agents must be appointed to handle the applications.

While CPM dealers do not need to register individual products, they are required to provide information on the CPM which they intend to import or manufacture, and are only allowed to deal in approved products. Generally, CPM dealers must ensure compliance with the requirements on: 1) labels and packaging materials (must not stipulate any of the 19 diseases/conditions specified in the First Schedule of the Medicines Act. Examples are cancer, diabetes, hypertension and sexual function); 2) Importers must submit documents showing absence of western drugs, and test results of toxic heavy metals and microbial contents for every consignment of CPM imported. 3) obtain a permit for the advertising and sales promotion of CPM.

2) Research and Development in Pharmaceuticals

Among ASEAN members, Singapore has the greatest capabilities for R&D of new drugs. These capabilities are available across the entire value chain, from basic research to clinical trials, product and process development, full-scale manufacturing and healthcare delivery. This is, in large part, a result of Singapore government's policies.

The Singapore government has taken initiatives to make Singapore a hub for biotechnology and research in the Asia. In recent years, it has taken various steps to provide strong infrastructures and venture capital for the development. A number of research institutes have been established. Examples are Institute of Molecular and Cell Biology, Genome Institute of Singapore, Bioprocessing Technology Centre, Bioinformatics Institute, Institute of Bioengineering and Nanotechnology. In 2003, the Biopolis research center, which has a capacity for 2,000 researchers, was opened.

Over the years, Singapore has attracted a number of major pharmaceutical companies, for instance, Glaxo-Smith-Kline, Shering-Plough, Aventis Pharma, Novartis, AstraZeneca, Pfizer, and Merck & Co, to this island nation. Many of these global pharmaceutical companies operate multi-purpose plants with the capability to manufacture a broad range of active pharmaceutical ingredients.

With the ASEAN harmonization process gaining momentum in recent years, new drugs developed by these efforts should benefit from more standardized approval process in the broader ASEAN market in the near future.

5.9 Vietnam

Since the Vietnamese Communist Party Congress adopted "doi moi" (economic renovation) policy in 1986, the country has engaged in rapid economic and social transformation. In the pharmaceutical sector, new trends emerge in different areas due to "doi moi." Most evident among them are

- the growth in pharmaceutical consumption, production, and import
- the institution of new regulation and guidelines,
- privatization and the increase in the number of private drug distribution channels, manufacturers and importers,
- modernization of manufacturing facilities

From 1995, the domestic production outputs increased by an average of 15% per year, and reached US$ 251 million in 2003. This was accounted for 35% of the Vietnam market share, the rest was covered by imports. The products were distributed through hospitals and 10,500 retail pharmacies.

The pharmaceutical industry is made up of public and private manufacturing facilities. At the end of 2003, there were 20 state firms, 590 private firms, and 28 projects with foreign investment capital in the pharmaceutical business. The number of GMP-certified firms increased greatly from 2 in 1997 to 41 in 2003.[26]

The Ministry of Health is responsible for drug regulation. The Drug Law regulates the manufacture, importation, and distribution of drugs. Three departments, the Drug Administration (formerly known as the Pharmacy Department), the Pharmaceutical Inspection Department, and the National Institute of Drug Quality Control, are charged with drug regulation and report directly to the Vice Minister for Pharmaceuticals. Registration is required for both imported and locally produced drugs.[27]

Although Vietnam has moved a long way from the centrally-planned model in the past, the State still manages economic sectors that deem critical to its development. Pharmaceutical is one of these sectors. In addition to registration and licensing, the government also control drug prices and managed the imports of pharmaceuticals with the aim to ensure affordability and control trade deficit.[28]

ASEAN Harmonization

Collaborations among the member states of ASEAN in the pharmaceutical sector was first initiated as a broad framework called the ASEAN Pharmaceuticals Project. The Project began in 1979 and activities in selected areas have been implemented since 1982. Over the years, the collaboration has resulted in the development of several guidelines related to different functions of drug regulation. Among them are guidelines and manuals on various aspects of pharmaceutical manufacture and quality assurance, ASEAN Good Manufacturing Practice (GMP) Guidelines and inspection manual, ASEAN Operational Manual on Drug Evaluation

[26] Vietnam Statistical Yearbook 2003
[27] Wondemagegnehu (1999)
[28] McCarty (1999)

and Control, non-pharmacopoeial analytical methods. In addition, 116 ASEAN reference substances have been established to aid quality assurance and drug evaluation and control.[29]

The latest major ASEAN collaborative endeavor on pharmaceuticals is harmonization of standards and rules in a number of economic sectors, which includes pharmaceuticals, among its member countries. This undertaking will probably be turned into policies that have expansive and extensive impacts on drug regulation in the region for decades to come.

Efforts toward ASEAN harmonization were initiated through the ASEAN Consultative Committee for Standards and Quality (ACCSQ), which was formed by the ASEAN Economic Ministers in 1992 to facilitate and complement the objectives of the ASEAN Free Trade Area (AFTA) and to eventually implement the mutual recognition arrangements (MRAs). Pharmaceutical is one of the sectors where harmonization at the regional level has been envisioned by the ASEAN ministers. Other sectors include electrical and electronic equipment, telecommunications equipment, cosmetics, and prepared foodstuff.[30]

A Pharmaceuticals Product Working Group (P-PWG) was established to work on the details in the development of harmonization guidelines for technical procedures and requirements applicable to the ASEAN pharmaceutical industry. Four areas in pharmaceuticals have been identified for harmonization—quality, efficacy, safety, and administration data.[31]

Key documents resulted from the work of P-PWG include:

- ASEAN Common Technical Requirements (ACTR) for pharmaceutical product registration (for human use)
- ASEAN Common Technical Dossier (ACTD) for pharmaceutical product registration (for human use)
- ASEAN Guidelines on the following areas: analytical validation, bioavailability and bioequivalence studies, process validation, stability study.

The new harmonized system has been put to use, starting 2004, in parallel to existing systems in member countries. There are differential requirements based on the members' readiness in the implementation of the common requirements and dossiers. For example, product applications to be registered in Laos based on ACTR and ACTD format are allowed to use bioequivalence studies conducted in a foreign country.

In Thailand, the ACTR and ACTD format has been made an acceptable format for registration with the Thai FDA from June 2004. Pharmaceutical industry can choose to register a product either under the traditional format or the new ASEAN format. For the few months after implementation, there have been a number of new drug applications using ACTR and ACTD submitted to the Thai FDA.

Experiences from this pilot phase will serve as the basis for further fine-tuning in the move towards Mutual Recognition Agreement (MRA) for the member states.

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[29] WEPRO (1998) http://www.wpro.who.int/public/policy/50TH/Ch_10.html Accessed Dec 2004

[30] ASEAN annual report 2002-03

[31] http://www.aseansec.org/accsq/sqdir.htm, and http://www.bpfk.gov.my/berita%20-%20berita/April%202001%20asean.htm and http://wwwapp1.fda.moph.go.th/drug/zone_mixs/files/mix005_04_info_view.asp?infoID=42 Accessed 30 Dec 2004

Eventual region-wide implementation of the harmonized pharmaceutical product registration regimes is currently expected by the end of 2008.

While ASEAN was working on its harmonized pharmaceutical registration, another international collaboration for harmonization of pharmaceutical registration was taking place in parallel. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), established in 1990, has worked to develop technical guidelines for registration of pharmaceutical products to achieve greater harmonization. Because ICH is an initiative involving regulators and pharmaceutical industry associations in the industrialized countries--the EU, Japan, and the US, with WHO holding an observer status in ICH. Since nations that are originators of the ICH process are those with strong research-based pharmaceutical industry, the focus for harmonization of guidelines is naturally placed on new pharmaceutical entities. ICH decisions have no direct effects on implementation, except to the extent participating countries adopt the standards. The production of ICH guidelines has enabled the ICH countries to harmonize technical requirements for the registration of new pharmaceutical products to a substantial extent.

As the International Conference on Harmonization (ICH) process started before the ASEAN harmonization process, ASEAN Pharmaceutical Product Working Group has consulted ICH technical information in the process of its ACTR, ACTD and guideline development as well.

The key feature in the ASEAN common technical requirements and dossiers for pharmaceutical registration is the emphasis on the registration of generic drugs. This is due to the fact that the majority of local pharmaceutical industry in this region is a generic industry. Therefore, products registered in ASEAN member countries are primarily generic products. However, the new common registration requirements are considered more stringent than requirements currently employed by the drug regulatory agencies in many member states. With the emphasis on quality, application data required by the ACTR and ACTD are generally more extensive in details than those of most ASEAN members. For example, process validation, which is not at present mandated by a number of drug regulatory bodies of member states, is required under the common framework. For new chemical and biological drugs, the ASEAN safety standards are basically in line with ICH requirements; efficacy evidence required is also in line with that of ICH. The sequences of data entry in the application form between the two differ, however.

7. Drug Regulation and Incentives for R&D in ASEAN

How do the regulatory frameworks in ASEAN countries affect incentives for research and development? This section provides an analysis to respond to the question related to drug regulation and its impact on R&D, as well as raises a number of issues and observations relevant to regulation, innovation and access.

7.1. How do drug regulation frameworks in ASEAN affect incentives in R&D?

Since drug regulation in ASEAN members, as in other countries, rests heavily on pre-marketing controls, the emphasis is placed on analyzing how pre-marketing controls affect incentives for R&D. Specifically, it focuses on examining whether drug regulation systems in ASEAN, particularly market authorization of products and

licensing of pharmaceutical firm, pose negative incentives on pharmaceutical R&D investments and activities.

1) Is technical requirement a problem?

Based on the available data, it is not possible to determine with confidence whether drug regulatory regimes in ASEAN countries influence the incentives for R&D. However, it can be observed that regulatory requirements demanded by these drug regulatory agencies (DRAs) are not any more stringent than those used elsewhere. ASEAN harmonized standards, which are closer to requirements used in developed countries, are more rigorous than requirements currently employed by most ASEAN members. Therefore, the current technical requirements imposed for drug registration are far from excessive to the level that might hinder incentive of introduction of new drugs.

2) Is registration fee a problem?

From the information on fee rates available in the 5 countries, fees charged by drug regulatory authorities in ASEAN are extremely low compared to developed countries. The amounts of fee charged for new drug registration in the five ASEAN countries are presented in figure 4. The same set of numbers is charted again in figure 5 for comparing registration fees from this study with a WHO study using the same scale. Note that these numbers represent one-time registration fees which do not include maintenance and renewal fees, which exist in some countries.

It is clear that the fees charged for market authorization of a new drug are much lower than those charged by some other developed and developing countries. Therefore, fee as a cost for pharmaceutical business in ASEAN is negligible compared to in many other countries.

Figure 4: New drug registration fees in five ASEAN countries in US$

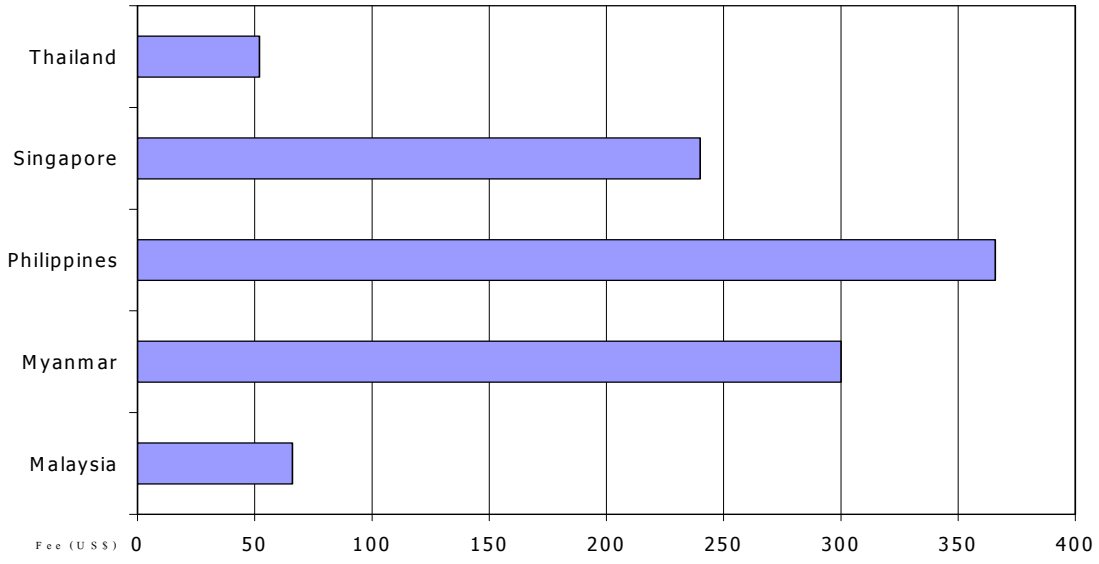
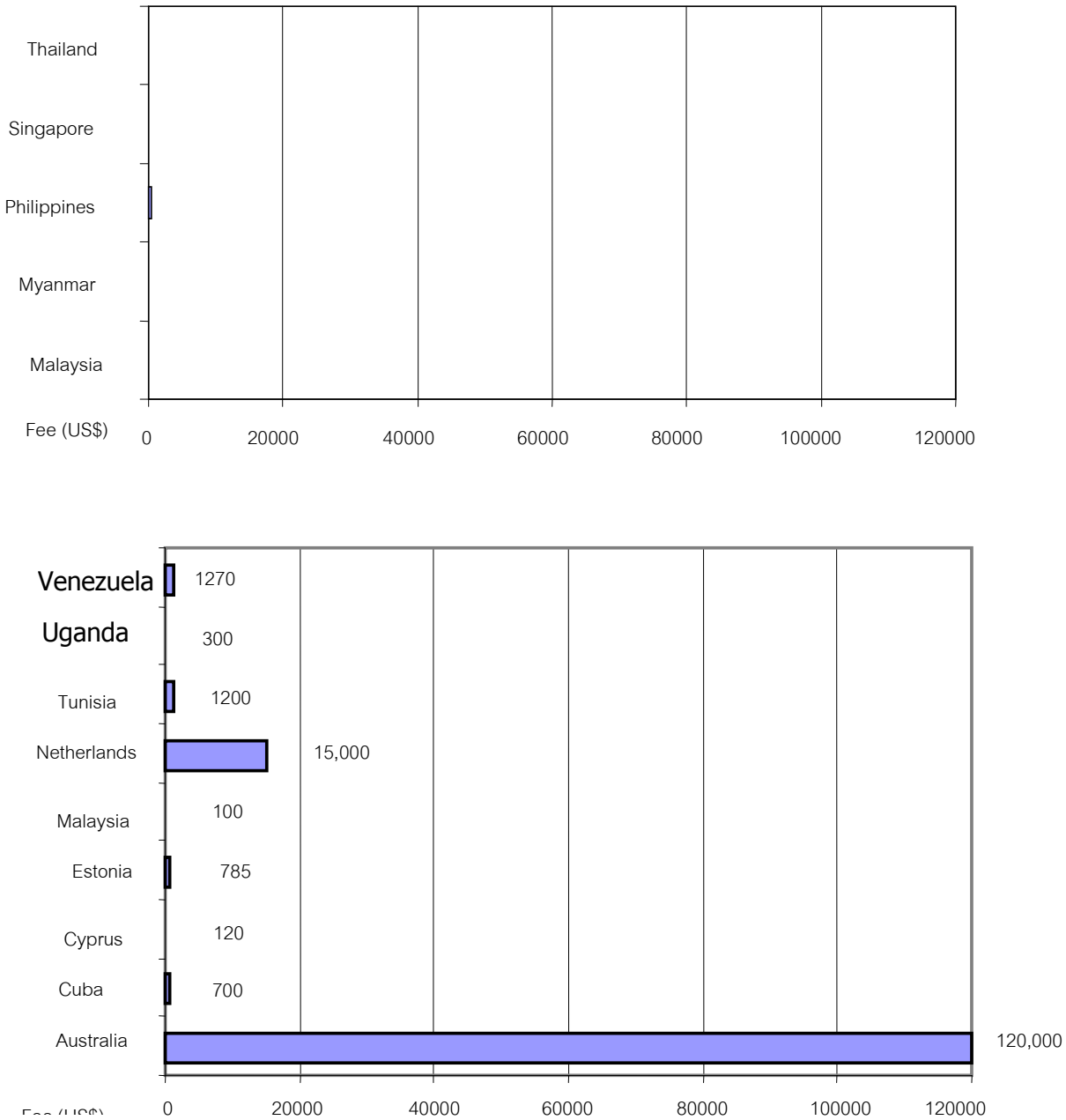


Figure 5: New drug registration fees in five ASEAN countries compared with new registration fees in countries from other regions, using the same chart scale.



Note: Malaysia is included in both groups. The difference in the fee rate for Malaysia between the two charts is due to the change in exchange rate used for calculation
Source: Ratanawijitrasin & Wondemagegnehu (2002)

3) Is registration processing time a problem?

No data from the present review are available for analysis on this issue.

A WHO study which addressed the issue of registration time reveals that registration time vary vastly both among DRAs in different countries and among

different products applied to a DRA.[32] There is no standard as to how long it should take for market authorization review. However, if too little time is allocated to the evaluation process to the extent that safety, efficacy and quality of drugs may be compromised, it will eventually jeopardize public health. On the other hand, unnecessary bureaucracy imposed on the process will be a disservice to public health.

7.2. Contrasting the two extremes in drug regulation in ASEAN

Does the existence of a strong drug regulatory system deter incentives for R&D? In the ASEAN experience, the answer is "No."

Brunei Darusalam and Singapore are the two ASEAN members with highest GDP per capita in this region.

While Brunei does not have a system for drug registration, Singapore has one that is considered the most systematic and strongest regime.

While Brunei does not have a pharmaceutical industry and it relies on imports for all its consumption needs, Singapore has the most advanced pharmaceutical industry in this region with the highest revealed comparative advantage value and highest investments in research and development among ASEAN members.

With strong government policies on industry development and intellectual property protection, Singapore is able to attract significant investment in R&D from top multi-national pharmaceutical firms.

Elsewhere in ASEAN, drug regulatory regimes are probably not more restrictive compared to that of Singapore, and other developed countries. Yet, no country is able to bring in as much foreign investment in pharmaceuticals. Not even with the lure of cheap labor costs.

The high level of R&D activities in Singapore is a result of its investment and research environment, not a result of a compromised and weak drug regulation system.

Table 14: Comparing pharmaceutical industry and regulation in Brunei and Singapore

	Brunei	**Singapore**
System of drug regulation: market authorization	none	strong
Local pharmaceutical manufacturing	none	high
Investment in pharmaceutical R&D	-	highest in ASEAN
Capability for new drug development and commercialization	none	high

7.3. Use of trusted drug regulatory authorities for product assessment

Singapore is the only country in ASEAN whose drug regulatory agency makes use of system where it relies on the result of product assessment and approval of certain 'competent' drug regulatory agencies (DRAs) in other countries for its own evaluation. This mechanism helps save time and resources needed for reviewing technical documentation on the part of the CDA. Such method of identifying and relying on trusted DRAs in regulatory review also employed elsewhere.[33] It interesting to observe that in ASEAN, the richest country with the most advanced

[32] Ratanawijitrasin & Wondemagegnehu (2002)
[33] Ratanawijitrasin & Wondemagegnehu (2002)

R&D and regulatory capability is the only country making use of such resource-saving mechanism.

7.4. Harmonization: ASEAN and ICH Schemes

A key concern about using the ICH scheme as "international" standards relates to ICH increasing reliance on advanced pharmaceutical technology in its standard setting, as well as more stringent requirements for raw materials.

In many countries, essential drugs required for the prevention and treatment of locally endemic conditions are generally supplied by local industry, which are generic manufacturers. If ICH standards are made international norm, and the local suppliers are unable to meet these more rigorous standards, the adverse impact of the withdrawal of these drugs on the health of the population might be far more dramatic than that of any risk posed by failing to achieve the level of quality in the ICH standards.[34]

In the development of ASEAN harmonization standards, the supply and demand conditions in the region were taken into account. Similar to many other developing countries, the local pharmaceutical industry in this region is a generic industry. Most new drugs are researched and developed outside the region. Some domestic manufacturing firms in ASEAN countries produce finished products for multinational firms on contract. A large proportion of new finished pharmaceutical products is imported.

Considering these regional realities, a key emphasis of the ASEAN common technical requirements and dossiers for pharmaceutical registration is on the registration of generic drugs. And for market authorization of new chemical and biological drugs, ASEAN standards are basically in line with those set by ICH.

Even with these considerations, the new ASEAN common registration requirements are still more stringent than requirements currently employed by the drug regulatory agencies in many member states. Facing this situation, ASEAN member states rely on the Association's unique culture of collaborations, i.e. the culture of consensus building. Timelines for implementing common standards are set differently for members with different levels of readiness. Some member countries are also allowed compromised requirements for the pilot phase. For example, reports of bioequivalence studies conducted in a foreign country are allowed for registration applications in Laos.

It is still too early to evaluate impacts of ASEAN harmonization. However, it is not too early to devise research frameworks that would allow policy makers to assess the effects of harmonization on the region's pharmaceutical industry and public health.

7.5. Policy issues in ASEAN vs. policy issues in developed nations

As reviewed above, among the ASEAN members, only Singapore has substantial R&D investments and new drug development capability. With the current structures of pharmaceutical industry in the region, no matter how relax these countries' drug regulatory systems become, chances are that it will not have an effect in increasing incentives for R&D.

Most of the countries have drug regulatory system in place, with laws, administrative rules and regulatory agencies. However, most have a problem with lax enforcement of laws. Substandard drugs, counterfeit drugs, and illegal drug outlets

[34] WHO (2002)

have been found in this region.[35] Key policy questions regarding drug regulation in developing countries appear to differ from those in developed countries. The more serious problem is thus better law enforcement, and improved access to quality products, at affordable price and to have necessary drugs available to solve health problems.

V. Thailand's Drug Regulation: the System and Its Environment

This section provides a more zoomed in view of drug regulation, research, and its environment by focusing on a member country of ASEAN--Thailand. Drug regulation system, its industry and health sector environment will be described, and will then be followed by analysis.

1. Health Insurance and Health Sector Reform

As noted earlier, health service determines demand of pharmaceuticals. Once a drug is made available in a country through drug regulation process, the ability to pay, the way drugs are paid, and the pattern of health care delivery determine demand for drugs.

In the past decade and a half, the Thai health sector has undergone several major changes. With the introduction of the Social Security Act B.E. 2533 (1990), Thailand instituted for the first time a major social health insurance scheme. The scheme covers employees of private businesses in the formal sector. Substantial movements for health sector reform started in mid 1990s, aiming to institute universal health insurance for the country. The reform efforts inculcated in 2001 with the introduction of a new government program—the 30 Baht health insurance program to bring universal coverage to the population. The program is so named because of the 30-Baht co-payment it charges for each visit. This was followed by the enactment of the National Health Security Act (B.E. 2545) in 2002 to provide legal basis for universal health insurance.

This new insurance program consolidated several previously existed government welfare and small-scale health insurance programs. At present it operates along side the other two major public health insurance schemes—the Social Security Scheme, and Civil Service Medical Benefits Scheme, as well as private health insurance.

1) Civil Service Medical Benefits Scheme covers government employees and their dependents. The beneficiaries number about 4-7 million people.[36] It is financed by taxes, and pays for drugs on a per item basis.

2) Social Security Scheme covers private business employees, which number about 7.5 million people. It is financed by equal contributions from employees, employers, and government. Payment to contracted hospitals is made on a capitation basis (with additional payments based on utilization). Cost of drugs is included in the overall per person payment.

3) The 30-Baht Health Insurance Scheme is the largest insurance program covering approximately 51 million people. According to the National Health Security Act, any one who is not covered under the two public schemes above is eligible under this scheme, regardless of economic status. All costs in this scheme are funded by taxes. The scheme pays for services with capitation plus diagnostic-related group

[35] USP (2004) and Wondemagegnehu (1999)
[36] The actual number is not known. Estimates given by different agencies vary.

(DRG) methods. Payment for drugs is not separated, but included in the capitation and DRG rates.

4) A multitude of private health insurance policies is offered by insurance companies. A large number of people buy private insurance either for additional benefits on top of the public programs they are eligible to, or simply forgo the public insurance and use services covered by private insurance they purchase. Since private health insurance is voluntary, those who choose to enroll pay premium to the insurance companies. The insurance pays for services on fee-for-service basis. This means that drugs are paid per item.

At present, hospitals—both private and government-owned, health centers (government owned), and a small number of physician clinics (privately-owned) are eligible to participate in providing services under health insurance. However, drugstores are excluded. Those who use drugstore services pay out-of-pocket.

The main features in the sources of finance and provider payments for out-patient and in-patient services are summarized in table1, with payments for pharmaceuticals presented in a separate column. Note that this table indicates only major payment mechanisms; there are minor variations in the payment methods—for example, additional payment for outlier cases--which are not presented here.

Table 1: Main features in the financing and payment of health insurance schemes in Thailand

Scheme	Finance Source	Provider Payment		
		OP	IP	Drugs
30 Baht	Tax	Capitation	Capitation/ DRG	Capitation (included)
SSS	Tri-partite	Capitation (all inclusive)		
CSMBS	Tax	FFS	FFS	Per item
Private	Premium	FFS	FFS	Per item

The different payment methods employed by these health insurance programs create differing financial incentives and pressures on the part of health service providers. It has been found that patients who are beneficiaries of the Civil Service Medical Benefits and private insurance received higher proportion of new drugs and originator products than those with the Social Security and 30-Baht Schemes.

2. The Pharmaceutical Market

Although the Thais consume both western and oriental medicines, western medicines (also called modern medicines) have been the mainstream for about a hundred years. Western medicines, therefore, take the vast majority of share—in both volume and value--in the Thai market. In 2001, manufacturing outputs for oriental (also called "traditional") medicines constituted only 3% of the outputs for modern medicines in terms of value, while imports of traditional medicines are valued at only 1% of imports for modern medicines.[37] The modern medicine sector will be the focus of this paper.

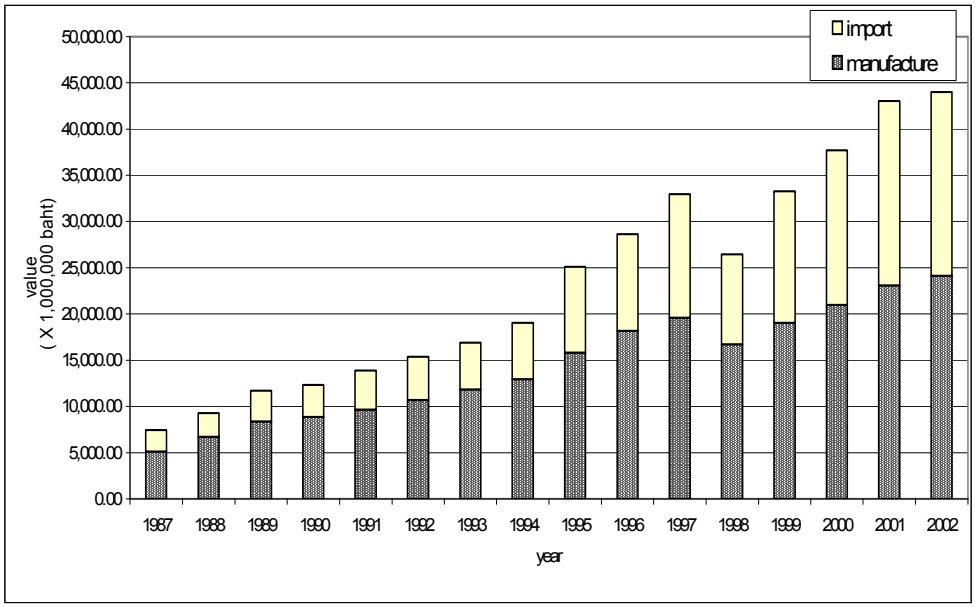
As with the majority of its neighbors in ASEAN, pharmaceutical industry in Thailand is basically a formulation industry. Finished pharmaceutical products sold in the country are either imported as finished products or made by the local manufacturers with imported raw materials. Consumption has been showing escalating trend for over a decade, except for a one-year drop in 1998 due to economic crisis.

In 2002, the total value of production and import amounted to 44,012.51baht (about US$1143.18 million). Finished products locally manufactured took up 24,144.56 million Baht or 54.9% share of the market. These include both generics mainly manufactured by factories owned by local businesses and brands produced by subsidiaries of multi-national firms as well as local firms produced under license of multi-nationals. Pharmaceutical products are distributed to the consumers via hospitals, health centers, wholesale and retail drugstores, and a small proportion through outlets of the Government Pharmaceutical Organization.

Figure 1 shows the local production and import values of modern finished pharmaceutical products for human use for the past decade and a half. In the 1980s, the values of products manufactured in the country were significantly higher than imports. Proportion of imports rose with accelerating rates during the period of the nation's high economic growth in the early and mid 1990s. It was during that time when the Thai Patent Act was amended extensively to include product patent for pharmaceuticals. From 1992 when the new Patent Act went into effect, rate of growth in the share of the original drugs in the Thai market increased 14 to 23% between 1993 and 1997.[38] However, since pharmaceutical product patents had not been granted during that time, the trend might not be an impact of the patent. It is not known if that trend was a result of income effect or another government policy granting market exclusivity for pipeline product (SMP) introduced in 1987, or other factors.

[37] calculated from Thai FDA data <www.fda.moph.go.th>
[38] Supakankunti et al (1999)

Figure 1: Trends of local production and import values of modern pharmaceutical finished products for human use (in Baht) between 1987-2002



Note: Charted with data from the FDA (www.fda.moph.go.th Accessed Feb 2005)

A drastic drop in both the values of local manufactured and import pharmaceutical products was observed in 1998, the year following the economic crisis. This drop can be explained by three possible consequences of the crisis: 1) the price effect--due to the depreciation of the Thai Baht, which led to increased price of finished products and raw materials, which in turn led to decrease import; 2) the income effect—due to collapse of businesses and a hike in unemployment rate; 3) government policies to control use of medicines and shifting to domestically produced drugs. These three factors were interconnected and difficult to separate.[39] The rising momentum surprisingly picked up in 1999, and has kept moving forward at an accelerated rate since.

[39] Supakankunti et al (1999)

3. Pharmaceutical Industry

With the exception of manufacturing facilities under the Government Pharmaceutical Organization, the Military Pharmaceutical Organization, and small scale production in some government hospitals, the majority of pharmaceutical production lies with the private sector.

There are 174 manufacturers and 527 importers of modern medicines in the country, all of which are small and medium size enterprises (SMEs). These production facilities import almost all their raw materials and turn them into finished products. The largest proportion of their outputs is reserved for domestic consumption; only a small portion is for export. Data from 2000-2002 indicate that the values of export remain slightly less than 10% of locally manufactured values.[40] The main export market is ASEAN.[41]

Table 2: Number of manufacturers, importers and drugstores (Year 2003)

License Type	Bangkok	Other Provinces	Total
Manufacturer of modern drugs	115	59	174
Manufacturer of traditional drugs	279	582	861
Importer of modern drugs	490	37	527
Importer of traditional drugs	170	14	184
Modern drugstore (class A)	3,393	4,832	8,225
Modern drugstore (class B)	565	4,088	4,653
Traditional drugstore	420	1,686	2,106

Source: http://wwwapp1.fda.moph.go.th/drug/zone_search/files/sea001_d08.asp

Note: The number of manufacturer of modern drugs has decreased in early 2005 after the enforcement of the GMP requirements

Since Thailand is a net importer of pharmaceuticals—both for finished products and raw materials, it is greatly dependent on the supply and research and development of pharmaceuticals in other countries. It is also influenced significantly by the international trade and exchange rate. The reveal comparative advantage index for pharmaceuticals ranges only 0.1 –0.24, indicating that this sector has low level of competition capability in the world market.[42]

Thailand manufactures only a few raw materials for pharmaceutical preparations. There are some 10 manufacturers of pharmaceutical raw materials with the Government Pharmaceutical Organization (GPO) as a key player. GPO manufactures on its own as well as through joint venture with private companies.[43]

The raw materials produced locally include both active ingredients and additives. However, the existing capacity produced only a few items. All the active ingredients locally made are low priced, widely used drugs which have been in the market for decades.

[40] Calculated from Thai FDA data
[41] Thai pharmaceutical export %ASEAN-to-non-ASEAN was 56.42% in 1997. (Janjaroen et al 1999)
[42] Janjaroen et al (1999)
[43] Thai Drug System Study Project Committee (2002)

Table 3: Examples of pharmaceutical raw materials manufactured in Thailand

Active ingredients	▪ Ampicillin Trihydrate ▪ Cloxacillin Sodium Monohydrate ▪ Amoxycillin Trihydrate ▪ Aluminium Hydroxide compressed gel ▪ Magnesium Hydroxide compressed gel ▪ Aspirin ▪ Paracetamol ▪ Trimethoprim ▪ Pyrazinamide ▪ Rifampicin ▪ Erythromycin Stearate, Erythromycin Estolate, Erythromycin Ethylsuccinate ▪ Kanamycin sulfate (sterile) ▪ Calamine Powder ▪ Gentamycin sulfate (sterile) ▪ Tramadol hydrochloride ▪ Medroxy progesterone acetate ▪ Ranitidine hydrochloride ▪ Acetic acid ▪ Anaesthetic Ether ▪ Sodium Chloride USP/BP (injectable grade)
Excipients	▪ Sorbitol ▪ Saccharin ▪ Alcohol Absolute

Note: Compiled from data in Supakunkunti et al (1999) and Thai Drug System Study Project Committee (2002)

4. Pharmaceutical R&D

The level of research and development in the pharmaceutical sector in Thailand is low. Several surveys have been carried out over the years attempting to map existing R&D investment and activities within pharmaceutical firms. Yet, these attempts have produced only sporadic and patchy information. The surveys gave the amount of R&D expenses around 0.5-5% of sale revenues for the local plants[44] to an estimated best case of 20% of sale revenues for the multinational firms.[45] According to one of the surveys that was conducted in 1993, responsibilities of the R&D units in local firms were formulation development, validation, stability study, development of drug analysis methods, and clinical study.[46]

Although the actual research and development tasks performed and the extent of investment allocated to R&D are not known, it is generally agreed that pharmaceutical industry in Thailand invests little on R&D, and the small investments, where available, are mainly used to conduct the D—development of product formulation, rather than the R—research for new products. Overall, the country does not posses adequate capability for new drug discovery.

As to clinical study, which is a critical phase in drug development process, limited capacity is available in the country. With the introduction of new requirements for new generic drug registration in 1989 which mandates bioequivalence studies,

[44] Thai Drug System Study Project Committee (2002)
[45] Supakunkunti et al (1999)
[46] Thai Drug System Study Project Committee (2002)

enhanced awareness and development of capability for conducting clinical studies have been observed, especially among the tertiary care hospitals. An effort has also been made by the Consortium of Medical Schools and the Health System Research Institute to systematize multi-center clinical studies in the country by forming a Clinical Research Collaboration Network. Only a few settings have the capacity to offer clinical trials for phase-III drug development.

Experts identify the insufficient number of human resources and the difficulty to get approval from ethical committee as two main obstacles for more clinical research in Thailand. Human resources take time to develop and/or acquire. But the bureaucratic manner most existing ethical committees in various agencies handle clinical study protocols begs immediate actions for change.

5. Government roles in the pharmaceutical sector

The Thai government regulates the pharmaceutical sector both directly and indirectly. It enacts laws to control the manufacturing, importation and sale of drugs directly. This will be elaborated in the next section. The government also regulates purchase of drugs through its own hospitals. In addition, attempting to boost economic activities, it has adopted a number of policies aiming to promote local pharmaceutical industry.

5.1 Public Sector Procurement

The majority of hospitals in Thailand are government owned. In addition to hospitals, the government also operates health centers both in the urban and rural areas. Therefore, the Thai government has a major role in the delivery of health care services. To manage the costs of providing services, government issues rules for procurement. All government agencies have to follow the Rules on Government Procurement established by the Office of the Prime Minister which sets directives to guide all government purchases. Public health facilities are no exception. The main objectives of this set of rules are to prevent fraud and to save costs in utilizing government budgets.

The Office of the Prime Minister's Rules on Government Procurement includes a special section on drug procurement. In essence, it mandates public health facilities to use no less than 60 % of their drug budget (80 % for health facilities under the Ministry of Public Health) to buy drugs listed in the National List of Essential Drugs (NLED), and that the prices of drugs purchased must not exceed the median price. Median price is thus made the ceiling price for the purchase of an essential drug. The Rules also give the Government Pharmaceutical Organization (GPO) a certain privilege over other suppliers. The requirement on percentage of budget to purchase essential drugs does not cover the budget generated by health facilities, e.g. revolving funds and donations. Health facilities are free to use budgets in those categories to buy non-essential drugs.

In actual implementation, however, hospitals have not strictly follow on the budget limits set for procurement of essential drugs. A large number of hospitals, especially secondary and tertiary care settings using larger than the indicated proportion of budget to buy drugs not listed in the EDL.

5.2 Promotion of local industry

Achieving self sufficiency in pharmaceuticals is one of the goals set forth by the Thai National Drug Policy (NDP), first adopted in 1982 and was revised

in 1993. The policy includes the promotion of local pharmaceutical industry as well as building capability for manufacturing pharmaceutical raw materials as key policy components.

Implementation of the policy, however, has been minimal comparing to what was initially envisioned. The FDA amended certain registration rules and streamlined procedures to facilitate registration process. It also provided local manufacturers with training, in areas such as good manufacturing practice (GMP).[47]

With the emergence of biotechnology, Thai government has developed strategic plans, set up organizations, and provided funds to promote research and development in biotechnology. The National Science and Technology Development Agency (NSTDA) was established to be the umbrella organization for a variety of high technology research units and Science Park. It operates outside the normal framework of civil service and state enterprises. The unit under NSTDA which is key to the development of pharmaceutical is the National Center for Genetic and Biotechnology (BIOTEC). Aside from conducting and coordinating research projects, NSTDA provides a number of services to support R&D and industry, for example, technological advice, sponsoring research, help on patent application, training, and identifying sources of loans.[48]

Recent interest in traditional medicines has led to increased use. With government policies and funding, research and development on herbal medicines has gained increased momentum. However, commercialization of those research works is still limited. Manufacturing, sale and use of herbal medicines remain mostly in the traditional sector.

6. Intellectual Property Protection

6.1 Patent Act

Thailand adopted its first patent law in 1979. Pharmaceutical products were exempted from patent protection under this law. Considering the inadequacy of the country to conduct research and development that would lead to the discovery of a new chemical entity, the 1979 legislation only allowed for pharmaceutical process patent, but not a product patent. Under this legal environment, the Thai pharmaceutical industry which had started as a formulation industry grew further by supplying more and more generic versions of originator products to the local market. Local pharmaceutical firms registered for generic drugs, imported raw materials and produced the preparation to compete in the local market based on lower prices. Meanwhile, R&D for new pharmaceutical entities had generally been ignored by the local industry.

In the late 1980's, with pressure from the US and a number of European countries that resulted in a quid-pro-quo in trade and legal structure, the Thai government revised its patent law. The Patent Act of B.E. 2535 (1992) provided for protection of intellectual property on pharmaceutical products, as well as production process. It, nevertheless, included a provision intended to protect consumers from impacts of high prices by establishing a Committee on Pharmaceutical Patent to monitor and compare drug prices, and to propose corrective actions when inappropriate price behavior was found.[49] During the approximately six-year time after the 1992 Act came into effect, this mechanism did not function in practice, however.

[47] Thai Drug System Study Project Committee (2002)
[48] http://www.nstda.or.th/pr/
[49] Patent Act (1992)

When the patent law was revised again and the third law was enacted in 1999, the special provision for pharmaceutical patent was left out. Another major change in the 1999 Patent Act from the previous one is the inclusion of petty patent. This allows a simple invention which has industrial applicability but is not necessarily a groundbreaking invention the possibility to enjoy patent protection. The simpler requirements make it is easier to be granted a petty patent than a full patent, but the protection goes for a period of six years for petty patent instead of twenty for a full patent.

Although patent protection is purported to be a key policy to promote innovations, and for developing countries, to accelerate technology transfer and foreign investment. A study carried out in 1999, did not find evidence to suggest much foreign direct investment and technology transfer in the Thai pharmaceutical industry since 1992.[50]

6.2. Trade Secret Act

A related law is the Trade Secret Act of B.E. 2545 (2002) which stipulates that information submitted by pharmaceutical companies for drug registration is considered trade secret, and is thus protected by law. The law also imposes heavy penalties on the part of violation by government officers handling registration information of pharmaceuticals and chemicals used in agriculture.[51]

For pharmaceutical trade secret, a set of rules is being drafted by the Ministry of Public Health to elaborate on the details related to the handling of registration data. The current debate centers on how long, from the time of submission, the registration information provided by pharmaceutical firms is considered trade secret, and thus protected by law.

The adoption of the law on trade secret aims to prevent 'unfair commercial use' of confidential data submitted to a drug regulatory agency as a condition of approving the marketing of pharmaceutical products. Yet, it also amounts to restricting the use of the originator's data for assessment of generic drug applications and, consequently, might delay the public's access to cheaper generics.

7. Overview of Drug Regulation

The legal basis of drug regulation in Thailand is the Drug Act of B.E. 2510 (1967), which has been amended over the years to bring the law up-to-date with new changes. The scope of regulation covers the following functions related to the trade of pharmaceuticals in Thailand: 1) licensing of manufacturing, importation, wholesale and retail sale of drugs, 2) product assessment and registration, 3) GMP inspection, 4) inspection of distribution channels, 5) quality control of products, and 6) control of drug promotion and advertising. These functions fall under the jurisdiction of the Thai Food and Drug Administration, Ministry of Public Health.

Licensing of manufacturing, importation and sale of drugs is required by law. Only a licensed pharmaceutical manufacturer or importer is qualified to apply for drug products registration. Pharmaceutical manufacturing plants have to comply with the Good Manufacturing Practices (GMP) standards. They are subject to inspection by the FDA.

Quality testing is carried out regularly by the Department of Medical Science (DMS), also within the Ministry of Public Health. Each year, the FDA and the DMS jointly develop plan for drug samples collection and testing.

[50] Supakankunti et al (1999)
[51] Trade Secret Act (2002)

Promotion and advertising of drugs are also activities being regulated. Thai laws mandate pre-approval control of drug promotion and advertising. Materials for such purposes have to be submitted to the FDA for approval before they can be released.

As for reporting of adverse drug reactions, the FDA relies on voluntary reporting. A section within the FDA handles ADR reports sent by health professionals.

Thai laws also provide for drug price regulation. Price control functions are designated to the Department of Internal Trade, Ministry of Commerce. The government imposes price control only for those goods considered basic and essential to the populace. Traditionally, the Thais see drugs as one of the four essential staples in life, along with food, clothing, and housing. Control of drug prices, therefore, has long been seen as imperative when it comes to initiatives to hold down the rise in living costs for the general public.

However, the degree of price regulation is relatively limited. In practice regulatory price control has normally been placed on manufacturers' and importers' listed price and on requiring that drugs distributed through drugstore sector have their retail prices displayed. Although manufacturers and importers are required to submit for approval for price increase, the said drug price applies to drug companies' listed price rather than to the actual sale price to health care providers. Health care providers—hospitals, drugstores, and clinics—usually buy drugs at discounted price. Discounts can be in cash or in kind, i.e. as percentage reduction from listed price, as extra drugs added to the amount ordered, or as 'gifts' given to the purchaser.

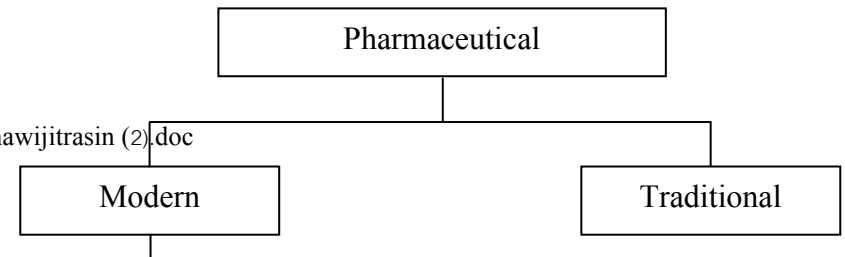
8. Registration of Pharmaceutical Products

The structural design for product assessment and registration as specified by the 1967 Drug Act is of a commission format. According to the law, a Drug Committee is appointed to advise the Minister of Public Health on both regulatory and technical aspects concerning administration of the drug control. The committee renders decisions on approval of pharmaceutical registration and withdrawal or suspension of product licenses. The committee can then appoints subcommittees to assist them in matters authorized by the Drug Committee. Drug Control Division within the FDA is the government administrative agency handling the registration process.

8.1. Product Classification

Registration requirements and procedures for pham products for human use in Thailand vary depending on the level of novelty and technology. Drugs are classified into two major groups – modern and traditional drugs. Modern drugs include chemical and biological entities. The FDA then further classifies modern drugs for the purpose of regulatory assessment into 3 categories, differing in the type of dossiers required of them. They are generic drugs, original new drugs, and new generic drugs.

Figure 2: Legal classification of pharmaceutical products



The present rules for new drug registration was introduced in 1989 as an administrative mechanism to grant market exclusivity for pipeline products that are not eligible for protection under the 1992 Patent Act. The rules devise different requirements for market authorization of 'original new drugs' and 'new generic drugs'

1) Original New Drug

Products to be registered in this category include new chemical entities, new indications, new combinations, and new delivery systems. An application has to be submitted along with evidence or technical data on efficacy, safety and quality of the drugs, samples, and other documents such as certificate of free sale. The dossier requirements for this type of registration are the most demanding compared to other types.

Once a new original drug passes the product assessment process and market authorization is granted, it is registered with conditions. The new drug is subject to certain restrictions while enjoys the benefits of monopoly under the safety-monitoring program (SMP) for a period of two years. The program requires that new original products be sold only in medical institutes with close supervision of doctors, in which safety monitoring can be proceeded. This means that it can be sold to hospitals and physician clinics, but not drugstores. The product sponsor is mandated to monitor adverse drug reactions associated with the use of the drug in Thailand and submit report to the FDA within two years. Extensions for the safety monitoring period are allowed if approved by the FDA. If there is no evidence indicating serious side effects or it is considered that benefits outweigh the risks, the product will be approved unconditionally and allowed to distribute widely through other channels as well.

During the conditional registration period, the holder of the new drug license has the benefit of monopolistic supplier status. Other pharmaceutical companies are not allowed to sell the generic version of such drug, regardless of the patent status of that drug.

2) New Generic Drug

New generics are medicines with the same active ingredient(s), dosage form and strength as those of the new compounds registered as original new drugs.

Any new drug whose conditional registration status has ended, the right to market exclusivity is also terminated, provided that no patent is granted to the product. Other drug companies that want to manufacture such drug can submit application for registration to manufacture or import the drug. This is then considered registration of a new generic. In this case, the sponsor has to submit information as required by generic drug application, plus a bioequivalence study report to provide evidence of equivalency with the original product.

3) Generic drug

This class includes pharmaceutical products with the same active ingredients and the same dosage forms as those of the original products (for products registered before the 1989 rules) or new generics (for products registered as above), but manufactured by a different license holder.

The dossier requirements for application in this group are the least complex among all modern drugs. The sponsor has to submit documents related to the finished product specification (drug formula, physical information, etc), label and insert, packaging information, storage information, manufacturing method, product quality control and analytical methods, stability, manufacturer/importer information, certificate of free sale (in case the product is imported), and drug sample.

4) Biological product

Biological products which registration is required include active immunizing agents (e.g. vaccines, toxoids), passive immunizing agents (e.g. snake antivenin, heapatitis B immunoglobulins, tetanus antitoxin), blood products (e.g. factor IX, plasma albumin), diagnostic agents (e.g. tuberculin test), immunomodulators (e.g. interferon, erythropoietin), and others as identified by the FDA.

For the purpose of assessment and registration, biological products are classified into original new drugs, new generics, and generic drugs, in parallel to the scheme used for registration of chemical entities.

Special restriction imposed on biologics in addition to those required of chemical products is the control at lot level. A certificate of lot release for biological products issued by the Thai Department of Medical Science (in case of locally-manufactured and imported products) or by relevant agency in the manufacturing country (in case of imported products) is required before the sale of each batch of biologicals.

5) Traditional drug

Traditional drugs are products whose ingredients are derived mainly from herbal and other ingredients in traditional medicines and following the pharmacopoeia of traditional medicines or those declared by the Minister of Public Health as traditional drugs

The control and registration of drugs in this group is less stringent than those of the modern drugs. Applicants provide product, labeling and packaging information, but not information on analytical methods.[52]

[52] Thai FDA (1999)

The salient points on data requirements for registration and unique regulatory features for each of the product categories are summarized in table 4 below.

Table 4: Key regulatory features for registration categories

Product Category	Key regulatory features for the category
Generic drug	Require product information, analytical methods
Original New Drug	▪ Information required of generic drug registration ▪ Scientific evidence on efficacy and safety ▪ Initial 2-year conditional registration status: product to be sold only in hospitals and clinics, monopolistic supply protection
New Generic Drug	▪ Information required of generic drug registration plus ▪ bioequivalence studies
Biological product	▪ Dossier requirements are the same as registration of chemical entities—original, new generic, and generic ▪ Lot release is required
Traditional-drug	Require product information

Table 5 provides a glimpse of the type and number of product licenses approved in recent years. The total number of registered modern drugs in Thailand is 24,895.

Table 5: Number of pharmaceutical product licenses for human use approved in fiscal years (October-September) 2003-2005

Year	Manufactured		Repackaged		Imported		Total
	Single drugs	Combined drugs	Single drugs	Combined drugs	Single drugs	Combined drugs	
2003	581	165	16	2	411	85	1260
2004	471	124	26	0	594	126	1341
2005*	113	32	8	2	93	28	276
# Registered total**	15,004	4,726	226	56	3,899	984	24,895

Note: * 2005 data at 1 March 2005 (applications approved between 1 oct 2004-28 feb 2005)

** Current total number of licenses for pharmaceutical products for human use

Source: Thai FDA. Accessed Feb 2005.
http://wwwapp1.fda.moph.go.th/consumer/stat/drug/dstdlc002.asp?statnm=สถิติจำนวนทะเบียนตำรับยา&rid=2

8.2. Registration fees

The Thai FDA charges fee for product registration. Under the current law, a product license for modern medicine costs about US$ 52, and is valid for a lifetime. Registration fee is charged only once; there is no maintenance or renewal fee.

Table 6: Fee rates for product registration and facility licensing in Baht (USD)*

Category	Modern Drugs	Traditional Drugs	Note
pharmaceutical product license	2,000 (52)	500 (13)	no renewal or annual maintenance fee required
manufacturer license	8,000 (208)	1,000 (26)	annual renewal required
importer license	10,000 (260)	5,000 (130)	annual renewal required

Note: * Based on 38.50 Baht per US$ and rounded up

With this fee structure, it costs more on the part of the government to evaluate the dossiers submitted than the fee the product's sponsor actually pay to the government. Attempts to charge product sponsors more have not yet been successful.

8.3. Registration Tracks and Time

Two registration tracks, which incur different process lengths, are available for pharmaceutical product registration. These are regular track (dubbed standard review) and fast track (dubbed accelerated review).

1) A standard review is the regular mode of registration, and is applied to all drugs other than those allowed under the accelerated review track.

2) Accelerated or Priority review is a fast tract registration. This track has been created for

- drugs that are deemed for alleviating urgent public health and personal health needs,
- drugs that are intend to treat severe diseases such as AIDS, cancer,
- drugs that are results of research and development carried out mainly in the country,
- drugs that are also manufactured for export.

According to the Thai FDA indicated time line, new drug registration through a standard review process takes 210-280 days, while one that goes through a fast track takes only half of the time. (See table 7)

Table 7: Required time for product registration (work days)

	Standard Review	Accelerated Review
New chemical entity	210: if subcommittee's deliberation is not required 280: if subcommittee's deliberation is required	100: if subcommittee's deliberation is not required 130: if subcommittee's deliberation is required
New generic drug	110	70

Source: compiled using data from Thai FDA website. Accessed 3 Aug 2004.

How much time does registration actually take? Actual time taken for registration is determined in part by how efficient the handling of assessment process is, and in part by whether there is sufficient number of expert reviewers, i.e. the workload each reviewer takes. At present, the number of experts on biologics is still in short supply.

In terms of the lag time for product introduction—defined here as the time between the submission of a product registration application to the time when a product license is obtained, available figures do not allow meaningful picture to answer the question whether registration process is unnecessarily delayed.

According to a study of registration time for 'modern' pharmaceutical products from 1986 to 1997, shown in table 8, the number of days it took for market authorization of product license for a new drug ranged from 11 to 2147, with an average of 535 days. For generic applications during the same period, the minimum number of days was a super short time of 1 day, while the maximum was 1979 days. The mean registration time for the generic group was 223 days. Note that these data came from submissions before the FDA set the target registration processing time scale as in table 7 above.

Table 8: Registration time for pharmaceutical product applications between 1986 and 1997

Type of application	# of applications	Time for registration (days)		
		mean	Min	max
New drug	328	535	11	2,147
generic	12,444	223	1	1,979

Source: Thai Drug System Study Project Committee (2002)

Unfortunately, these figures provide a rather simplistic picture of the lag time for product authorization. The study fails to address the distribution of the data on registration time, nor does it handle outliers to present meaningful interpretation of the application time. Therefore, the figures do not offer any useful information for determining which types of products took longer than necessary in the process and which did not, and where improvements can be made.

In recent years, product assessment and registration processes have been expedited by a number of administrative arrangements introduced. Probably the most notable among them is the one-stop service section that pools resources from different sections within the FDA to make it convenient for the businesses to submit applications on a number of things. For pharmaceutical product registration, applications for manufacturing and importation of product samples for registration, for testing, lot release for biologicals, for example, can go through this channel.[53]

9. Drug Regulation and Incentives for R&D in Thailand

Does drug regulation in Thailand affect, or more specifically discourage, pharmaceutical research and development?

Since drug regulation in Thailand, as in other countries, rests heavily on pre-marketing controls, following the same framework used for ASEAN in earlier section,

[53] http://www.fda.moph.go.th/governance/information/onestopservice.asp

analysis here will examine how technical requirements, fees, and processing time needed for market authorization affect R&D incentives.

Three specific questions are addressed in this section:

- Does drug regulation in Thailand, particularly market authorization of products and licensing of pharmaceutical firm, pose negative incentives on pharmaceutical R&D investments and activities?
- How factors in the pharmaceutical sector environment, particularly patent and trade secret protection, national essential drug list, and health insurance affect incentives on pharmaceutical R&D?
- Does drug regulation play a role in facilitating the registration of generic drugs and thus improve access?

9.1. Drug Regulation

To obtain market authorization of a product, pharmaceutical firm has to comply to technical requirements, and bear the cost of fees as well as time required for the process. Therefore, the specific question here is whether the technical requirements, fees charged and time taken for registration pose undue difficulty on the part of the product sponsor.

1) Is technical requirement a problem?

In Thailand, almost all new drugs are introduced into the market by multi-national companies. Submission of evidence on efficacy and safety from clinical trials and other studies is required. Reports of studies conducted outside Thailand are allowed. This means that product sponsors do not have to redo clinical trials in Thailand in order to obtain a product license. Clinical studies performed in Thailand are required only after the product license is granted and has to follow Safety Monitoring Program (SMP)'s requirements. However, SMP does not demand random control trials (RCT) for the clinical studies product sponsors have to do. The conduct of clinical studies for fulfilling SMP requirements can be easily accomplished in the country. Note that this program mandates submission of clinical reports only once; product sponsors are not requested to do more clinical studies after the unconditional license is granted to the product. And ADR reporting as post-market monitoring measure is voluntary. According to sources from multi-national firms, the registration process does not have an effect to discourage the introduction of new drugs into the Thai market.

As for new generic drugs, registration applicants are mostly local manufacturers, some importers apply in this category as well. The institution of requirement on bioequivalence study report for registration of product in this category results in increased expenses and some delay for registration application on the part of the local industry. Sources indicate that if the sale volume is high, manufacturers do not consider bioequivalence study a problem. It is for drug items where demand is small that manufacturers do not see much incentive to invest in the study and production processes. For manufacturers of new generic drugs, in determining which drugs to apply for registration, the firms consider potential sale volume and the technological feasibility and complexity as key decision factors. Drug regulation is taken as a given which does not affect competition, because every product has to be registered.

2) Is registration fee a problem?

Thai FDA charges only 2000 Baht (approximately US$ 52) for registration fee. There is no annual maintenance fee; neither is there a renewal fee

because it is a life-long license which lasts as long as the life of the firm. The fact that registration fee is very low should not cause any difficulty to the pharmaceutical companies. To the contrary, the low fee and the absence of expiry of product license led to over registration. It is generally known that some pharmaceutical firms simply submit applications without plan for production. And once a license is granted, they keep it with or without actually manufacturing the product.

Another implication of low registration fee is the public subsidy of private interest. The amount of budget spent by the FDA as expenses is far higher than the fee amount received for the review of registration applications. Actual expenses include the process of handling application, expert reviews, committee meetings, etc. Ultimately, the taxpayers support pharmaceutical firms to introduce pharmaceutical products into the Thai market. This subsidy should be considered wasteful if the registered product introduced into the market does not play a significant role in enhancing health or prevent or cure diseases. It worths the taxpayers' money only if the subsidization brings about better health.

3) Is registration processing time a problem?

Registration processing time used to be an issue in the past. With the introduction of target processing time and fast track registration by the FDA, the facilitation through the one-stop service stations, and the streamlining of the process, the time length of product registration is no longer a cause of complaints. From the point of view of the pharmaceutical manufacturers and importers, the current registration time does not impose burden to their businesses, and therefore do not see this as a problem. The key process facilitation lies instead on certainty and regularity of the relevant rules and the application of those rules.

Do other regulatory controls affect incentives on investment in pharmaceutical establishment? Current laws on licensing of pharmaceutical establishments, GMP requirements, pre-approval control on drug promotion and advertisements are what pharmaceutical businesses have to meet in addition to marketing authorization of products. Since these legal controls are not any more stringent than in other countries, and licensing fees are also low, industry people interviewed see no negative impacts of these factors on decisions to establish pharmaceutical firm in the country.

9.2. Other factors in the pharmaceutical sector environment

1) Patent and trade secret protection

Legal protections of intellectual properties and trade secrets have been in place in Thailand. These frameworks provide incentives for R&D in pharmaceuticals and for introducing new drugs into the market.

At present, evaluation for patent application in Thailand does not include a pharmacist in the review process. Therefore, sources from the industry question the level of 'novelty' in some products which patents have been granted. If in fact patents are granted to products with key features that are not actually innovative, an implication can be that it would hinder the opportunity for other pharmaceutical firms to introduce a generic version of such product into he market.

2) Essential drug list

What roles does essential drug list play in regulation and access to medicines in Thailand?

National Essential Drugs List was first introduced in 1982 as procurement list and was initially served as the list for procurement control in government's health facilities. After the economic crisis in 1997, the Cabinet decided to use the essential drug list as a reimbursement list for Civil Service Medical Benefits Scheme. The beneficiaries have to pay out of pocket for drugs not contained in the EDL. Nevertheless, exceptions can be made if the prescription for non-essential drugs is signed by hospital drug committee members to allow for checking the appropriateness of prescribing such drugs.

As indicated earlier, the government procurement rules for procurement of essential drugs are not strictly followed in actual implementation. Neither has the reimbursement requirements strictly followed. Prescriptions with non-essential drugs are regularly signed, endorsing them for reimbursement without actual review for appropriateness of non-essential drug prescribing.

In sum, the Thai government uses essential drug list as a cost containment tool, and does not link the list to drug registration. So far, as a result of the ways it is implemented, EDL has not achieved its intended effect as a tool to achieve policy objectives.

3) Health insurance

Since the various health insurance schemes in Thailand employ different methods in paying for pharmaceuticals, they introduce different types of financial pressures and incentives to the health service providers. Recent studies have found different patterns of drug prescribed to beneficiaries of different insurance schemes. Beneficiaries with the schemes paying for drugs on a per item basis—such as Civil Service Medical Benefits and private health insurance are prescribed more new drugs and more drugs from originator companies; while those with the 30-Baht and Social Security schemes, which pay provider on a capitation/DRG, receive more generic drugs. Studies also show that patients with insurance schemes that pay on a capitation basis have much lower probability of receiving newer drugs than those covered by insurance policies that pay for drug on a per item basis.[54]

Insurance coverage and payment methods constitute strong influence on the level of demand for the type of drugs in the Thai market. With the large proportion of the population covered by social insurance using capitation payment methods, and if the planned consolidation of the three main public insurance programs materialized, demand for new and original drugs will be affected. This might eventually influence the incentives for introduction of new drugs.

9.3. Drug regulation and access to generics

Does drug regulation facilitate the marketing approval of generic medicines?

Applicants for registration of generic drugs are not required to conduct clinical studies or to submit evidence of efficacy and safety of the product. These simplified requirements, therefore, help reduce the time and the costs of market authorization of generics, and consequently expedite access to the generic version of a drug.

Access to drugs is generally not a problem in Thailand. However, access to orphan drugs remains an unsolved problem. In 1994, the Thai FDA listed 43 drugs as orphan drugs (and has not updated the list since then). In 1998, it exempted

[54] Limwattananon et al (2004)

certain orphan drugs from the Safety Monitoring Program. Yet, it appears that more is needed to produce the impetus for increased introduction of drugs in this group into the market.

VI. Conclusion: Drawing from Experiences of ASEAN on Issues Related to Drug Regulation and Research

ASEAN member countries share a number of common characteristics with regards to their pharmaceutical sector and regulation. Some of these characteristics can be said to reflect what found in developing countries in general. Drawing from evidence in ASEAN, key points relevant to the theme of this paper are listed below:

- Drug regulatory frameworks in ASEAN member countries do not appear to discourage research and development of drugs and vaccines.
- Drug regulatory capacities in the majority of ASEAN members are constrained by limited human and financial resources.
- Gaps exist between written regulation and actual enforcement in a number of ASEAN member countries. For example, despite laws prohibiting counterfeit/substandard drugs, surveys found such products in many countries.
- Among the member countries, only Singapore—which has the most advanced R&D and regulatory capability in the group—adopts a registration system that relies on product assessment and approval of other competent DRAs.
- All ASEAN countries are net importers of pharmaceuticals. All except Singapore do not have capability for new drug development.
- Evidence from some ASEAN members shows that R&D capability is a result of a country's investment and research environment, not a result of a compromised and weak drug regulation system.
- The process of development and implementation of ASEAN harmonized registration standards follows the traditional ASEAN culture of consensus building and flexibility.
- Levels of health insurance coverage among the populations of ASEAN members vary. In many countries, the majority of the population pays out-of-pocket for drugs. Consequently, even when drugs are available, affordability is a significant issue for access to necessary drugs. For countries with health insurance systems, high drug price affects system sustainability and service quality.

VII. Reframing Policy Questions and Recommendations

Societies aim to protect consumers from the harms that unsafe and inefficacious drugs might bring, and to promote R&D for the discovery of new drugs that will help prevent and solve health problems at the same time. Compromising necessary consumer protection to facilitate availability of drugs will not lead to appropriate solution to achieve both aims. As noted elsewhere, it is simplistic to simply attempt to speed up registration process to improve access.[55] The question, then, does not lie in how to redesign drug regulation to strike a balance within the regulatory framework that can accommodate faster market authorization for drugs.

[55] Hill and Johnson (2004)

Rather, the question lies in how to strike a balance among the multitude of public policies targeting pharmaceutical sector that can lead to accomplishment of the multitude of goals placed upon this sector.

It is imperative to have a drug regulatory system that is strong enough to provide necessary evaluation to ensure efficacy, safety, and quality, but without unnecessary bureaucratic inefficiency that causes undue delay and difficulty. It is also imperative to have public policies, either through essential drug list or through health insurance, that enable population to acquire quality pharmaceutical products at reasonable price when needed, and that the health system is sustainable. Promotion of pharmaceutical R&D demands a set of public policies that institutes incentives in investment and an accommodating industry and trade environment. And these policies must be designed and implemented in a systematic way to move the countries towards the achievement of multiple goals.

Since the majority of developing countries lack adequate capabilities in both drug regulation and research and development, key policy questions, then, are 1) how to improve these capabilities? and 2) how to do better given existing limitations? Some efforts can be made at the national, regional, and international levels.

1. Recommendations for improving drug regulatory capability

- Risk management[56]

  This is a method for prioritizing and streamlining work process to enhance efficiency within the existing DRA capacity. The idea is to use a tiered approach in which the level of regulation commensurate with the degree of risk. Pharmaceutical products and facilities are classified according to the degree of risk they might cause to public health. Thus prescription drugs and new drugs posses higher degrees of risk than non-prescription drugs; facilities for manufacturing sterile products posses higher degrees of risk than those manufacturing cream for external use. The DRA then channel resources to regulate more intensively on high-risk items and less on the low-risk ones. This will help streamlining human and financial resources into areas needing more scrutiny.

- Make use of "reference" or "trusted" or "competent" or "reputable" DRAs[56]

  Product assessment, especially for new drugs and vaccines requires relevant expertise. Developing countries constrained in human resources and expertise for drug evaluation can rely on product evaluation by other DRAs to help alleviate these constraints. Several countries have currently employ this approach by identifying DRAs in a number of developed countries as reference.

  A number of concerns and questions have been raised regarding the reliance on developed country approvals for market authorization decision in developing countries. For example, a legitimate concern involves the difference in risk/benefit considerations between developed and developing countries due to differences in disease patterns and other factors. Ongoing international and regional efforts on harmonization also lead to cross-country reliance on standards and process of drug regulation.

[56] For country experiences on these approaches, see Ratanawijitrasin and Wondemagegnehu (2002)

Moreover, there are questions related to the possibility, feasibility, appropriateness and consequences of establishing an international body/network or expanding regional body to perform the function of evaluating pharmaceutical products.

These are issues that will likely bring about important consequences in drug regulation in the near future. While there are a lot of details left to be determined and potential consequences to be evaluated, the trend reflects increased interest and greater willingness to collaborate in the international community. Therefore, the international community should closely assess these proposals, monitor these developments and work closely together for proposals that will help strengthen regulatory capability in developing countries.

For this particular recommendation, however, the basic idea is to make better use of available information on product evaluation decisions generated by DRAs with high level of competency in order to supplement the capability shortcomings in developing countries. In this case, the developing country itself identifies the DRAs to be used as reference. Information from the evaluation by reference DRAs becomes input for product assessment by the developing country's DRA. The authority for making final decision on product approval lies entirely within the developing country's DRA.

- Continuous improvement

  Regulatory requirements are as good as the country's ability to implement them. Drug regulation should be seen from a dynamic perspective from which countries strive for currently possible best practice under resource constraint, and set a realistic yet serious plan to make progress, to strive for better and better performance over time.

- Human resource development

  Traditional HR development focusing on training of DRA officers is still needed for long term expertise development. International and regional organizations can play important roles in this area.

- Reduce enforcement gaps

  In many developing countries, it has often been found that the written laws may not necessarily be the same as actual practice. The DRAs should place stronger emphasis on enforcing regulation.

- Get rid of unnecessary bureaucracy

  Unnecessary bureaucratic rules and standard operating procedures produce inefficiencies that delay product evaluation process without any added value. They should be reviewed and, if found, repealed.

2. Recommendations for improving R&D capability

- Government commitment and investment

  Promotion of R&D in pharmaceutical calls for strong and consistent policies as well as substantial resources. In countries where some capabilities exist, government commitment and investment in

research and development is feasible and is critical to the advance of pharmaceutical sector in the country.

- International collaborations

  Because of constraints in financial and human resources, developing countries should collaborate and support each other in drug R&D, especially in drugs needed for neglected diseases and emerging diseases. This approach applies to developing countries where certain levels of R&D capacity exist. It calls for pooling of resources, expertise and markets from the collaborating parties. The ASEAN collaboration in developing reference substances can be a starting model that expands into more areas of collaboration to share resources for R&D. A possible starting point can be identifying priority areas of R&D and mapping capabilities among the collaborating countries. Needed R&D activities can be divided among the parties according to existing expertise and resources. Results of the efforts are then pooled together. Members of the collaborating group learn from each other, utilize facilities and other resources of each other, and consider the expanded markets in the collaborating countries for potential demands. This approach requires strong commitment, good planning and management.

3. Recommendations for improving knowledge management

A great number of new ideas and new developments have taken place in recent years. Over time they evolve into different policy models. A big challenge to the international community is to be able to learn from these models lessons of success and failure. It is important to identify with what features and under what conditions one model works while another does not.

For example, the international community can begin to evaluate the impacts of harmonization by starting systematic research now. In view of ASEAN, the experience in implementing harmonization of registration requirements should be of great interest to the international community, especially other developing countries, in gaining lessons on application of common standards to market authorization of drugs. To enable the international community to benefit more fully from developments currently being carried out in different places, systematic studies should begin now by developing research framework and evaluation indicators, and collecting data to assess pre-implementation state that will allow comparison of the post-implementation data later.

References

Abdul Razak D. Multi-country Study on Effective Drug Regulation: Malaysia Country Report. Unpublished paper commissioned by the World Health Organization. 1999.

Angell M. The Truth about the Drug Companies. NY: Random House. 2004.

ASEAN Secretariat. ASEAN Annual Report 2002-2003. http://www.aseansec.org/accsq/sqdir.htm. Accessed Dec 2004.

ASEAN Secretariat. ASEAN Statistical Yearbook 2004. http://www.aseansec.org/Statistics%202004/04_Macro.pdf. Accessed Dec 2004.

ASEAN Secretariat. http://www.aseansec.org/64.htm. Accessed Jan 2005.

ASEAN Secretariat. AFTA Reader vol. II: Questions and Answers on the CEPT for AFTA. Jakarta: ASEAN Secretariat. 1995.

Biomed Singapore. http://www.biomed-singapore.com/bms/sg/en_uk/index/about_biomedical_sciences.html Accessed Feb 2005.

Cambodochin DAO. Demand Survey: Pharmaceuticals and Natural Products in Cambodia. Prepared for International Trade Centre UNCTAD/WTO, Geneva and Ministry of Commerce, Kingdom of Cambodia. 2004. http://www.moc.gov.kh/devlopment_study/market_size.html. and http://www.moc.gov.kh/devlopment_study/potential_consumption.html. Accessed Feb 2005.

Centre for Drug Administration, Health Sciences Authority, Singapore. Guidance on Medical Product Registration in Singapore, 2004. http://www.hsa.gov.sg/html/business/cda_medicines_overview.html. Accessed Feb 2005.

Department of Health, Republic of the Philippines. "Regulation of Drugs and Pharmaceutical Specialties." http://www.bfad.gov.ph. Accessed Feb 2005.

DiMasi JA, HansenRW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics 22 (2003) 151–185.

Dukes G. The Effects of Drug Regulation: A Survey based on the European Studies of Drug Regulation. Langcaster, UK: MTP Press. 1985.

Dukes MNG, Haaijer-Ruskamp FM, de Joncheere CP, Rietveld AH (eds). Drugs and Money: Prices, Affordability and Cost Containment. Amsterdam: IOS Press. 2003.

Engel S. "Risky Business," R&D Directions. 1998, 4(3): 3.

Food and Drug Administration, Thailand. Current Status and Practice in Pharmaceutical Regulations and Technical Requirements in Thailand. Unpublished document. 2004.

Food and Drug Administration, Thailand. ACTR and ACTD for Pharmaceutical Registration of ASEAN. 2004.

Gross, A. Overview of Asia, Healthcare Markets and Regulatory Issues in the Region. 2001 Pacific Bridge, Inc. http://www.pacificbridgemedical.com. Accessed Nov 2004.

Hill S, Johnson K. "Emerging Challenges and Opportunities in Drug Registration and Regulation in Developing Countries," London: DFID, 2004.

Janjaroen WS, Sitti-amorn S, Supakankunti S, Ratanawijitrasin S, Pinitpuwadon K, Pongpanich S, Somrongthong S. Preliminary Study of the Impacts of Free Trade and Service Policy on the Thai Society and Health Care System. Bangkok, Thailand: College of Public Health, Chulalongkorn University. 1999.

Kettler HE. Updating the Cost of a New Chemical Entity. London: Office of Health Economics. 1999.
Lim HH. "The Pharmaceutical Industry and the ASEAN Free Trade Area—Current Initiatives on Tariff Reduction and Intellectual Property Protection," Australian Prescriber 1997, 20(suppl 1):217-221.
Lim MK. "Shifting the burden of health care finance: a case study of public-private partnership in Singapore," Health Policy 69 (2004): 83-92.
Limwattananon S, Limwattananon C, Pannarunothai S. Rapid Penetration of Cox2 Inhibitors in the Non-Steroidal Antiinflammatory Drug Market: An Implication for Hospital Cost Containment Policies. Poster presentation at the International Conference on Improving Use of Medicines, 2004.
McCarty A. Vietnam's integration with ASEAN: Survey of non-tariff measures affecting trade. UN Development Project. Hanoi 1999.
Ministry of Health. Statistical Yearbook Vietnam. Hanoi: Ministry of Health. 2003.
National Science and Technology Development Agency, Thailand. http://www.nstda.or.th/ Accessed Feb 2005.
Pharmaceutical Services Division, Malaysian Ministry of Health. "Regulatory Control of Pharmaceuticals and Cosmetics." http://www.pharmacy.gov.my. Accessed Dec 2004.
Philhealth. http://www.philhealth.gov.ph/faq.htm. Accessed Feb 2005.
Quirk, Paul J. "Food and Drug Administration," in Wilson James Q. (ed.) The Politics of Regulation. NY: Basic Books. 1980.
Ratanawijitrasin S and Wondemagegnehu E. *Effective Drug Regulation: A Multi-country Study.* Geneva: World Health Organization. 2002
Ratanawijitrasin S. *Systems of Health Insurance: Experiences from Ten Countries.* Nonthaburi, Thailand: Health System Research Institute. 2001.
Royal Thai Government. Patent Act of BE 2535. 1992.
Royal Thai Government. Trade Secret Act of BE 2545. 2002.
Supakankunti S, Janjaroen WS, Tangphao O, Ratanawijitrasin S, Kraipornsak P, and Pradithvanij P. Study of the Implications of the TRIPs Agreement for the Pharmaceutical Industry in Thailand. Bangkok, Thailand: WHO Collaborating Centre for Health Economics/ Chulalongkorn University, Regional Office for South-East Asia/ World Health Organization. 1999.
Thai Drug System Study Project Committee. Thai Drug System. Nonthaburi, Thailand: International Health Policy Development Office. 2002.
United States Pharmacopeia. A Review of Drug Quality in Asia with Focus on Anti-Infectives. Feb 2004.
Wondemagegnehu E. Counterfeit and substandard drugs in Myanmar and Vietnam. Report of a study carried out in cooperation with the governments of Myanmar and Vietnam. Geneva: World Health Organization. 1999.
World Health Organization. The Impact of Implementation of ICH Guidelines in Non-ICH Countries. Report of a WHO Meeting, Regulatory Support Series #9. Geneva: WHO. 2002.
WHO-Regional Office for the Western Pacific. Essential Drugs and Medicines Policy 8 June 2004: III(1) <http://www.wpro.who.int/pdf/rcm55/R&D/12_HTP_1.pdf> Accessed feb 2005.

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APPENDIX

Key ASEAN Statistics

Table A1: ASEAN Demographic Statistics

Area	4.48 million square kilometers	Approx. 3.3% of the total size of the world (135.64 million square kilometers)
Population	537.11 million	Approx. 8.6% of the world population (6,271.70 million)
Nominal GDP	US$686.3 billion	Approx. 1.9% of the world GDP (US$36,356.2 billion)
GDP per capita	US$1,278	Approx. 22.0% of the world's average GDP per capita (US$5,797)
Trade (Import and Export)	US$758.7 billion	Approx. 5.8% of the world's trade value (US$12,996.4 billion)

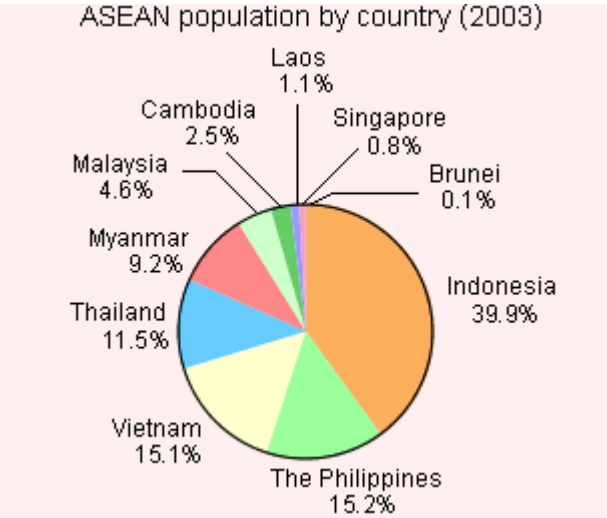
Source: ASEAN-Japan Center. http://www.asean.or.jp/eng/general/base/glance2004.html Accessed Feb 2005
Note: Data of 2003, except for area size (1999)

Table A2: Comparative Demographic Statistics: ASEAN and Other Regional Economic Groups

	Members	Population	Nominal GDP	GDP per Capita	Trade (Import and Export)
ASEAN	10 countries	537.11 million	US$686.3 billion	US$1,278	US$758.7 billion
European Union (EU)	15 countries -1)	379.74 million	US$10,482.7 billion	US$27,605	US$4,752.1 billion
	25 countries (2004.5) -1)+2)	453.90 million	US$10,970.2 billion	US$24,169	US$5,090.3 billion
North American Free Trade Agreement (NAFTA)	3 countries U.S.A., Canada, Mexico	424.97 million	US$12,342.1 billion	US$29,043	US$2,698.9 billion
Mercado Comun del Sur (MERCOSUR)	4 countries Argentina, Brazil, Paraguay, Uruguay	224.0 million	US$639.1 billion	US$2,853	US$150.0 billion

Source: ASEAN-Japan Center. http://www.asean.or.jp/eng/general/base/glance2004.html Accessed Feb 2005
Note: Data of 2003

Figure A1: ASEAN Population by Country



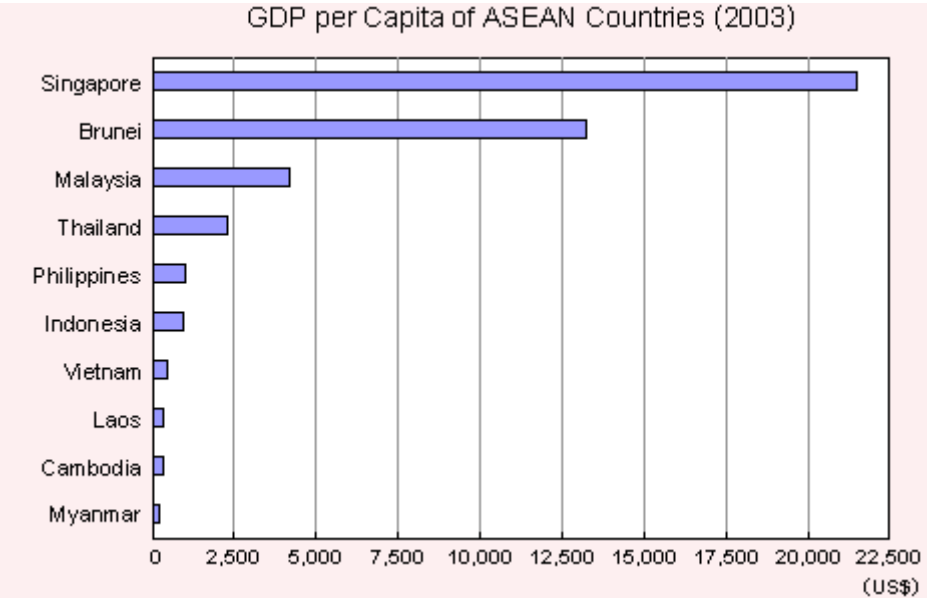
Source: http://www.intracen.org/sstp/Survey/pharma00/Singapore-pharmacafe00-sds.pdf Accessed Feb 2005

Table A3: Gross Domestic Product per capita of ASEAN Member States between 1996-2003 (in US Dollar)

Country	1996	1997	1998	1999	2000	2001	2002	2003
Brunei	17,096	16,227	11,961	12,670	12,751	12,121	12,070	12,971
Cambodia	317	320	265	295	291	283	296	310
Indonesia	1,167	1,128	488	693	731	688	820	973
Lao, PDR	396	360	259	285		328	333	362
Malaysia	4,766	4,672	3,257	3,485	3,881	3,698	3,924	4,198
Myanmar 1/	109	100	144	189	210	162	175	179
Philippines	1,184	1,157	896	1,018	980	924	959	973
Singapore	25,127	25,147	20,892	20,611	22,757	20,553	20,823	20,987
Thailand	3,134	2,656	1,900	2,046	2,029	1,887	2,050	2,291
Viet Nam	337	361	361	374	403	415	439	481
ASEAN*)	1,505	1,429	947	1,079	1,128	1,058	1,153	1,266

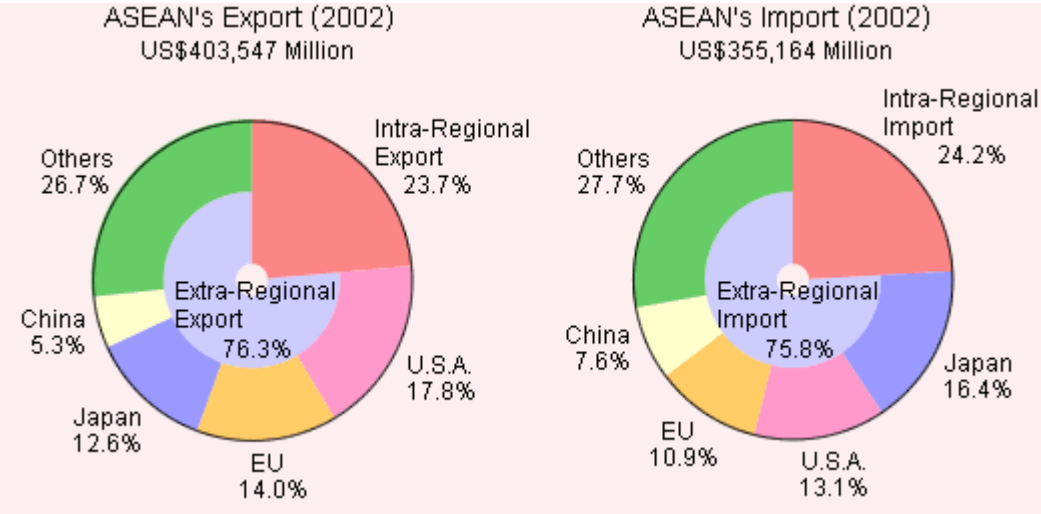
Source: ASEAN Secretariat. http://www.aseansec.org/macroeconomic/aq_gdp22.htm Accessed Feb 2005.
Statistics from ASEAN Finance and Macroeconomic Surveillance Unit (FMSU) Database
1/ Fiscal year beginning in April and ending in March of the following year
*) As a proxy, combined GDP of ASEAN is computed as the sum of the GDP of ASEAN Member Countries, and the GDP per capita as GDP/number of population
Note: Overall drop around 1998 due to economic crisis in the region started in Thailand

Figure A2: Gross Domestic Product per capita of ASEAN Member States in 2003



Source: http://www.intracen.org/sstp/Survey/pharma00/Singapore-pharmacafe00-sds.pdf Accessed Feb 2005

Figure A3: Exports and Imports of ASEAN as a Whole



Source: http://www.intracen.org/sstp/Survey/pharma00/Singapore-pharmacafe00-sds.pdf Accessed Feb 2005