CHAPTER I

INTRODUCTION

1.1 Rationale

A large number of new drugs have been launched into the market continuously. Every year, 40 to 60 new chemical entities (NCEs) are brought into the market worldwide (Avorn, 2001). In the United States during 1987 to 1993, 169 New Molecular Entities (NMEs), or approximately 24 NMEs per year, were registered, while in the EU, 125 NMEs were listed during 1995 to June 1999 (Abraham & Lewis, 2000). In Thailand, new drugs were launched into the market with varied rates ranging from 38 to 51 drugs per year (Patanawong, 2001; Tantivess, Jierapong, Jitraknatee, & et al, 2001; Thai FDA, 2001). With this increasing number of new drugs, the issue of public safety has been raised.

New drug safety evaluation is usually achieved through two mechanisms: pre-marketing approval system and post-marketing surveillance system. In the process of pre-marketing approval system, regulatory agency approves new drugs depending on data of drugs' safety and efficacy gathered from clinical trials. With limitations during pre-marketing process, for example, limited number of subjects enrolled in clinical studies, exclusion of special populations including pregnant women, the elderly and children, and limited study time, post-marketing surveillance is thus highly needed to assure safety of new drugs (Strom, 1994).

In post-marketing safety surveillance system, a variety of new drug safety monitoring mechanisms has been used. These include intensive monitoring programs for specific groups of patients and less intensive monitoring programs suitable for non-specific patient populations. The most popular safety monitoring mechanism is adverse drug reaction Spontaneous Reporting System (SRS) in which adverse events are voluntarily reported to the Thai Food and Drug Administration (Thai FDA) by health care providers. In addition to SRS system, an intensive monitoring system has also been in place in Thailand. This kind of intensive monitoring system is well

known in various countries, for instance, the post-marketing commitment in the United States, the Prescription Event Monitoring (PEM) in Japan and the UK and the Early Post-marketing Phase Vigilance (EPPV) in Japan (Coulter, 2002; Heeley, Riley, Layton, Wilton, & Shakir, 2001; Japan Pharmaceutical Manufacturers Association, 2002; Kubota, 2002; World Health Organization, 2002). With socioeconomic and political differences, Thailand SRS system, namely the Safety Monitoring Programme (SMP) (Thai FDA, 2001), is inevitably different from the programs in those countries.

1.2 The Safety Monitoring Programme (SMP) of Thailand

The Safety Monitoring Programme (SMP) is Thailand's new drug safety monitoring system. It was officially implemented in 1991 with a purpose of profiling new drug safety among Thai people (Patanawong, 2001). Although politically originated by Thai government as a means to negotiate with the United States Trade Representatives (USTR), it has been an important measure of the country's new regulations on pharmaceuticals (Kiatying-Angsulee, 2000; Patanawong, 2001; World Health Organization, 2000). This SMP system monitors various new drugs for human use including products with new chemical entity (NCE), new indication, new combination and new delivery system (Patanawong, 1995; Thai FDA, 1999).

In this SMP system, new drugs are registered with conditional approval. The drug product packages bear the triangular labeling to show this conditional approval status. These products can only be distributed through hospitals or healthcare facilities and used under close supervision of physicians for two years. Reports of adverse drug reactions from the pharmaceutical companies are mandatory during this 2-year period of safety monitoring (Drug Control Division Thai FDA, 2001; Thai FDA, 1999).

At the end of safety monitoring period, pharmaceutical companies can submit the comprehensive summary reports to the Thai FDA. These include report of adverse drug reaction (ADR), drug consumption, and detailed drug experiences from other countries. Drug product with no evidence of serious adverse events or with benefits that outweigh its risks will receive unconditional approval. The product is then allowed to distribute through its normal channels (Drug Control Division Thai FDA,

2001). Generic products, of which the patented original is subject to safety monitoring, could not be registered until unconditional approval of the prototype is granted. In addition, these generic products need to demonstrate their quality and efficacy compared to their counterpart original products. Therefore results of bioequivalence study of these generic products are mandatory (Drug Control Division Thai FDA, 2001).

After more than a decade-long operation of the SMP, some problematic issues have arisen, for examples, inconsistent number of new drugs launched into the market through the SMP, unequal duration under the SMP restriction for different drugs, low proportion of ADR of new drugs under the SMP, insufficient quality of ADR report, insufficient participation of health professionals in ADR reporting process, confidentiality in new drug releasing from the SMP, and market exclusivity of new drugs. However, these issues have not been recognized in an official or systematic manner to adequately describe the genuine situation in the SMP. These issues are elaborated below.

1.2.1 Inconsistent Number of New Drugs Launched into the Market through the SMP

The annual average number of new drugs launched into Thailand market was in a relatively narrow range, from 38 to 51 drugs (Patanawong, 2001; Tantivess et al., 2001; Thai FDA, 2002). In contrast, a more fluctuated number of new drugs through SMP was observed where only 7 new drugs were off the SMP restriction in the first year of SMP implementation (1991), and so many as 159 in 1998 (Thai FDA, 2002). The number of new drugs fluctuated greatly between 1998 and 1999. The reason for a dramatic increase in number of unconditional new drug approval in 1998 was a result of the decision of the Secretary General of FDA (FDA-SG) in accordance with pressure from the industry (Kiatying-Angsulee, 2000). On the contrary to the understanding that SMP could hinder the influx of imported drugs, it encourages more importation of new drugs. However, the fluctuating number of new drugs launched in each year needs a clear explanation.

1.2.2 Unequal Duration under the SMP Restriction for Different Drugs

The SMP period is expected to be 2 years. Nontheless, the average time that new drugs with conditional approval could get through the SMP period and receive unconditional approval are relatively varied ranging from 1 to 6.5 years. This variation is visually evident in Figure 1.1 (Tantivess et al., 2001). In addition, it took almost 7 years for the first new drug issued in 1991 to receive an unconditional approval. The standard period for safety monitoring of new drugs in other countries are considerably different, from 6 months to 3 years depending on types of new drugs and safety monitoring system in individual countries (BNF, 2001; Japan Pharmaceutical Manufacturers Association, 2002; Kubota, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001). This situation leads to a few legitimate questions including "What is the appropriate time of the SMP period in Thailand?" and "Are there any factors affecting the SMP period?" Only with a thorough explanation to these questions a practical SMP period can be established to best serve the purpose of drug accessibility to safe drugs in Thai health care system.

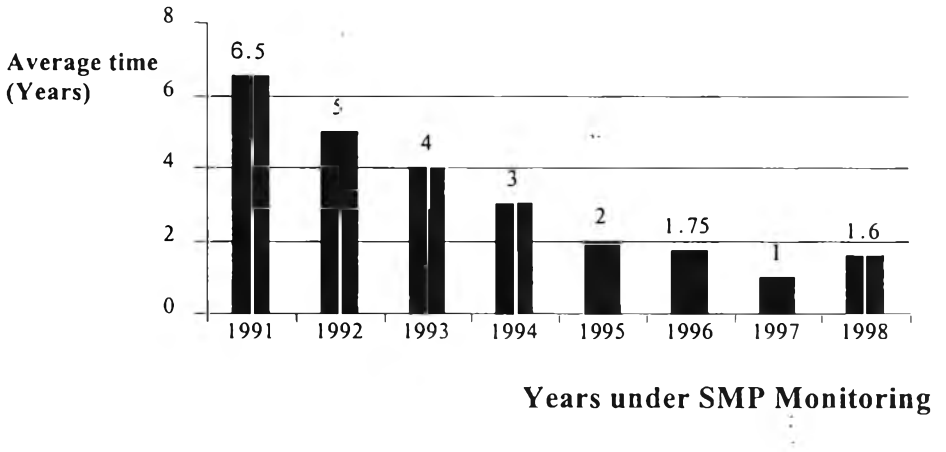

Figure 1.1 Average time of new drugs with conditional approval in the SMP

Source: Tantivess , Tangcharoensatien, & Kaewpanurangsi,(2003)

1.2.3 Low Proportion of ADR Reports of New Drugs under the SMP

After the SMP establishment in 1991, number of ADR reports of new drugs significantly increased. The proportion of ADR reports of new drugs to all ADR reports increased from 3.2% in 1996 to 10.8% in 1998. The ADR reports of new drugs were accounted for a relatively small portion with an average annual number of 695 or 6.65% of the total number of reports. This proportion of ADR reports of new drugs in Thailand was somewhat low compared with a 22.4% reported in the United States during 1989-1993 (Faich, 1996). Despite an increase in number of new drugs under the market, ADR reports of these drugs has not increased proportionally. A low number of new drug ADR reports is definitely signaling problems in the SMP process. It highly needs a thorough exploration so that the whole situation can be clarified and the appropriate strategy in profiling new drug safety can be set.

1.2.4 Insufficient Quality of ADR Report

In addition to number of ADR report of new drugs submitted, quality of the report is also a crucial component of the SMP success. During 1996 to 1999, the quality of ADR reports of new drugs was low where only 8.6 % out of 21,324 ADR reports of new drugs was found complete and accurate (Kaewpaneukrangsee, 2000). The issue of incomplete or inaccurate ADR reports possibly continues to be a crucial factor to determine quality of ADR report and needs a closer attention.

1.2.5 Insufficient Partnering of Health Professionals in ADR Reporting Process

Thailand has established the Spontaneous ADR Reporting System (SRS), the drug safety evaluation program in post-marketing drug surveillance of existing drugs since 1983 (Thai FDA, 2001). Reporting ADR in this system is voluntary. In contrast to existing drugs, ADR reporting of new drugs during the SMP period is mandatory. However, in practice, reporting ADR of new drugs has not been successful. Healthcare professionals treat this reporting similar to that of the voluntary SRS reporting. Therefore, number of reports entirely relies on voluntary cooperation

among health professionals (Tantivess, Tangcharoensatien, & Kaewpanurangsi, 2003).

Other evidences emphasizing weaknesses in ADR reporting process were that as high as 72% of hospitals in Thailand had no ADR committee, and only 57.6% of hospitals had assigned persons responsible for reporting the ADR of which the majority was pharmacists. Furthermore, in the majority of hospitals, there were no regular meetings of the ADR committee (82.9%) and no summary of ADR reports (71.2%). As opposed to pharmacists, physicians and nurses took a relatively negligible part in reporting the ADR (Hutangkabodee, Kongpatanakool, Wimonwatanaphan, & et al, 2000).

A low involvement in reporting ADR among health professionals could be explained by various reasons including a lack of knowledge in ADR reporting system, insufficient financial support to the system, less available time to report ADR due to a high workload, unawareness of the importance of ADR reporting probably because of not being well informed, lack of knowledge among persons responsible for ADR reporting, insufficient motivation to report ADR and no legal enforcement for reporting (Hutangkabodee et al., 2000). To clearly demonstrate such pitfall in the ADR reporting, findings from a study suggested that almost two-thirds of physicians (64.7%) did not know the existence of new drug safety monitoring system. Among physicians who stated that they used to detect ADR, only half (53.7%) recorded the detection in patient profiles and a very small portion of them (14.3%) informed pharmacists or nurses so that the ADRs reports could be filed (Suwankesawong, 1999). These situations suggested that ADR reporting processes is very ineffective especially at the hospital level. The situation calls for an improvement of action at both organization and individual levels.

1.2.6 Confidentiality in New Drug Releasing from the SMP

Criteria for releasing new drugs from the SMP depend on the decisions of the Subcommittee on Approval of New Drug Registration. Criteria for releasing new drugs from the SMP have never been available. The questions of why drugs that entered the SMP at the same time were released from the monitoring at different times

have never been answered clearly to the public. At present, although some studies suggested that there might be political pressures on the SMP, none of the previous studies could identify the criteria for drug release from the SMP (Kiatying-Angsulee, 2000; Supakankunti, Janjaroen, Tangphao, & et al, 2001).

1.2.7 Market Exclusivity of New Drugs.

It seems that the SMP has become a market exclusivity tool for some drugs especially new original drugs. This detrimental effect to the public caused by the SMP process could be explained by very few studies. Tantivess S. et al. (2001) indicated that **market exclusivity** of original products generated by the provisions of new drug registration led to 4-7 years delay in approval of generic products. Very few generic products (11 from 366 products, or 3%) were approved during 1991 to 1999. The prices of original products were not reduced during the first two years of generic entry. All generic prices were lower than that of their prototypes. The favorable effects of **generic entry** on the reduction of hospitals' drug expenditures and more importantly the improved accessibility to drugs have been demonstrated. Cost saving relating to switching to generic versions of new drugs was a crucial measure of cost-containment in most hospitals. Therefore a delay in generic entry by market exclusivity caused by the SMP process could also harm wellness of the public. The issue of drug market exclusivity is highly complicate and needs a large amount of time and resources to investigate. Despite importance and urgency of the problem, the issue of market exclusivity was not a focus in this study.

All these issues in the SMP mentioned above need more understanding. However, most issues especially the ones relating to drug safety profile were scarcely studied. With the aim to understand the problems, this study performed situational analysis on the SMP system and ways the SMP ensures safety of new drugs in Thailand. Due to the dynamic and sophisticated nature of the SMP processes, the study was conducted with a systematic approach using the Total Quality Management (TQM) framework. The structure, process, and outcome model based on the TQM were used to fit and explain the entire SMP system. The main purposes of this study were not only to understand the existing structure, process, and outcome of the SMP, but also to trace back processes affecting safety profile and regulatory measures of

new drug. The understanding will hopefully contribute to improving appropriate solutions for an effective management of the SMP system. The fruitful information from this study will pave the way of performing an effective new drug safety profile for health system of Thailand in the future.

1.3 Research Question

How effective is the SMP in ensuring safety of new drugs in Thailand?

1.4 General Objectives

This study is aimed:

1.4.1 To perform situational analysis of new drug Safety Monitoring Programme (SMP) in Thailand.

1.4.2 To identify safety indicators of the SMP system.

1.5 Specific Objectives

1.5.1 To perform situational analysis of the SMP system using the structure, process, and outcome model.

a) Structure component composed of policy, law, regulation and guideline related to the SMP, organizations and personnel in Thai FDA, drug company and hospital and information system.

b) Process component consisted of evaluation process for new drug application to the SMP, ADR management system and evaluation process for releasing new drugs from the SMP.

c) Outcome component including administrative, safety and regulatory outcomes.

1.5.2 To identify safety indicators of the SMP and assess the SMP system via these indicators.

1.5.3 To elaborate process affecting safety profile and regulatory measures of new drugs.

1.6 Definition of Terms

1.6.1 The Safety Monitoring Programme (SMP) is an early post-marketing period of a new drug with the main objective to identify ADR of newly marketed drugs. Since 1991, all new drugs are primarily registered with conditional approval. Under this conditional approval, drug packages bear a triangular labeling and can be distributed only through hospitals or healthcare facilities and used under close supervision of physicians for two years. Mandatory reports of adverse drug reactions from the pharmaceutical companies are required during the 2-year period of safety monitoring. After the end of safety monitoring period, pharmaceutical companies have to submit comprehensive summary reports including adverse drug reaction (ADR) report of new drugs obtained in Thailand, drug consumption, and information of drug experiences from other countries to the Thai FDA. If benefits outweigh risks, the drug will be granted an unconditional approval and allowed to distribute through its normal channels (Drug Control Division Thai FDA, 2001)

1.6.2 New drugs are new human drugs including products with new chemical entity (NCE), new indication, new combination and new delivery system, which have never been approved in Thailand before the date of registration submission (Patanawong, 1995; Thai FDA, 1999).

1.6.3 Structure component of the SMP is a component in the SMP composed of policy, law, regulation and, guideline, organizations, personnel in the Thai FDA, drug company and hospital. And also included information system related to the SMP system.

1.6.4 Policy was any policies from the Thai FDA or the Ministry of Public Health or pharmaceutical company relating to or affected by the SMP either at the organizational level or individual level.

1.6.5 Law was any laws amended by the Thai FDA or the Ministry of Public Health relating to or affected by the SMP either at the organizational level or the individual level.

1.6.6 Regulation was any regulations relating to or affected by the SMP either at the organizational level or the individual level. These regulations may originate from the Thai FDA or the Ministry of Public Health or pharmaceutical company.

1.6.7 Guideline was any guidelines or manuals relating to the procedures in the SMP for all involving stakeholders, for example, the Thai FDA, pharmaceutical company and health care facilities.

1.6.8 Organizations were parties involving the SMP process which could be classified into 3 groups:

Group 1: Thai FDA represented mainly by two agencies, the New Drug Unit in the Drug Control Division, and the Adverse Product Reaction Monitoring Center (APRMC) under the Technical and Policy Administration Division.

Group 2: Pharmaceutical company, either distributor, manufacturer or importer.

Group 3: Healthcare facilities including hospital, medical institution, clinic, and drugstore.

1.6.9 Personnel was individual who worked on the issues related to the SMP from the involving organizations mentioned as follows:

a) Thai FDA: FDA officers both pharmacist and non-pharmacist who performed the activities related to the SMP regarding the new drug application process, the safety monitoring period and the releasing process from the SMP.

b) Pharmaceutical company: pharmacists or non-pharmacists whose work related to the SMP process in the Department of Regulatory Affairs in the company. These persons dealt with matters relating to drug registration and might work for summarizing safety profile of new drug during the SMP period. In some companies, certain persons from department of Research and Development were assigned to handle all drug safety issues. Individuals from Marketing Department were also involved in the SMP in collecting ADR reports from healthcare facilities.

c) Healthcare facilities: health personnel who worked in hospital, medical institution, clinic and drugstore located in Thailand.

1.6.10 Information system was all information related to the SMP system regarding information in the Thai FDA, drug companies, hospitals or healthcare facilities, academic. It also included information related to new drug from worldwide and dissemination of information of new drug among these organizations.

1.6.11 Process component of the SMP referred to any components in the SMP including evaluation process for new drug application to the SMP, ADR (risk) management system of new drugs and evaluation process for releasing new drugs from the SMP.

1.6.12 Evaluation process for new drug application to the SMP was the procedure in evaluating quality, efficacy and safety of new drugs applied to the SMP. It also included components of expert opinions and criteria for rejecting or accepting from the SMP.

1.6.13 ADR management system was a systematic approach to manage ADR at both national and local levels. It was composed of risk detection, risk assessment, risk minimization, and risk communication.

a) ADR detection was the procedure in detecting ADR or risk of a newly marketed drug in the SMP in an accurate and timely manner.

b) ADR assessment was the procedure in assessing ADR of new drug to verify the seriousness and causality of the ADR.

c) ADR minimization was the procedure in managing or minimizing the ADR to the patient or public.

d) ADR communication was the procedure in disseminating the information related to the ADR to health professional and /or to public.

1.6.14 Evaluation process for releasing new drugs from the SMP was the procedure in evaluating safety of new drugs applied for releasing from the SMP. It also included components of expert opinions and criteria for rejecting or accepting.

1.6.15 Outcome component of the SMP was a component in the SMP composed of administrative, safety and regulatory outcomes.

1.6.16 Administrative outcomes were indirect measures to assess the performance of the administrative output of the SMP including number and type of new drugs entered or released from the SMP, and average time of new drug under the SMP monitoring period.

1.6.17 Safety outcomes were indirect measures to assess the performance of the safety outcomes in the SMP including ADR incidence of new drug, number and quality of ADR reports of new drugs, type and seriousness of ADR of new drug and time to detect the first ADR of new drug.

1.6.18 Regulatory outcomes were indirect measures to assess the performance of regulatory outcome in the SMP including type of regulatory measures or activities relating to safety issues of new drugs. There were several regulatory activities from Thai FDA such as drug withdrawal, suspension, restriction, information or labeling changes, and informing and warning for the risks to health professional or to public.

1.6.19 Adverse Drug Reaction (ADR) is any reactions of a drug which noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. This would not include intentional or accidental poisoning, or drug abuse. This definition excludes accidental or deliberate excessive dosage or mal-administration (World Health Organization, 2002).

1.6.20 Safety indicator of the SMP was a tool identified in this study for assessing the safety in the SMP system. The indicators might be the issues in any steps of the structure or process or outcome in the SMP system.