CHAPTER II

LITERATURE REVIEW

This chapter provides concepts, theories and research findings relating to the new drug safety monitoring system to better understand the situations and guide the issues in the study of the Safety Monitoring Programme (SMP) in Thailand. In addition, to comprehend the effect of country context, comparisons between existing new drugs safety monitoring system in other countries are also detailed. The contents in this chapter are organized as follows:

1. Concepts of new drug regulations and post-marketing surveillance; providing the rationale for safety monitoring of new drugs, and mechanisms of new drug safety monitoring system.

2. New drug safety monitoring system in four countries i.e. the United States, the New Zealand, Japan and Australia and comparisons of post-marketing system of Japan, the New Zealand and Australia.

3. The Safety Monitoring Programme (SMP); providing the emergence, the objectives and current system of the SMP, procedures in the SMP.

4. Related research in new drug Safety Monitoring Programme (SMP).

5. Indicators for assessing new drug safety system.

6. Model for exploring the SMP: Total Quality Management (TQM); structure, process and outcome.

7. Conceptual framework for the analysis of the SMP.

Details of each topic were presented as follows:

2.1 Concepts of New Drug Regulations and Post-marketing Surveillance

A large number of new drugs have been launched into the market continuously. Every year between 40 and 60 new chemical entities are brought into the market world wide and annual pharmaceutical sale is approximately 250 billion US$ in the world market (Avorn, 2001). In the United States during 1987 to 1993 there were 169 New Molecular Entities (NMEs) registered, approximately 24 NMEs

per year, while in the EU during 1995 to June 1999, 125 NMEs were registered (Abraham & Lewis, 2000). With this increasing number of new drugs, the issue of public safety has been raised.

2.1.1 Rationale for Safety Monitoring of New Drugs

New drugs regulations are not only the system for registering new drug items but also for ensuring that new drugs offer benefits that outweigh risks. Before new drugs are licensed for clinical use, their efficacy and safety are rigorously assessed by regulatory agency in most countries. Although drug development process covers the time period nearly 12 years from the laboratory to the market, evaluation for safety and efficacy is still confined (Kongpatanakul & Strom, 2001; World Health Organization, 2002b). Drug development process starts with the investigational new drug (IND) application prior to human testing. This step includes chemical and laboratory analysis, non-clinical pharmacology, and animal toxicology (Kongpatanakul & Strom, 2001).

Then, phase I trial is conducted on a small number of healthy human subjects, usually not more than 30. The information received from this step is metabolism of the drug in human, a safe dosage range in human and common toxic effects not detected in the prior animal studies (Kongpatanakul & Strom, 2001).

Phase II clinical trial is conducted in patients with target disease, normally with less than 200 subjects. The purpose of phase II study is to obtain more information on pharmacokinetics profile, additional toxic effects, preliminary efficacy and dosage regimen of the drug that will be tested in more details in phase III study (Kongpatanakul & Strom, 2001).

Phase III study is conducted on a greater number of patients, ranging from several hundreds to several thousands. This step assures drug efficacy in a larger patient population (Kongpatanakul & Strom, 2001).

Once approved for drug efficacy in phase III, a new drug is placed under the evaluation and review by the regulatory agency. If the benefits outweigh the risks, a new drug can be marketed. The newly marketed drug is subject to safety monitoring

study. This step is usually called phase IV study. The study aims at gathering information previously uncovered due to limitations in pre-marketing phase of drug development (Kongpatanakul & Strom, 2001).The reasons for conducting post-marketing safety monitoring, as stated by the WHO (World Health Organization, 2002b) are as follows;

- *Information in animal to predict human safety is insufficient.*
- *The conditions in drug development do not adequately represent the actual use of drugs, including selective patients in clinical studies, and limited time and number of human subjects.*
- *By the time of licensing, only common adverse drug reactions due to exposure of less than 5,000 human subjects were reported.*
- *ADRs with an incidence of 1 in 10,000 exposed individuals could be potentially missed since at least 30,000 people are needed in the treatment to be able to detect such rare events.*
- *There is a lack or unavailability of information regarding rare and serious ADRs, chronic toxicity, drug interaction, and use in special groups of population, such as children, the elderly, and pregnant women.*

With all these shortcomings of pre-marketing drug study, post-marketing safety monitoring surveillance is highly crucial for detection of less common, but potentially serious ADRs of a new drug.

2.1.2 Existing Mechanisms of New Drug Safety Monitoring System

Normally, new drug regulation is achieved through a pre-marketing approval system and post-marketing surveillance. For pre-marketing approval system, new drugs cannot be marketed without approval by regulatory agency or delegated authority. When data of new drugs' quality, safety and efficacy are satisfactorily established, approvals can be granted. Then post-marketing surveillance monitors the safety of drugs in real practice. If found unsafe, regulatory agency will use measures of risk management on these drugs, for instance, license withdrawal, labeling change, and limitation of distribution (Leape, 2002).

Existing systems of new drug evaluation vary greatly from country to country due to different country contexts. Various mechanisms are established in pre- and post-marketing phases of new drugs. These mechanisms reflect the regulatory agency's ability to regulate the entire process of pharmaceutical product assessment (Rattawijitrasin & Wondemagegnehu, 2002).

a) Mechanisms in Pre-marketing Phase

Major mechanisms of new drug approval are legal enforcement by controlling new drug entry's number, quantity, quality and distribution channel (Rattanawijitrasin & Wondemagegnehu, 2002). These mechanisms are also known as marketing authorization and product licensing and are carried out by drug regulatory agencies or authorities.

During 1960s to 1970s, there was rapid development in laws, regulations and guidelines for reporting and evaluating the data on safety, quality, and efficacy of new drugs (Santosa, 2001). Despite these regulatory developments, controversies regarding new drug regulations still occur in various countries due to imbalanced information between public and private sectors (Rattanawijitrasin & Wondemagegnehu, 2002). Some developing countries approve a new drug based solely on data from foreign studies with less concern about the quality of the studies (Santosa, 2001).

Technical and administrative data of a new drug are evaluated before drug regulatory agency can decide whether to approve or reject the drug. The indicators of new drug assessment in pre-marketing approval vary depending upon drug category and country context. Some indicators are often used to demonstrate effectiveness of new drug regulation process. These indicators may include number of approved NCEs, approval time, number of rejected NCEs, number of industrial appeals, and number of reintroduced NCEs (Abraham, 2002; Center for Drug Evaluation and Research, 2001; Charatan, 2002; Moynihan, 2002; Rawson, 2000). The effective mechanism of new drug assessment and registration requires a legal foundation, an adequate number of qualified staff, a sustainable resource, and an effective data retrieval system. All these elements of the assessment and registration are to ensure

freedom from conflicts of interest, accountability and transparency (Rattanawijitrasin & Wondemagegnehu, 2002).

b) Mechanisms in Post-marketing Phase

Post-marketing monitoring surveillance, also known as phase IV study or pharmacovigilance, may be conducted once a new drug is approved. There are four major goals of post-marketing monitoring surveillance; a) to recognize new adverse drug reactions as early as possible, b) to refine and add information on suspected or known reactions. c) to review the merit of the drugs against other therapies, and d) to communicate with practitioners regarding risks and benefits of new drugs (Edwards 2001). The process of evaluating drug safety is needed in the post-marketing phase. However, the WHO stated that in many countries the safety monitoring surveillance is not sufficiently intensive to new drugs or to significant therapeutic advances (World Health Organization, 2002a). It is asserted that with a stronger national system of pharmacovigilance and ADR reporting, the process of new drug approval can be accelerated (World Health Organization, 2002a).

The utility of reporting adverse effects of new drugs is important to public health. Avoidable adverse reactions are considered non-systematic problems, such as wrong doses or dosages, wrong drugs, poor patient compliance, for instances. These avoidable adverse effects can be used as a notification to manufacturers to write a warning letter to all doctors to draw attention regarding potential hazards (Santosa, 2001).

Safety monitoring system also plays an important role in introducing generic products, and in reviewing safety profile of established products, where new safety issues may have arisen. Main information on safety of drugs in actual use is obtained by means of doctor's reports of clinical concerns, published case reports from health professionals, post-marketing clinical studies, controlled retrospective or prospective studies, and case series (Edwards, 2001).

There are 2 major mechanisms in post-marketing surveillance (PMS) for reporting safety of a drug: voluntary and mandatory mechanisms. The differences between these 2 mechanisms are presented below.

c) Voluntary vs. Mandatory Safety Mechanisms in PMS

Voluntary and mandatory mechanisms are used in post-marketing surveillance. Voluntary mechanism is often preferred as 54 countries have voluntary ADR spontaneous reporting system (Edwards, 2001). Advantages of ADR voluntary reporting include its low cost, simple operation, applicability to the whole life cycle of all drugs and whole population, reflection on true prescribing habits, and usefulness in studying long-term severe ADRs. Limitations of spontaneous reporting system are obvious. These include under reporting, limited amount of clinical information, and no direct information on ADR incidence due to the fact that prescribing pattern does not correspond with reporting rate (Baum, Kweder, & Anello, 1994; World Health Organization, 2002b).

Mandatory mechanism might be required by the regulatory agency as a condition for approval, as seen, for example, in the United States (the post-marketing commitment), Japan (the Prescription Event Monitoring; PEM and the Early Post-marketing Phase Vigilance; EPPV), the UK (the Prescription Event Monitoring; PEM), The New Zealand (Intensive Medicine Monitoring Programme; IMMP) and also in Thailand (the Safety Monitoring Programme: SMP) (Coulter, 2002; Heeley, Riley, Layton, Wilton, & Shakir, 2001; Japan Pharmaceutical Manufacturers Association (JPMA), 2003; Kubota, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001; Thai FDA, 2001; World Health Organization, 2002a). This mandatory mechanism is an intensive activity particularly to new drugs and drug that need special monitoring to ensure safety. Although mandatory reporting can facilitate achieving true ADR incidence, its pitfalls are inevitable including its high cost, cumbersomeness, and time-consuming operation (Leape, 2002).

2.2 Situation of New Drug Safety Monitoring System: Cross- country Comparison

Safety monitoring systems of new drug are established in various countries. Among these countries, there are several differences such as selecting methods of new drugs to be in the intensive monitoring system, government requirement imposed to

pharmaceutical companies to report ADR, and safety monitoring periods. The followings are the examples of the intensive monitoring system in some countries.

2.2.1 A Post-marketing Commitment: the U.S' System

One example of mandatory intensive mechanism is that of the United States (US FDA, 2001). In the US, all drug companies are required to conduct **a post-marketing commitment** before or after FDA has granted approval of new drugs. The commitment may be conducted as a study or studies, or otherwise gathering additional information about a new drug safety, efficacy, or use, or further evaluating chemistry or manufacturing issues. There are two types of Post-marketing Commitments in general; Required and Agreed Upon Post-marketing Commitments.

a) Required Post-marketing Commitment is needed for drugs that require clinical benefit studies to verify clinical benefit after approval or those that require pediatric studies to assess safety and efficacy in all relevant pediatric sub-populations.

b) Agreed upon Post-marketing Commitment is mandatory for drugs that FDA and company agree that it is necessary to address specific aspects of drug safety or efficacy.

Biologics and drugs will be evaluated by Center for Biological Evaluation and Research (CBER) whether they should be included in post-marketing commitment. CBER will request the conduct of post-marketing investigations only when the study or additional information deems necessary to clarify, verify, or otherwise substantiate the identity, purity, potency, safety or efficacy of the product. The company should report annually within 60 day of the anniversary date of the drug approval. Final report should be submitted to CBER at the end of the study.

2.2.2 Intensive Medicine Monitoring Programme (IMMP): The New Zealand's System

Safety monitoring in the New Zealand is called the Intensive Medicine Monitoring Programme (IMMP) (Coulter, 1998, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001). The prospective observational cohort study

on selected new drugs in the early marketing period is performed to identify signals of unknown ADRs and to establish safety profiles for each drug. Medicines Assessment Advisory Committee (MAAC) usually recommends inclusion of novel agents into the programme. Physicians are requested to report to Centre for Adverse Reactions Monitoring all suspected adverse events occurring in patients receiving IMMP medicines. Pharmacists are requested to submit all dispensing records of these medicines (New Zealand Medicines and Medical Devices Safety Authority, 2001). Reporting rates in the IMMP has been 10 to 20 folds higher than that in spontaneous reports of the same drugs (Coulter, 2002). All advertising and promotional materials and the data sheet of the IMMP drugs need to be identified by the drug companies. Six-monthly sales figures should be supplied to the Medical Director of the IMMP. The monitoring period is 2 years and annually thereafter (New Zealand Medicines and Medical Devices Safety Authority, 2001).

2.2.3 Prescription-Event Monitoring (PEM) and Early Post-marketing Phase Vigilance (EPPV): Japan's System

In general, there are three systems in Japan's post-marketing surveillance (Japan Pharmaceutical Manufacturers Association, 2002) namely the ADR reporting, the re-examination and the re-evaluation systems. In addition, the intensive monitoring system consists of the Prescription-Event Monitoring (PEM) and the Early Post-marketing Phase Vigilance (EPPV) which is for new drugs. The EPPV was lately established in responding to the Good Post-marketing Surveillance Practice (GPMSP). The GPMSP is applied as standards requiring compliance by manufacturers or importers when performing post-marketing surveillance or studies, and as compliance criteria for data preparation. The systems of reporting adverse reactions and infections, and periodic safety reporting also became law.

By law, pharmaceutical company has to provide resources for the establishment and administration of a department called the Post-marketing Surveillance Management Department in the company. The responsibility of this department is to conduct post-marketing surveillance independently from all other divisions responsible for drug marketing.

PEM system: Patients are firstly identified by prescriptions in individual pharmacies where drugs are dispensed. Two questionnaires asking to report ADRs are sent for each patient, one to the physician and another to the pharmacist (Kubota, 2002). All ADRs reports are sent to the Ministry of Health, Labour, and Welfare (MHLW) and then are analyzed (Japan Pharmaceutical Manufacturers Association, 2002).

Early Post -marketing Phase Vigilance is defined as vigilance for the first 6 months after marketing of new drugs which is the duration that medical representatives promote highly cautious use by various ways including periodic visits to physicians. It is performed to gain a rapid and comprehensive understanding of information on serious adverse reactions and infections (Usuki, 2003).

In addition to PEM and Early Post-marketing Phase Vigilance, there are also other intensive monitoring mechanisms in Japan namely the use-results surveillance, the special surveillance, and the post-marketing clinical studies.

(a) Use-results surveillance is the survey conducted to assess the incidence of adverse drug reactions and other information on proper use specifically to use of the concerned drugs in daily clinical settings,

(b) Special surveillance is the survey conducted to detect and confirm proper use information regarding drugs with concerns in special groups of patients such as pediatric patients, elderly patients, pregnant women, patients with renal and/or hepatic disorders, and patients using the drugs for a long period of time.

(c) Post-marketing clinical studies are clinical studies conducted to verify information or obtain additionally required information regarding proper use of drugs unobtainable by routine medical practice or information pertaining to quality, efficacy, and safety of the drug with concerns based on an evaluation and analysis of data from clinical studies or other studies conducted after an approval.

2.2.4 Multi-method: Australia's system

There are many post-marketing activities performed in Australia for to monitor safety of health product (TGA, 2004). The Therapeutic Goods Administration

(TGA) shares this responsibility with sponsors, manufacturers, healthcare professionals and patients. These various activities are;

- monitoring adverse events reporting;
- review of safety related information;
- randomly and targeted product monitoring of the Electronic Listing facility for listed medicines;
- desk-top reviews of randomly selected products (listed products);
- full safety and efficacy reviews of products and substances;
- monitoring of medicines problem reports;
- sample testing by the Therapeutic Goods Administration Laboratories (TGAL);
- GMP auditing of manufacturers ;
- recalls and;
- surveillance.

Main objective of these activities is to identify risk of health product in a timely manner to carry out a proper action to society.

The "surveillance" activity employed in Australia is called the Company-Sponsored Post-marketing Surveillance (PMS) Studies (ADRAC, 2003). The surveillance activity includes cohort observation study mostly. However other study types such as case-control, intensified monitoring and various forms of record release can also be performed. The purpose of this surveillance is to gather safety and toxicity data of marketed drug in approved indications. A scientific approach is required to gain information of drug safety. With initiative by a drug company or other suggested or requested parties, this activity will generate true drug safety signals. A study protocol should be notified to the Adverse Drug Reactions Advisory Committee (ADRAC) with the following;

a) the aims and objectives;
b) the question of clinical significance to be investigated;
c) the proposed methodology for conduct of the study, including data collection and analysis procedures;
d) the designated officer in the company responsible for the study.

Furthermore, a report on the outcome of the study will be undertaken and disseminated to physicians and ADRAC by the company. In doing this, the company is not allowed to disguise marketing or promotional approaches. Medical professionals can be paid by the company but the payment must be appropriate and proportionate to the works involved.

2.2.5 Comparison of Post-marketing Systems: Japan, the New Zealand and Australia

Since current activities in the SMP in Thailand focus on monitoring the safety of new drug, this comparison is performed to better understand the actual system of post-marketing safety monitoring in other countries. The comparisons of structure, process and outcome components of each system in Japan, the New Zealand and Australia were detailed (Japan Pharmaceutical Manufacturers Association, 2002; Japan Pharmaceutical Manufacturers Association (JPMA), 2003; New Zealand Medicines and Medical Devices Safety Authority, 2001; TGA, 2003). Table 2.1 and 2.2 present the summarized information among the three countries; Table 2.1: structure component, Table 2.2: process and outcome component.

2.2.5.1 Structure Component

a) Similarities

The post-marketing surveillance system (PMS) of Japan, the New Zealand and Australia are structured in a similar way. The similarities are that they all have 1) responsible body for the PMS, 2) evaluative body for ADR, and 3) guideline for performing the PMS.

- **Responsible bodies** are named Pharmaceutical and Food Safety Bureau (PFSB) in Japan, Medsafe in the New Zealand and Therapeutic Goods Administration (TGA) in Australia.
- **Evaluative body for ADR data** in Japan is Pharmaceutical and Medical Devices Evaluation (PMDEC), in the New Zealand the Pharmaceutical Management

Agency Ltd.(PHARMAC), and in Australia the Adverse Drug Reactions Unit (ADRU).

- **The guidelines for performing the PMS** are established among these countries namely Good Post-marketing Surveillance (GPMSP) for Japan's, New Zealand Regulatory Guidelines for Medicines 5^{-th} Edition 2001 for the New Zealand, and a few guidelines for Australia including 1) Joint ADRAC-Medicines Australia Guidelines for the Design and Conduct of Company-Sponsored Post-Marketing Surveillance (PMS) Studies, 2) Australian Guideline for Pharmacovigilance Responsibilities of sponsors of registered medicines.

b) Differences

There are some deviances in PMS among these countries in various aspects including components of evaluation team, activities in PMS, aspects of products to monitor, and organization in drug company assigned by law.

In terms of **components of evaluation team**, in Japan and the New Zealand evaluation team consists of internal and external experts while Australia is employing only external experts. Adverse Drug Advisory Committee (ADRAC) in Australia is composed of independent medical experts for evaluation of medicine safety. These medical experts are practitioners from 8 medical practices including nephrology, hepatology, clinical pharmacology, pharmacoepidemiology, complementary medicine, pediatrics, neurology, and general practice.

Regarding **activities in PMS**, it can be concluded that there are 2 types of PMS activity, 1) active or intensive activity and 2) passive activity. The active activities exist in Japan as "Early Post-Marketing Phase Vigilance (EEPV)" with 6-month monitoring of newly marketed drugs, and also in the New Zealand as Intensive Medicine Monitoring Programme (IMMP) for monitoring previously assigned new drugs (by MAAC). In addition, there is the Prescription Event Monitoring (PEM), another intensive activity in Japan. This activity monitors ADRs of prescription drugs through the computer system.

For passive activity, the Spontaneous Reporting System (SRS) is performed in the New Zealand and Australia.

In terms of **aspects of products to be monitored,** the New Zealand's PMS is rather different from the others since it focuses not only on safety of the product but also quality of the product, manufacturer and pharmacies. While other monitoring systems (in Japan and Australia) focus somewhat solely on medicinal products. In Japan, particular infections while taking the drug are also monitored in this system. Another interesting issue is categorizing new drugs into various types. This can be learned from the New Zealand's categorizing new drugs into three groups depending on types of new drugs which are (a) new higher-risk medicines, (b) new intermediate-risk medicines, and (c) new lower-risk medicines. The benefits of categorizing new drugs are found in many countries from the phases of submissions of application to the post-marketing surveillance (New Zealand Medicines and Medical Devices Safety Authority, 2001).

The difference in the aspect of **organization in the drug company assigned by law** is obvious. In Japan, government concerns have led to the establishment of Department of Post-marketing Surveillance Management in all pharmaceutical companies in the country (Japan Pharmaceutical Manufacturers Association, 2002). This department is assigned by the Pharmaceutical Affairs law to manage post-marketing surveillance independently from all other divisions responsible for drug marketing of the company. This establishment aimed to enhance drug safety monitoring from the beginning step to the launch of drugs into the real world clinical use. While strongly founded in Japan, the formal enforcement of this system is not done in Australia or the New Zealand.

Table 2.1 Comparisons of structure components in post-marketing drug surveillance in Japan, the New Zealand, and Australia (Japan Pharmaceutical Manufacturers Association, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001; TGA, 2003)

Structure	Japan	New Zealand	Australia
Type of drug	New drug and established drug	New drug and established drug	New drug/ vaccine/ OTC/ complimentary drug
Responsible agency in the Ministry of Health	PFSB (Pharmaceutical and Food Safety Bureau)	Medsafe	TGA (Therapeutic Goods Administration)
Responsible agency outside the Ministry of Health	Drug company by Post-marketing Surveillance Management Dept.	Drug company	Drug company
Existing guideline	GPMSP (Good Post-marketing Surveillance)	New Zealand Regulatory Guidelines for Medicines 5-th Edition 2001	1. Joint ADRAC-Medicines Australia Guidelines for the Design and Conduct of Company-Sponsored Post-Marketing Surveillance (PMS) Studies 2. Australian Guideline for Pharmacovigilance Responsibilities of sponsors of registered Medicines Regulated by Drug Safety and Evaluation Branch
Administrative agency for PMS	PAFSC	CARM	ADRU a business unit under TGA
Evaluative body for ADR	PMDEC	MARC	ADEC
Teams of evaluation for ADR	NIHS, NIID, OPSR (KIKO)	Internal staff, external expert, MAAC, MARC	ADRAC (8 medical experts in ADRAC)

Table 2.1 Comparisons of structure components in post-marketing drug surveillance in Japan, the New Zealand, and Australia. (Continued)

Structure	Japan	New Zealand	Australia
Activities in PMS	1. Early Post – marketing Phase Vigilance 2. Use-results surveillance 3. Special Surveillance 4. Post- Marketing Clinical studies	1. SRS 2.IMMP 3.Routine Monitoring; drug quality standard 4.Auditing and licensing manufacturer, pharmacies 5. Company reporting overseas safety issues	1. SRS (Blue card) 2. Observational studies; cohort. Case-Control; intensified monitoring conducted by pharmaceutical company (payment may offered to medical professional)

2.2.5.2 Process Component

Comparisons of process components in post-marketing system in various countries followed the 4 processes in ADR management procedure. These include ADR detection, ADR assessment, ADR minimization, and ADR communication.

a) Similarities

These three countries perform all 4 major steps of ADR management Procedure. However some deviances exist which are detailed in the following subtopic (2.5.2.2 Difference). SRS is the most popular technique for the existing drugs. Monitoring adverse events of all new drugs are in intensive manner.

b) Differences

In terms of **ADR detection**, among these three countries, most ADR reporters are physicians, drug companies and pharmacists. However, in Australia, consumers can report the ADR. Furthermore, in the New Zealand, media can perform this reporting activity directly to Medsafe.

Australia is the only one of the three countries mentioning payment from company to medical professional for the work involved in PMS study (surveillance). In addition, there are some processes in Australian system that imply a good system, such as an attempt to protect health care professionals from reporting ADR or no provision on medical advice (Table 2.2: topic what action cannot be action). The Australian system also makes various sources of ADR reports available in all the time, such as ADR report form in electronic file, hard copy of report form at ADR unit, ADR report form inserted in the Schedule of Pharmaceutical Benefits, and ADR report from designed by the company or hospital.

Regarding **ADR assessment**, all ADR reports are usually submitted to the ADR Unit before the assessment of the ADR of suspected drugs can be performed. While detail of assessment procedure of the system of Japan and the New Zealand are not available, some information showing a comprehensive step in assessing the ADR can be found in Australian system (Table 2.2).

In terms of **ADR minimization**, a variety of activity in minimizing the ADR is demonstrated ranging from no action to the activity with the most intensity, such as drug withdrawal (details in topic of 2.5.3 Outcome Component).

2.2.5.3 Outcome Component

a) Similarities

After assessing the ADRs, most activities involve the regulatory action. The existing regulatory measures for drug safety issues among these three countries are (a) drug withdrawal either mandatory or voluntary, (b) suspension and requirement for post-marketing study from the company, (c) restriction on use in specific patient groups or institutions, (d) close intensive monitoring, (e) information changes in labeling or leaflet, and (f) informing or warning about risks to health professionals (details in Table 2.2).

b) Differences

The available information suggests some differences in Australia's system. The performance standards with respect to the processing of reports of suspected adverse reaction is set for a period of health professional staff review will take 3 working days and entering data into the database will take 2 working weeks of receipt.

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Japan Pharmaceutical Manufacturers Association, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001; TGA, 2003)

Process/outcome	Japan	New Zealand	Australia
Which product to report?	All products	All products including blood products and new drugs in IMMP recommended by MAAC	Report of suspected adverse reaction to 1. prescription medicines/vaccines 2. OTC 3. Complementary medicines
What to report?	1. All adverse events and infections to drugs newly launched within 6 ms. 2. Serious adverse events to established drugs	1. All suspected reactions to new drugs recommended by MAAC (IMMP listed in New Ethical catalogue) be monitored for 2 yrs. 2. All suspected reactions to new drugs. 3. All suspected drug reactions. 4. Serious reactions which are suspected of significantly affecting a patient's management, including reactions suspected of causing: 4.1 death, 4.2 danger to life, 4.3 admission to hospital, 4.4 prolongation of hospitalization	1. All suspected reactions to new medicines 2. All suspected reactions to Drugs of Current Interested Listed in the Australian Adverse Drug Reaction Bulletin. 3. All suspected drug reactions. 4. Unexpected reactions, i.e. not consistent with product information or labeling 5. Serious reactions which are suspected of significantly affecting a patient's management, including reactions suspected of causing: 5.1 death, 5.2 danger to life, 5.3 admission to hospital,

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Continued)

Process/outcome	Japan	New Zealand	Australia
What to report? (continued)		4.5 absence from productive activity, 4.6 Birth defects 4.7 all adverse events listed in Prescriber Update as Adverse Reaction of Current Concern 5. Local or overseas media report for medicine safety issues.	5.4 prolongation of hospitalization 5.5 absence from productive activity, 5.6 increased investigational or treatment costs 5.7 Birth defects
Who report the ADRs	Physicians, companies, pharmacists, dentists. Companies are mandated to report ADRs within 15 days for serious unexpected and unknown ADRs/infections, and 30 days for serious known/moderate unknown/ CA/disability or new indication/new occurrence.	Physicians, companies, pharmacists, media	Anyone can voluntarily report; Physicians, companies, community pharmacists and consumers.
Where to get report from?	1. Electronic format or 2. At Adverse Drug Reaction Unit.	1. Electronic format, 2. Postage paid cards in the New Ethicals catalogue. 3. For Blood products from electronic format and at local blood center.	Blue Card prepaid reporting form, available in 1. electronic format or 2. at Adverse Drug Reaction Unit or 3. at the front of the schedule of Pharmaceutical Benefits providing to physician, dentist and pharmacist 4 times/year 4. company/ hospital

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Continued)

Process/outcome	Japan	New Zealand	Australia
What happens to reports?	1. All reports are assessed by PPAS of PAFSC. 2. If necessary, further evaluated by CSD.	All reports are assessed by CARM but media report to MEDSAFE	1. assessed by a health professional and entered into the Australian Adverse Drug Reactions System (ADRS) 2. All reports of serious reactions, reports for vaccines (serious and non-serious), and reports for complementary medicines (serious and non-serious) are forwarded to the (ADRAC) for the further assessment 3. at ADRAC reports are 3.1 triaged by a professional staff or a medical officer. If ADR is serious or ADR is from new drugs, reports are reviewed by ADRAC at 1 of 8 annual meetings. 3.2 coded 3.3 causality assessed according to a standard protocol.

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Continued)

Process/outcome	Japan	New Zealand	Australia
Decision of evaluator		CARM/MARC report for a decision to MEDSAFE	ADRAC's decision for a report; - No further action - Request for additional information from the reporter - Analysis of the ADRS database reports to investigate potential safety signals and then case control be studied to prove association - Request for information from the drug sponsor of manufacturer - publication in the Australian Adverse Drug Reactions Bulletin or medical journals to raise awareness of the reaction - referral to other areas of the TGA for the further investigation - discussion of the reaction with international medicines regulatory agencies - recommendation to amend the medicine's product information

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Continued)

Process/outcome	Japan	New Zealand	Australia
Decision of evaluator (continued)			- recommendation to restrict the availability of the medicine
What actions can be taken?	Possible regulatory actions vary from continuing observation to canceling the registration of the drug. Other possibilities include: • orders for emergency safety information circulation to inform health care professionals and consumers about the risks. • re-vocation approval or re-assessment of the benefit-risk profile of a medicine. • revision of product labeling changes(including the addition of contraindications, warnings, precautions and adverse reaction information). • changes in the designation or regulatory classification to poisons, narcotics, prescription drugs. • suspension of the manufacturing/marketing / or product recall. • requesting post-marketing studies and review from company.	1. re-vocation of consent. 2. advice company to withdraw. 3. ask for more information from company.	Possible regulatory actions vary from continuing observation to canceling the registration of the drug. Other possibilities include: • Informing health care professionals and consumers about the risks • Re-assessment of the benefit –risk profile of a medicine • Requiring product labeling change (including the addition of the contra-indications, warning, precautions and adverse reaction information to the Product Information and Consumer Medicine Information) • Requesting post marketing studies

Table 2.2 Comparisons of process/outcome components in post marketing surveillance in Japan, the New Zealand, and Australia (Continued)

Process/outcome	Japan	New Zealand	Australia
What actions cannot be taken?	n/a	n/a	1. Legal action against health care professionals, 2. Provision of medical advice
Performance standards	n/a	n/a	Performance standards with respect to the processing of reports of suspected adverse reaction: • All reports are reviewed by professional staff within 3 working days of receipt. • All reports are entered into the database within 2 working weeks of receipt.

2.3 The Safety Monitoring Programme (SMP) in Thailand

2.3.1 The Emergence of the Safety Monitoring Programme (SMP)

Since 1979, Thailand as a member of the World Trade Organization (WTO), has had a patent law that protects only process patent for pharmaceuticals. In 1986, the United States Trade Representative negotiated with the Thai government to include the protection of rights for both pharmaceutical process and products. In 1992, the United States pressure led to the amendment of the Thai patent law. The amended version finally included pharmaceutical product patents, increased patent protection term from 15 to 20 years and provided protection for pipeline products which are the existing products patented in other countries during January 1, 1986 to September 30, 1991 (World Health Organization, 2000).

Under political pressure and the threat of the trade sanctions, in 1991, Thai government established "**the Safety Monitoring Programme (SMP)** as "**market exclusivity**" for pipeline pharmaceutical products not eligible for protection under the 1992 Patent Act. In addition, new original (patented) products promulgated since 1990 are also included in the SMP. These new pharmaceutical products are initially registered with conditions that they bear triangular labeling, are distributed only through hospitals or other healthcare facilities and are used under close supervision of physicians for 2 years (Drug Control Division Thai FDA, 2001).

According to the SMP, the term "**new human drug**" covers products of new chemical entity, new indication, new combination, and/or new delivery system that have never been approved in Thailand before the date of registration submission since 1989 (Patanawong, 2001).

Under the SMP, the pharmaceutical company has to submit the 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 Food and Drug Administration (FDA). If there is no evidence indicating serious side effects or it is considered that the drug's benefits outweigh the risks, the drug product will receive unconditional approval and will be allowed to distribute through normal channels (Thai FDA, 2001). In case of insufficient information, the SMP period of certain original product of pipeline drug may be extended up to two one-year periods (World Health Organization, 2000). This could lead to 4-year exclusivity of new drugs.

Generic products, of which its patented original product is subject to safety monitoring, cannot apply for registration until unconditional approval of the prototype is granted. Moreover, with a concern on quality, the companies of generic products should conduct bioequivalence study of their products compared with the originals (Drug Control Division Thai FDA, 2001).

Although the SMP was politically originated it is still an important measure of a new drug regulation in Thailand that had never existed before 1989 (Kiatying-Angsulee, 2000; Patanawong, 2001; World Health Organization, 2000).

2.3.2 Objectives of the SMP

According to current Standard Operating Procedure (SOP) of practices in the SMP of Thai FDA (Drug Control Division Thai FDA, 2001) the objectives of the SMP are;

(a) to confirm drug safety for Thais,
(b) to generate earlier safety signal within a collection of the adverse drug reactions of new drugs before granting unconditional approval and being marketed through normal channels of those drugs,
(c) to prevent or control more intensively new drug use
(d) to encourage health professionals to have more concern with drug safety, and
(e) to decrease unnecessary drugs use.

2.3.3 The Current System of the SMP

New drugs included in the SMP can be classified into three groups; (a) **newly patented drugs** which were promulgated since 1990, (b) **pipeline drugs** which are existing products patented in other countries during January 1, 1986 to September 30, 1991, and (C) **non-patented and non-pipeline drugs** (Drug Control Division Thai FDA, 2001).

In 2001, there were two major changes in the SMP procedure. Thai FDA changed the system of ADR reporting from the system that the company reports every patient profile regardless of the ADR occurrence to the system that only patient with actual ADR to be reported. Another change was accommodating for generic company to apply generic version of the original pipeline drugs that are still in the safety monitoring period to the Thai FDA. This kind of company should perform the SMP along with the original company does. And all safety data from both companies will be summed together to weight it's risk and benefit (Patanawong, 2001).

The current new drug regulation scheme is presented in figure 2.1

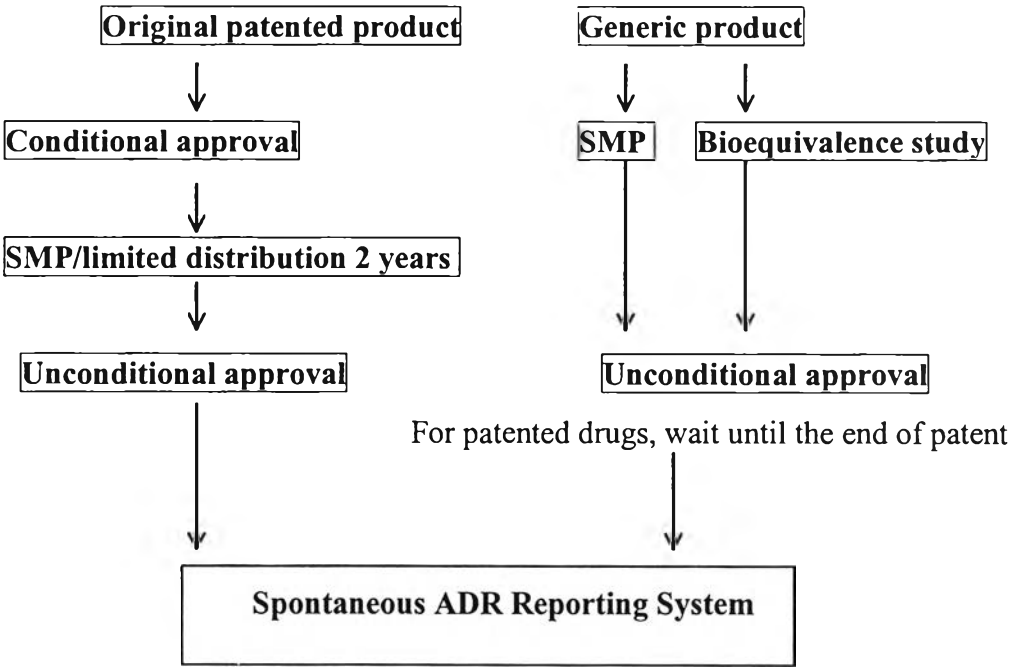

Figure 2.1 Current New Drug Regulation Scheme (Patanawong, 2001)

In conclusion, the SMP aimed at generating new drug safety profiles for Thailand using the intensive monitoring mechanism which has never been occurred in the country.

2.3.4 Procedures in the SMP

Current procedures in the SMP are as follows (Drug Control Division Thai FDA, 2001);

1. The Subcommittee on Approval of New Drug Registration performs a complete assessment on the new drug application based on sufficient evidence or technical data on efficacy, safety and quality of the drugs, and then decides whether to grant the conditional drug approval.

2. Be informed for tentatively granted a conditional approval from the Thai FDA staff, the company submits the protocol for safety monitoring of the new drug

including its labels and leaflets to the Drug Control Division, Thai FDA. These documents are subject to assessment by the secretary of the Subcommittee on Approval of New Drug Registration. Once found compliant with the standard guideline, the drug is granted **conditional** approval (NC).

3. After receiving a conditional approval, the company has to comply with the following procedures;

(a) Sell new drugs only in hospitals or medical institutes (government and private) with close supervision of physicians, where safety monitoring can be proceeded.

(b) Submit reports of the volume of drug production, import or re-packing every 4 months to Thai FDA.

(c) Submit reports of sale volume including names of purchasers every 4 months to Thai FDA.

(d) Collect all ADRs reports from the whole country using these criteria:

1. If there is a case of **death**, report to the FDA within 48 hours.
2. If the ADR is **serious and non-labeled** in registration process, report to the FDA within 15 days.
3. If the ADR is **serious and labeled** in registration process, report to the FDA within 2 months.
4. If the ADR is **not serious**, report to the FDA within 4 months.

It is noted that serious ADR refers to death, disability or absence from productive activity, cancer or tumor, congenital anomaly, life-threatening or admission to hospital or prolongation in hospitalization. The FDA may require more intensive monitoring from the company by conducting prospective or case-control or other epidemiological studies.

(e) Concisely record and evaluate all adverse drug reactions and make a comprehensive summary report to the Drug Control Division, FDA within 3 months after the end of the 2-year monitoring. The company needs to submit drug labels, safety profile of ADRs obtained in Thailand comparing to drug consumption, details of drug experiences in other countries, sale

volume and list of purchasers, and volume of drug production or import. The company can also identify the indicators for assessing safety of the new drug and submit to the FDA. The APRMC also receives each copy of ADR reports from health professionals and may investigate some healthcare facilities in order to assure the reporting system. If safety information is sufficient, the company can summarize a comprehensive report of the new drug before the end of the 2-year monitoring period.

4. Experts and the Subcommittee on Approval of New Drug Registration will assess the submitted comprehensive report and information. If the drug has no evidence of serious adverse events or its benefits outweigh the risks, it will be approved as **unconditional** (N) and permanent license is granted. The drug is then allowed to distribute through its normal channels. Its safety data are then gathered from the Spontaneous Adverse Drugs reporting system for existing drugs.

5. If the information is insufficient or incomplete, the SMP may be extended for another 6 months to 1 year. For the expensive and rarely used new drugs, the SMP extension may be one more year while the SMP of certain original product may be extended up to two one-year periods. All of these extensions must be done under the agreement of the Subcommittee on Approval of New Drug Registration.

In summary, under normal circumstances, new drugs are usually under the Thai SMP for 2 years (Drug Control Division Thai FDA, 2001; World Health Organization, 2000).

2.3.5 Time-limits for New Drug Approval Process

On August 3, 2004 the Thai FDA firstly launched the time-limits schedule for approving new drug as conditional (Thai FDA, 2004). New drugs are categorized into 2 groups. The first group is new drugs requiring a standard review and the second one is those requiring an accelerated or priority review. The time-limits from the dossier submitted to the Thai FDA to achieve unconditional approval and to be in the SMP period are 210-280 working days for the standard review group and 100- 130 working days for the accelerated group (Appendix A).

There is no evidence of the time-limits schedule for the SMP releasing process from the Thai FDA. At present, although some studies suggested that there may be political pressures on the SMP, none of the previous studies identify the criteria or tools in releasing from the SMP which is an important step of decision making for drug safety (Kiatying-Angsulee 2000; Supakankunti, Janjaroen et al. 2001).

2.4. Related Research in New Drug Safety Monitoring Programme.

Previous research showed some problematic issues related to the SMP. The important results from prior research were elaborated in this part to give a clear background of situation around the SMP, and help guide exploration of the issues most relevant to Thai drug safety monitoring system.

2.4.1 Some Features of New Drugs in Thailand

Existing research showed that there may be political pressures on the SMP releasing process resulting in a big chunk of new drugs released from the SMP in 1998 and an incredibly different duration for approving the new drug application to the SMP ranging from 11 to 2,147 days (Kiatying-Angsulee, 2000).

The SMP period is also studied (Tantivess, Jierapong, Jitraknatee, & et al, 2001). Although a 2-year period is known for the established SMP restriction, it was found that the actual SMP period ranged from 1 to 6.5 years. Different countries have different standard safety monitoring period from the first time of new drug launching, for example, Japan (6 months for Early Post-marketing Phase Vigilance Surveillance and 6 years for Re-examination), British: usually 2-year period), the United States' (3 years), and New Zealand's (2 years and annually thereafter) (BNF, 2001; Japan Pharmaceutical Manufacturers Association, 2002; Kubota, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001).

2.4.2 ADR Reporting

The success or failure of any safety reporting system depends on the active participation of reporters (World Health Organization, 2000). The existing studies in

Thailand showed insufficient of responsible persons and concerns in health professionals to report ADR (Hutangkabodee, Kongpatanakool, Wimonwatanaphan, & et al, 2000; Kiatying-Angsulee, 2000). Previous study pointed out that health professionals report ADR at very low rate due to the perception that reporting ADR or ADR monitoring reporting system is hardly beneficial to them (Tantivess, Tangcharoensatien, & Kaewpanurangsi, 2003). However, this kind of problem exists not only in Thailand but also worldwide (World Health Organization, 2002a). Every ADR intensive monitoring system involves the dedicated ongoing work of health care professionals including mainly physicians and pharmacists. These well known systems may include Thailand's SMP, the New Zealand's Intensive Medicines Monitoring Programme (IMMP), Japan's Prescription-Event Monitoring (J-PEM) and Early Post-Marketing Phase Vigilance Surveillance (EPPV), and the UK's Prescription Event Monitoring (UK-PEM) (Coulter, 1998; Japan Pharmaceutical Manufacturers Association, 2002; Kubota, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001; Thai FDA, 2001).

Theoretically, ADRs can be divided into 2 categories; (a) events that occur rarely in the population and (b) events that represent an increased frequency over a relatively common rate in the general population. The other categorization of ADRs based on the occurrence of the event relating to the use of drug are (a) the events that occur in short-term use, (b) the events that occur in long-term use, and (c) the events that occur long after the drug has been discontinued (Brewer & Colditz, 1999).

In the United States in 1995, 36 drugs accounted for one half of all ADR reports as death for the whole country. Of these 36 drugs, 23 (64%) were approved within 12 years and 4 (11%) were approved within 2 years (Chyka, 2000). The alarming point was that every year there were 4 new drugs that caused people deaths.

In addition to problems in safety monitoring system, low quality of ADR reports is one of the problems faced by many countries. In Thailand, during 1996 to 1999, the completeness and accuracy of ADR reports of new drugs were somewhat low as only 1,846 out of a total of 21,324 ADR reports (or only 8.8%) were found complete or accurate (Kaewpaneukrangsee, 2000).

2.4.3 Adverse Drug Reactions Most Frequently Reported

In terms of incidence of ADRs, it was found that, in 1997, the ADR rate reported from hospitals in Thailand was only 8 events per 10,000 in-patients and 5 events per 10,000 outpatients. However, a lack of completeness and accuracy of ADR reports found in the study may have confounded the ADR incidence rates (Hutangkabodee et al., 2000). In the US, the incidence of serious ADR in hospitalized patients was 6.7% (5.2 to 8.2%) (Lazarou, Pomeranz, & Corey, 1998).

Data from the Spontaneous Report of ADRs of Thai FDA showed that skin and appendages disorders, body and a whole-general disorders, and gastro-intestinal system disorders were the first top three of body system that ADRs occurred in each year from 1997 to 2000 (APRMC, 2002). These evidences were not consistent with the data in the United States where body and a whole-general disorders was the first ranked ADR, skin and appendages disorders the second, and nervous system the third ranked ADR.

In terms of causative drugs, the top three drug groups were systemic general anti-infectives, followed by musculo-skeletal system, and central nervous system drugs. The annual ADR reports in Thailand were presented for all drugs, not separated into new or existing drugs. To focus and understand more on ADR causality relating to new drugs, ADRs of these new drugs should be analyzed separately from the existing drugs (APRMC, 2002).

2.5. Indicators for Assessing New Drug Safety System

Several methods for assessing the health related system in research were established (Brudon P., Rainhorn J.D., & Reich M.R., 1999; Rattanawijitrasin & Wondemagegnehu, 2002) The indicators for assessing drug safety related issues were identified for various affairs, for example, national drug policy (Brudon P. et al., 1999) and drug regulation (Rattanawijitrasin & Wondemagegnehu, 2002)

In addition, the indicators of safety assessment for the newly launched drugs have been studied in various aspects, for example, withdrawal of the drug in relation

to time the ADRs are detected (Faich, 1996; Nordenberg, 1999), time required for drug approval related to the number of drug withdrawal (Rawson, 2000), and safety information causing a drug withdrawal(Abraham J. & Davis C., 2005). Furthermore, number of registered drugs banned in other countries compared with a total number of registered drugs was also used as an indicator for assessing the safety and efficacy of the registered drugs (Brudon P. et al., 1999).

2.6. Model for Exploring the SMP: Total Quality Management (TQM); Structure-Process-Output/Outcome Model

Avedis Donabedian, a leader of health quality assurance, has modeled quality process into a dynamic framework of three components namely structure, process, and outcome (Figure 2.2). The structure refers to material and health resources, operational characteristics, and organizational characteristics of the healthcare facility. The process refers to the actual giving and receiving of care by the health provider and other parts of the system. Outcome refers to health status, both of individual patients and entire communities (Donabedian, 1980).

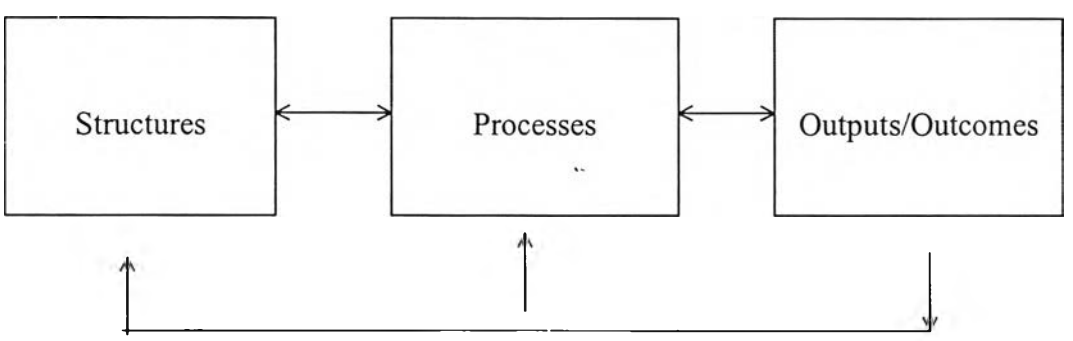

Figure 2.2 Model of Structures, Processes, Outputs/Outcomes

This model or Total Quality Management (TQM) model illustrates how healthcare quality has been defined over the last century. Research on relationships among structure, process and outcome has originated from organizational science and industrial engineering, where the first gain in health system research has been realized. With such disparate but interrelated components, the model helps explain

why many health system researchers prefer to take an interdisciplinary rather than multidisciplinary approach to health system research (Donabedian, 1980)

This kind of model has been applied in prior studies due to the fact that it shows a clear relationship among structures or input, processes, outputs/outcomes, and important role of feedback from the outputs/outcomes on the structure and process components has been taken into considerations (Brudon P. et al., 1999; Rattanawijitrasin & Wondemagegnehu, 2002; Steckler A. & Linnan L., 2002). Thus, the model views a service program as a 'system' characterized by structures/inputs, processes, and outputs/outcomes that can be influenced by feedback. With this feature, there are several advantages of this model as an integral part of measuring outcomes and managing results (Schalock & Bonham, 2003) as detailed below.

1. The structure/input component allows evaluators to focus on the predictors of desired outcomes, rather than focusing exclusively on the outcome per se. This advantage allows one to determine the factors that potentially influence or cause obtained results. Once the outcome determinant factors are defined, structures or resources anticipation will improve the desired outcomes.

2. The process component allows evaluators to better align services/activities and supports with the predictors of the desired outcomes. This arrangement involves aligning the organization's strategy, its staff, agency process or activities, consumer needs and customer outcomes. The advantage is that one can focus on the most valuable outcomes and improve the related processes or activities to achieve such outcomes.

3. There are three kinds of results ranging from results that can be perceived or measure more objectively to the ones with a more abstract in nature. The first type of results is outputs, which are the initial or immediate results. Outputs are primary results occur directly from the procedures or activities of the program. Second, the impacts are intermediate results that follow outputs. Third, the outcomes are the long-term results following the impacts. It is considerably flexible for the evaluators to measure these three-step results. It is also dependent upon the purposes of the evaluation to consider what results are the most relevant to measure.

4. The feedback allows the evaluators to better use the outcome-oriented data and the predictors of desired outcomes, rather than to view the outcomes only as a success or failure of a program.

Within the model of structure, process and output/outcome components, key properties of service or program that need monitoring to ensure quality are focused on the following aspects; effectiveness, efficiency, optimality, acceptability, legitimacy and equity (Schalock & Bonham, 2003): These quality-determined aspects of the health program are defined as the follows.

(a) *Effectiveness is the ability to attain the greatest improvement in health that can be achieved by the best activities.*
(b) *Efficiency is the ability to lower the cost of services without diminishing attainable improvements in health.*
(c) *Optimality is the balancing of costs against the effects of services so as to attain the most advantageous balance.*
(d) *Acceptability is the conformity to the wishes, desires and expectations of consumers and responsible members.*
(e) *Legitimacy is the conformity to social preference as expressed in ethical principles, values, norms, mores, laws and regulations.*
(f) *Equity is the conformity to a principle that determines what is just or fair in the distribution of services and of its benefits among the members of a population.*

The elements in the SMP were also focused on several key properties such as effectiveness, acceptability, and legitimacy.

This research used this model to explore the issues relating to new drug safety in the SMP because it clearly depicts how the SMP processes, and is applicable due to its dynamic and flexibility to all elements among the SMP system. Furthermore, this model can be used both in the SMP alone and in similar programs in other countries to compare the performance among countries. Comparisons of structural performances among countries can help identify relative weaknesses and strengths in every element of the SMP. Comparisons of process performances will demonstrate

activities to achieve efficacious and safe new drugs. Outcome comparisons can also help understand relative results among countries of which can be used to figure potential relationships with structure and process components.

2.7 Conceptual Framework for the Analysis of the SMP

The conceptual framework for the analysis of the SMP system in this study is presented in Figure 2.3. The elements in conceptual framework were detailed in chapter I: topic 1.6 Definition of Terms.

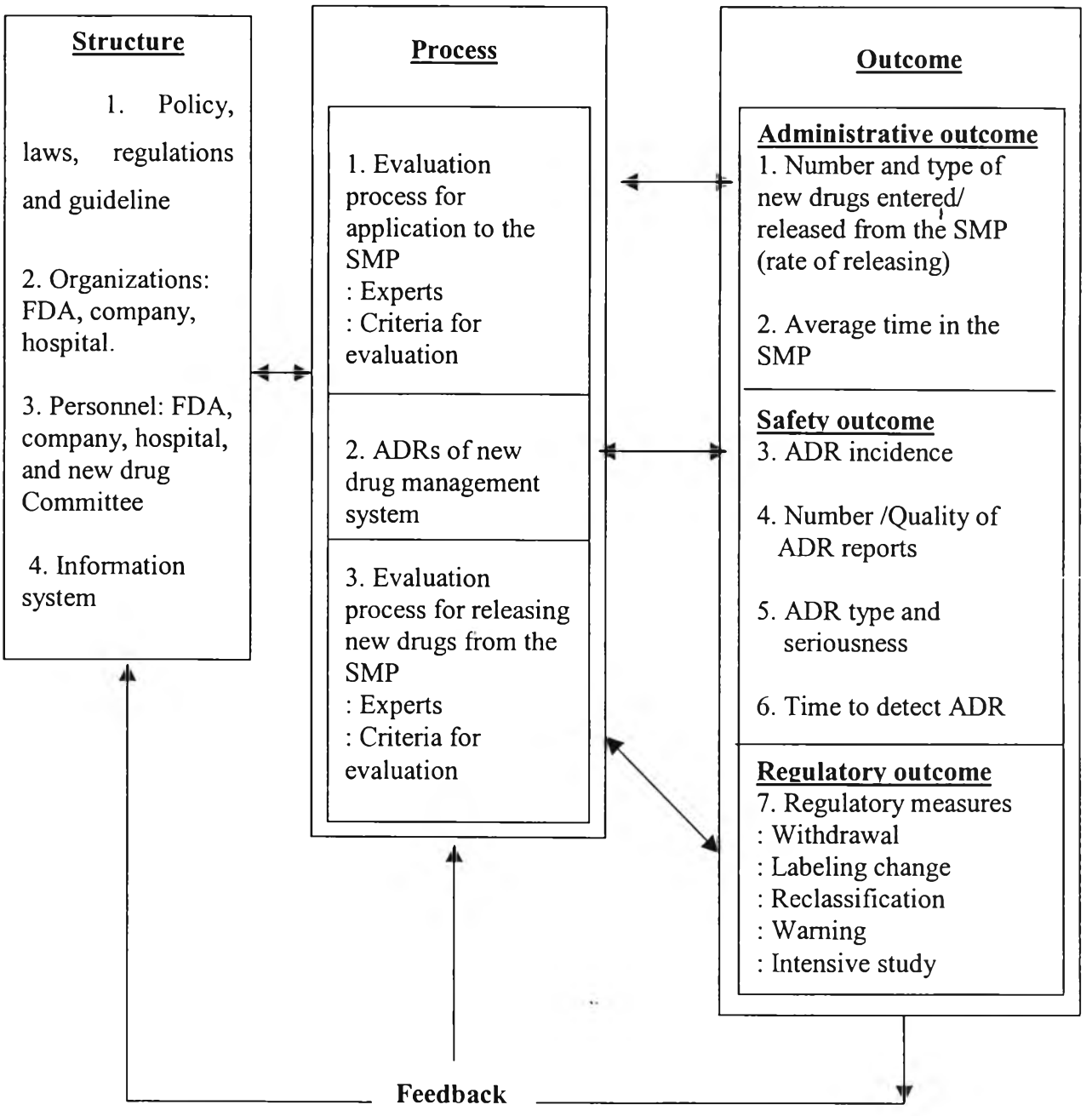

Figure 2.3 Conceptual Framework for the Analysis of the SMP