CHAPTER VI

SITUATIONAL ANALYSIS OF NEW DRUG SAFETY MONITORING PROGRAMME (SMP)

This chapter contains a comprehensive situational analysis of the SMP by illustrating the origin of the SMP and its current situation. To understand the situation of the SMP, various sources of data were gathered in this chapter. Secondary data were obtained by documentation review and investigation on database of ADR reports. Primary database was obtained by semi-structured interview and feedback information from modified Delphi method.

Situational analysis of the SMP was performed in a logical manner regarding the framework of structure, process and outcome components in responding to all issues involving in the SMP (Figure 4.1). For each component, the presentation begins with results from documentation analysis and database investigation. The evidences or data obtained by the interview and contextual feedbacks from Delphi are demonstrated to support the statement. Lastly, major findings are concluded for each element of the SMP components and the assessments of each component in the SMP were performed via the core safety indicators from Delphi method.

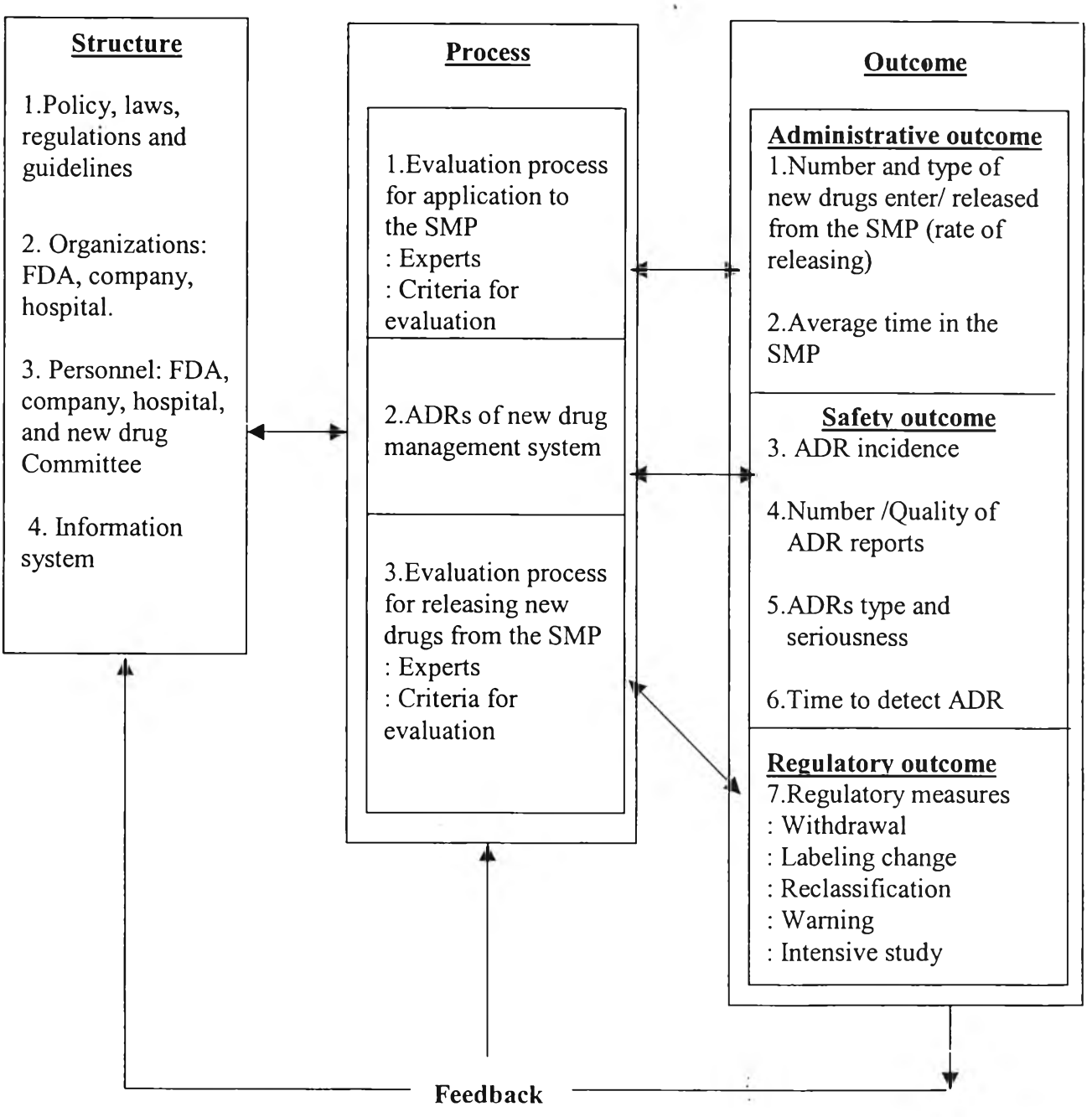

Figure 6.1 Conceptual Framework

6.1 Structure Component

The elements in the structure component of the SMP system are 1) policy laws, regulations and guideline, 2) organizations, 3) personnel and 4) information system in the SMP. The analysis of these elements in structure component are presented below.

6.1.1 Policy, Laws, Regulations and Guidelines

Policy for implementing the SMP

Based on documentation analysis, it is obvious that the SMP was politically originated in corresponding to the USTR pressure (Kiatying-Angsulee, 2000; Patanawong, 1995). Since Thai generic drugs could be manufactured almost immediately after the entry of original drug products as an interviewee stated that

"*... before the SMP, only 3 months after a new drug was imported, local made product was readily available in the market.*"

This was also supported by the findings from the interviews where 9 interviewees consistently stated that the SMP was not established for monitoring drug safety as in some interviewees said

"..as we known, the SMP was not for establishing new drug safety but for relief pressure from patent" (Interview 2) or

" the SMP was a tool for keeping a period for selling drug from original company without local competing" (Interview 49).

Why 2-year Monitoring

Regarding the mysterious 2-year monitoring period under the SMP, no documents showed reasons or mentioned any information that would give the clues why the duration was set for 2 years. However, from the interviews, two persons stated with confidence that the United States asked for a 5-year period. These two interviewees stated that

"..in the meeting of five key persons, there was a negotiation that 2 year period may be the most suitable since 5 years, as asked by the United States, was too long, and 1 year was too short to make any differences" (Interview 19,66).

The SMP Not as Law

Since the SMP was not law, but rather a government guideline for drug companies to follow, there is no penalty for those companies that distribute their drugs to places other than hospitals or healthcare facilities. This was evidently supported by at least 6 interviewees from both the Thai FDA and the drug company as in the statements from the interviewees below.

"The SMP was not a law if a company does not follow for example not report every ADR, the FDA cannot punish...the FDA only ask for voluntary activity from company" (Interview11)

" ...in case of SMP drug found in drug store, the FDA can do nothing to company, cannot withdraw drug license, just only inform the company."(Interview 2)

"..The SMP was not a law, it is a management tool."(Interview 19)

"..The SMP was not a law, there is no enforcement."(Interview 61)

Policy on the SMP system has effected not only the monitoring system of new drug, but also been applied to other national policies. The obvious example is the policy on selecting drugs into the national list of essential medicine. It has been agreed that only drugs off the SMP can be in the list (National Drug Committee, 2004). This effect was essential to all drug companies as found in all interviews from drug companies (19 interviews) and was confirmed by the interviews from 3 FDA officers. They all said ...

"Drug companies try to get their drugs off the SMP because putting their drug into the national list of essential medicine is the actual goal...to get more sell volume in all hospitals over the country."

Turning to Safety Concern

The interviews revealed that the practical approaches in the SMP have been changed to concern more on safety issues as the FDA officers said

" ..at present, the actual goal of the SMP is the same as in the SRS ...we try to early detect serious and non-labeled ADR after new drug is marketed." (Interview 1) and another FDA officer confirmed that " ..it's good, now the SMP aims at detect the ADR of new drug during the safety monitoring period."

Guidelines

Due to the fact that the SMP was not initially established for the new drug safety, procedures relating to the SMP processes have not been clearly understood enough by the FDA officers and drug companies as in the following statements

"....the SMP was not intentionally established for safety issue so it is not wondering that why the infra-structures are not well prepared for the safety procedures." (Interview 59)

" ..the concept of the SMP is good but there are some defects in practical procedures." (Interview 61)

A somewhat comprehensive guideline on standard SMP procedures was firstly published in 1995 (Patanawong, 1995). From documentation analysis, all works in the SMP emphasized more on paper works for drug registration for license approval while detail and steps in safety monitoring SMP protocols received attention and resources. While time-limits for registration were well defined, the ones for releasing from the SMP were not. Based on the interviews, drug companies tried to negotiate for an exact time-limits from the FDA in 2002 as told by four interviewees (Interview 7,45,64,69). Two years after the initiation from the drug company, time-limits for the new drug registration were finally set on August 3, 2004 (See also Appendix A). Drug industry has proposed a time-limit of 120 to 160 working days for releasing from the SMP after a comprehensive ADR reports were submitted. However, unlike the time-limits for registration, time-limits for releasing from the SMP have never been established.

Guideline for monitoring ADR in hospital has been published and disseminated from the Thai FDA. However the very first guideline was not known in the form of published document, i.e., published manual. From interviews found the attempts of the Thai FDA at the early stage of the SMP implementation to make the understandings among health professionals at the hospitals and also drug companies (Interview 2,10). Most of activities held by the Thai FDA were meetings. The latest version of the practice guideline for ADR monitoring was launched in December, 2000. It contained specific objectives of ADR monitoring in hospital, certain procedures, clearly specified responsible persons, how to evaluate causality of ADR, indicators of ADR monitoring, follow-up and prevention, sources of drug information, the protocol for report completion and submission to the FDA, and dissemination of ADR information to others (APRMC, 2001).

There was no guideline or criteria for the expert consideration in new drug evaluation process (Details in process component). In addition, politicians intervened in the appointment process of high-ranking staff instead of influencing the technical aspects, and directly influencing on the activities in the SMP system (Interview 17, 19, 65-66). As in one interviewee stated that

" ...policy makers has influenced on my work such as, new generic drugs are now under the New Drug Unit but in practice this should be under the Generic Unit not New Drug Unit. If the policy makers intend to move this activity to Generic Unit, it will be OK too." (Interview 15)

The policy of the FDA-SG is to ease and help in correcting drug applications until most passed resulting in vast variation of new drug approval time as stated by one interviewee that "...I had to released 248 new drugs within 6 months due to the policy from the FDA-SG." (Interview 2) Furthermore, there is no clear policy guidance of safety monitoring mechanisms especially at the hospital level that may result in insufficient and variety of the ADR monitoring system (Interview 35).

In summary, policy, laws and regulations regarding the SMP have been established with less attention on safety monitoring in the first place, but evolved over time in terms of practical approach to focus on new drug safety monitoring.

6.1.2 Organizations

Organizations involved in the SMP are both governmental and non-governmental organizations that can be distinguished into three major groups including the Thai FDA, drug companies and hospitals. The relationships between theses 3 organizations and other involving organizations are depicted in Figure 6.2.

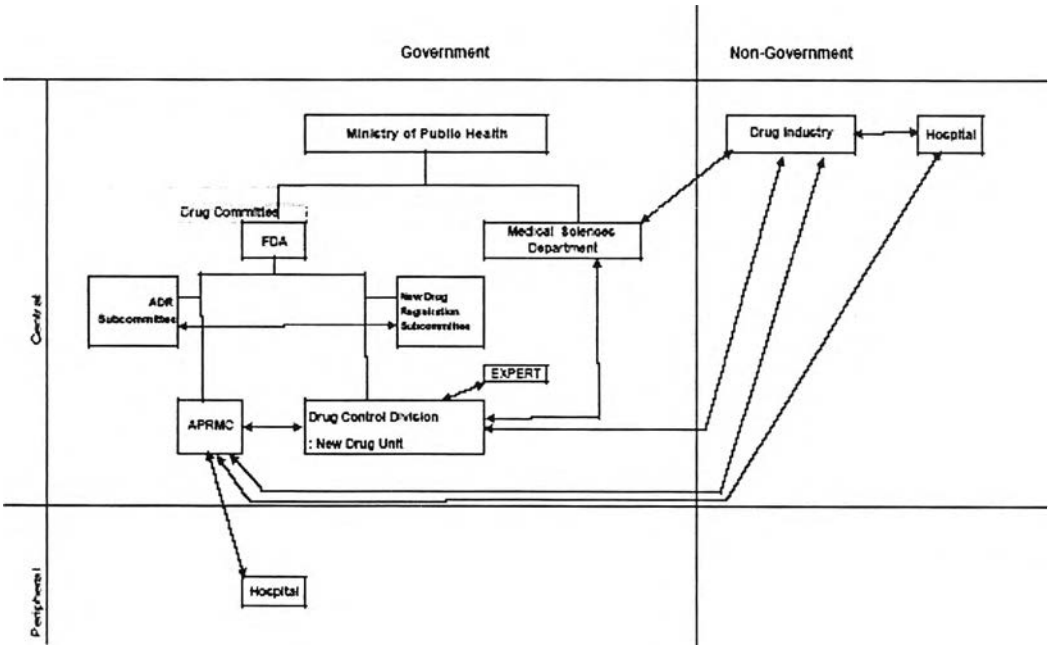

Figure 6.2 Organizations Involving the SMP System

Thai FDA

Thai FDA is the main responsible agent in the SMP system. Thai FDA exercised its registration power on new drugs through tasks carried out by the New Drug Unit under the Drug Control Division. For the safety issues, the APRMC under the Technical and Policy Administration Division is responsible for all academic-oriented activities relating to adverse reactions events all over the country (Drug Control Division Thai FDA, 2001; Patanawong, 1995; Thai FDA, 1999, 2001). The APRMC helped the FDA enacted new regulations and established new guidelines on

ADR-related issues by evaluating data of ADR gathered from ADR reports from hospitals. The center also disseminated drug safety information to public and parties responsible for reporting the ADR. For ADR reports gathered, the APRMC pooled these data and submitted to the Word Health Organization ADR center.

These regulatory and advisory agencies, the New Drug Unit and the APRMC respectively, usually cooperated with other authoritative bodies. Regarding the new drug approval process, the New Drug Unit usually consulted the experts called the Subcommittee on Approval of New Drug Registration. For the drug safety issue, the APRMC exerted its decision and advice through the Subcommittee on Research and Surveillance of Drug Safety.

The intensity and direction of drug approval and drug safety policy was usually dependent on the vision of the high rank officer, for instance, the Secretary General of the Thai FDA, and the Director of the Drug Control Division. The interviews also revealed that sometimes these high ranked officers intervened in the steps of workflow. This sometimes caused interruption or distraction of the whole process as said from one informant that " I used to get a note or a call from high rank officer asking for particular drug of which the experts were still evaluating...so pressured."(Interview 9)

Co-operation and Communication Between the Two Units

It was found that there was a room for improvements in co-operation and communication between the New Drug Unit and the APRMC. Experience from an interviewee suggested that 4-monthly summary of ADR of new drugs under the SMP from the APRMC was found difficult to understand and to use for the New Drug Unit. For example, a detail of class-effect of new drugs would be useful for initiate awareness on new drugs in that group. This detailed information was found not ready to use as the informant said

"...I cannot understand the information they sent since there were a lot of safety issues of many drugs listed but not presented with the suggestion or recommendation." (Interview 11)

Drug Companies

As of December 2003, there were 104 pharmaceutical importers and manufacturers of new drugs (Appendix E). In most drug companies, especially those big ones, there usually were 3 departments dealing with the SMP-related affairs. These departments included department of regulatory affairs, research and development (R&D) department, and drug marketing department (Interview 7, 8, 16, 24, 42, 44, 68,69). But for the local company, a clear responsible department was not clearly set as one informant from local company said *"...as a product manager but I've to do all activities such as regulatory affairs with the FDA, plan a promotional activity for some drugs and sometimes contact key opinion leader." (Interview 47)*

Functions, roles and responsibility of these 3 departments were different. The department of regulatory affairs dealt mainly on all registration activities from applying for the SMP entry, to the release from the SMP. The research and development, or medical department in some companies, was responsible for Policy Administration the safety activities, training personnel in sales and safety monitoring, and summarizing all safety data gathered from hospitals. The sales and marketing department also assisted in collecting ADR data, disseminating the ADR information, and also collecting feedbacks regarding all safety issues from health professionals.

According to the interviews, in some companies, regulatory affairs or research and development departments planned and supervised all activities regarding safety monitoring under the SMP. These two departments usually cooperated with marketing department to have sale persons collected ADR reports (Interview 7, 8, 44-45, 57-58, 67-69) as they said *" ...Most Regulatory Affairs in companies will set the number of ADR report required and inform the marketing department to collect the ADR from the hospitals."*

In addition, all interviews from 11 drug companies revealed that they all assigned the safety monitoring of new drug in the SMP under the safety system of all products in each company as in the statement *"...the SMP is only a part of safety system of my company."* (Interview 58)

Hospitals

In a given hospital, there were usually two units or agents active in ADR monitoring. These were ADR center and the Pharmacy and Therapeutic Committee (PTC). The ADR center was managed mostly by pharmacists as confirmed in the interview *"..in this hospital the ADR center is in under the pharmacy department, two fulltime clinical pharmacists responsible for reporting the ADR of all drug in hospital."* (Interview 20) The center set and managed a system to assure that the preventable ADR recurred. For the PTC, it was responsible for rational use of drugs in all steps of drug use including hospital drug formulary and drug use evaluation. In all hospitals, the ADR center worked under the supervision of PTC. Roles of the ADR center have been augmented by the provision of the up and coming hospital accreditation. These circumstances were based on 8 interviews from hospitals that had experiences of hospital accreditation (Interview 5, 25, 29, 35-56, 48). as the interviewees said *" Hospital accreditation help the ADR monitoring system in my hospital better works"* (Interview 39) or *" ..Hospital accreditation helps us set a teamwork in ADR monitoring activity of which assigned by the hospital director, we have physicians to confirm ADR case"* (Interview 40)

One hospital pharmacist argued that *"..hospital accreditation does not cause better system of ADR monitoring in my hospital but clinical pharmacists have performed this activity before the hospital accreditation implemented"*

Based on the provision of safety issues of new drugs, to enter the hospital formulary for a given new drug under the SMP was considerably difficult. This was because the PTC usually hesitated to enlist the drug into the formulary if uncertain about safety of the drug. In some hospitals, it was almost impossible to enlist the drug under the SMP restriction. This situation was confirmed by the interviewees from hospitals and drug companies (Interview 5, 7, 24, 35-36, 44, 64) as in the statement below

" ...New drug in the SMP cannot enlisted into the hospital formulary, I've to give some sample drugs to the hospital to use as the pilot test for 4 months...after that if the doctor still request to use, my drug can compete to be in the hospital." (Interview 24)

In conclusion, the organizations involving in the SMP were set to perform the activities in the SMP with different intensity. The Thai FDA was initially set the New Drug Unit to handle all the new drug application to the SMP while the APRMC was set for all activities related to adverse effects of all health products not for the specific new drug. Drug companies and hospitals also perform the activities serving for all drugs not a specific for new drug in the SMP. In addition, except New Drug Unit in the Thai FDA, most of activities and responsible of the organizations involving in the SMP were set as universal for all drugs.

6.1.3 Personnel

Personnel in the FDA

Roles and responsibilities of FDA personnel involved two kinds of expertise; one using scientific knowledge on pharmacology and pharmaceuticals, and another using coordination abilities. Performance levels of the FDA officers in the New Drug Unit and the APRMC were criticized with various, sometimes conflicting, views.

There were only 7 pharmacists working in the New Drug Unit (as of the interview on September, 2004). Their responsibilities included handling all registration profiles of new drugs categorized by pharmacotherapeutic action called the Anatomical Therapeutic Classification (ATC). Assigning new drugs to responsible persons based on therapeutic actions helped build up expertise among FDA officers. Based on interviews, this kind of work arrangement was advocated both by FDA officers and drug companies (Interview 7, 9, 11, 45, 67-68) as in the statement *"Today, it's better since the FDA officers are assigned to responsible for new drugs in particular group. This will help them get more depth-experiences."* (Interview 7 and 68) Nevertheless, some viewed this expertise of FDA officers was still inadequate, and needed improvement (Interview 15, 17, 64). The FDA officers said *"..to develop expertise in FDA officers, I have to use " on the job training" and there is no one enable to plan and develop my work."* (Interview 2) and *".Due to the workloads and too few staffs, we cannot improve our works."* (Interview 11). The

expert also confirmed as *" Staffs and team in the SMP system are too limited, government should concern more on technical staffs.. we need more."* (Interview 26)

Like the New Drug Unit, only 7 pharmacists were working at the APRMC. Their major roles were gathering ADR data from the hospitals and drug companies. These data were summarized as ADR profiles of all drugs and profiles of new drugs under the SMP. The latter profile was forwarded to the New Drug Unit periodically, for example, every 4 months. The APRMC staff also summarized a final ADR profile of the new drug requesting the release from the SMP. This final profile was compared with the comprehensive report submitted by the drug company by the Subcommittee on Approval of New Drug Registration. Based on the interviews, expertise of APRMC was not fully developed. The interviewees stated that *"..with a highly focused responsibility on ADR data evaluation and scientific support, the APRMC should be able to execute the scientific investigation by independently instead of hiring external experts to summarize scientific evidence regarding the current ADR events."* (Interview 11, 19)

Personnel in Pharmaceutical Company

Responsible persons in drug companies are mainly pharmacists and physicians. In the department of regulatory affairs, most workers were pharmacists, while in the research and development department, there were pharmacists and physicians working together. In the marketing department, workers were mainly pharmacists and some with other scientific disciplines.

Persons in regulatory affairs prepared all documents for submitting to the FDA. They were also responsible for acquiring additional documents and information requested by the FDA or the FDA external experts. Workers in research and development department handled all safety issues of new drugs and cooperated with marketing persons in collecting ADR reports from hospitals. To qualify for the ADR report collection task, persons in marketing department were trained by the research and development department. In companies with no research and development department, they were trained by persons from regulatory affairs, or by product manager.

Personnel in Hospitals or Healthcare Facilities

Major persons dealing with the SMP were pharmacists, followed by physicians and nurses respectively. Therefore the person most influencing the success of the safety monitoring and reporting clinical pharmacists (Interview 17, 34, 38, 62) as shown in the interviews of 3 physicians all agreed that *"..in my hospital, 2 clinical pharmacist can help the ADR monitoring system* works very well." (Interview 32, 48 and 51) However, textual feedbacks from the Delphi method suggested that physicians were the best initiator of ADR report in hospitals. From the practice guideline for adverse drug reaction monitoring, it was stated that, major roles of physicians and dentists included diagnosis and confirmation of suspected ADR, while roles of pharmacists focused on cooperation among health professionals, follow-up ADR cases, collecting data, and summarizing the ADR cases. Roles of nurses were also included in the guideline. Nurses were expected to be the persons with first contact with patients, especially those hospitalized patients. Nurses then notified physicians and pharmacists for further verification and correction of the problems. *Working in a team in ADR monitoring system were strongly evident in every interview (18 persons from 8 hospitals) as in the statement*

"Nurse observe suspected ADR in the ward and ask physician or pharmacist to confirm case, when physician assesses and confirms, then pharmacist will fill the ADR report form." In the interview found that" ..90% of ADR reports in my hospital were originated by nurses." (Interview 25)

Shortcomings among health professionals are apparent. Some health professionals had inadequate knowledge to recognize, verify, and manage the ADR or drug interactions in their settings (Interview 52-53) as revealed in the statement

"Number of physician who clearly understand the ADR is not enough, and we still need more pharmacists enabling to work in ADR." (Interview 25) Acceptability of pharmacists in detecting and managing ADR was however existed, including the private ones (Interview 13, 34, 35, 51).

There were essential evidences of "not known the existence of the SMP" as in the statement *" physicians don't know the existence of the SMP and don't know the meaning of triangular label at the box." And one interview with a member of medical school revealed " Oh! This is my new knowledge, I'll test my medical student about the SMP issue."* (Interview 48)

The development of potential in ADR management system was however promising. With a provision of hospital accreditation, the cooperation among health professionals, working as a health team, was growing (Interview 5, 25, 29, 35-56, 48).

6.1.4 Information System

The information system regarding new drug registration and ADR monitoring was found inadequate in many aspects. These included the insufficient quality of data, low usability of data, problems in management of information system, and ineffective information dissemination. These aspects were detailed in each source of data; new drug registration database and ADR report database.

New Drug Registration Database

Two databases of new drug registration were used in the new drug registration process; electronic file (Excel) database available on the Internet, and the book of New Drug Registration published annually, with availability of the editions of 1996 to 2002 covering drugs first entering the SMP system in the year 1991.

Internet-based electronic new drug registration profiles (2003) were separated into two files; file of new drugs under the SMP (or NC category) and file of new drugs off the SMP (N). Data fields in these two electronic files were shown in Table 6.1.

Table 6.1 Data Field in New Drug Registration Profile (as of December, 2003)

Field name	Definition
Number	Number of new drug in each file (running separately in each file, not link together).
Generic Name/Strength	Generic name including strengths, dosage form and/or package.
Trade Name	Trade name which may include strength or dosage form
Reg.No	Registration number or license number of each new drug defined type of drug namely, 1A = Local manufactured, single drug 2A = Local manufactured, combined drug 1B = Repacked, single drug 2B = Repacked, combined drug 1C = Imported, single drug 2C = Imported, combined drug Each registration number is ended with year in Thai
Importer/Manufacturer	Name of importer or manufacturer including name of the country the drug came from in parenthesis.
Indication/Therapeutic Action	Indication or therapeutic action of each drug.
Approval date	Date-month-year (in Thai year) on which the drug approved for on the SMP (NC) in the NC file or off the SMP (N) in the N file

In terms of data quality, it was found that only information of individual single license could be viewed. No summary information by a given drug or by year could be retrieved. Furthermore, only the most updated data were available, while those from previous years were not. This was disadvantageous since it was impossible to understand what had happened to some drugs.

There were a huge amount of mistakes in the database. These included typos such as a data in a field starting with space, inconsistent capitalized first letters, and misspells on drug names, dosage forms, units. Some data fields were complex which made the use of data impossible. These complex data fields were, for example, a

given field composed of information on generic name, strength, dosage form, and package.

Another aspect indicating low quality of data was the use of various nonstandard terms to refer to a single entity. The noticeable example was found in the data field of "Indication/Therapeutic Action." A given pharmacological agent were called by different terms, such as referring "statins" as antihyperlipidemics, antihyperlipidemia, antihyperlipidaemia, anticholesterol, anticholesterolemia, and lipid lowering drug.

In terms of information dissemination, the annual New Drug profiles were given to the hospitals and FDA experts in new drugs. It could be used for checking of the SMP status for formulary service. The information was 9 months late. Therefore, the use of the information is quite limited. In terms of information dissemination, the annual New Drug profiles were given to the hospitals and FDA experts in new drugs. It could be used for checking of the SMP status for formulary service. The information was 9 months late. Therefore, the use of the information is quite limited.

Based on these findings, one could conclude that it was almost impossible to use this dataset for system improvement and forecasting the trend. For example, when asked for summaries of annual number of SMP drugs, companies submitting drugs for the SMP, and number of drug off the SMP, the FDA officers were unable to respond to such questions, but rather gave a book of the annual New Drug Registration. Furthermore, as far as known to the public, this electronic database has never been used for any advanced and comprehensive analysis.

ADR of New Drug Database

There was only one source of data of ADR of drugs, namely the Spontaneous Report of Adverse Drug Reaction, available to public (APRMC, 2004). This report showed summary number of all ADR events by various aspects, including by drug names, drug groups, severity of ADR, patient age and gender, and resulting symptoms. Presentation of ADRs under the SMP started in 1996, almost 6 years since the start of the SMP system. Level of perceived importance of analysis and summary

of various aspects of ADR events depended on the leading person in the APRMC (Interview 1). The standard procedures or policy to guide what aspects of ADR events to analyze and disseminate to the health professionals and public has not been put in an established policy.

In terms of information system management, based on also the circumstances described previously, the effective data management system has not been set. Data structures for data shared among divisions were not clearly set. Therefore to share these data was somewhat problematic. For example, it was impossible to verify whether the ADR reported was a labeled or unlabelled ADR from the database of ADR. One had to retrieve data from the drug registration database, provided in the intra-network of the FDA. On the other hand, officers at the New Drug Unit also had hard time retrieving ADR events for a given new drug. To retrieve such information, request must be made to the APRMC. The evidences were found from various interviews as said

"There is a problem in an online database linkage in the FDA, in-time database cannot be retrieved among divisions." (Interview 10)

The usability of the Spontaneous Report of Adverse Drug Reaction was also limited. A given report contained data of ADR events that occurred 2 years before the publishing year (APRMC, 2002, 2004).

For ADR events data, only hospitals and academic (pharmacy schools and medical schools), were given the annual Spontaneous Report of Adverse Drug Reaction and the 4-monthly Medical and Health Products Bulletin. The Bulletin presented safety related issues including case reports in Thailand and worldwide, and summary of ADR events periodically in the given year. There was also warning letters when specific safety information issues that deserved public attention. It was found that warning letter was the most effective way to communicate ADR risks to health professionals and academics as stated by hospital pharmacists that *" I also receive warning letters from APRMC when there are some safety information of drug such as recently warning about class effect of Coxibs and Statins."* (Interview 20,35,36,53)

In shorts, the information system for new drug registration and related ADR events was inadequate in terms of usability both for the regulatory work of new drugs at the FDA and other health related organizations.

6.1.5 The Assessment of the Structure Component in the SMP System Using the Core Structure Indicators from Modified Delphi Method

Using indicators obtained from the Delphi method, existence of structure component in the SMP was assessed. Based on results from various analyses described previously, 6 elements of the structure component were found existing (Table 6.2). These included those measured by the indicators "certain guideline for new drug safety monitoring procedure in FDA," "systematic safety monitoring of new drug at hospital level" "safety monitoring system in drug company," "certain personnel in safety monitoring activities in drug company," "ADR of new drug database linkage and enabling to generate signal from the WHO database," and "information system of new drugs."

For the indicator " systematic safety monitoring of new drug at national level", it could be assessed as "No existence in the SMP". The other two indicators " experienced external experts in new drug" and " experienced responsible person in drug company", could be assessed as "?" which referred to "the evidence from this study is not clear to assess."

Table 6.2 Assessment of the SMP System Based on Indicators from Delphi: Structure Indicators

Type of indicators	No. in round 3	Final Safety Indicators of the SMP	Existence in SMP system
Policy, law, regulation and guideline (2)	1	Systematic safety monitoring of new drug at national level	No
	2	Certain guideline for new drug safety monitoring procedure in FDA	Yes
Organization (2)	3	Systematic safety monitoring of new drug at hospital level	Yes
	4	Safety monitoring system in drug company	Yes
Personnel (3)	5	Certain personnel in safety monitoring activity in company	Yes
	6	Experienced external experts in new drug	?
	7	Experienced responsible person in drug company	?
Information system (2)	8	ADR of new drug database linkage and enabling to generate a signal from the WHO database	Yes
	9	Information system of new drug from literature regarding; information in literature, Information of therapeutic index, drug interaction, ADR in clinical trial, Indication and contraindication, and regulatory measures of new drug in other countries.	Yes

Note: ? = the evidence is not clear to assess

6.2 Process Component

In considering process components, 3 continuing processes were analyzed. These included evaluation process for new drug application to the SMP, ADR management system, and finally evaluation process for releasing new drug from the SMP.

6.2.1 Evaluation Process for New Drug Application to the SMP

The evaluation process was one step occurring after the application document was screened and numbered by the FDA. The document was then sent to the experts (Figure 6.3).

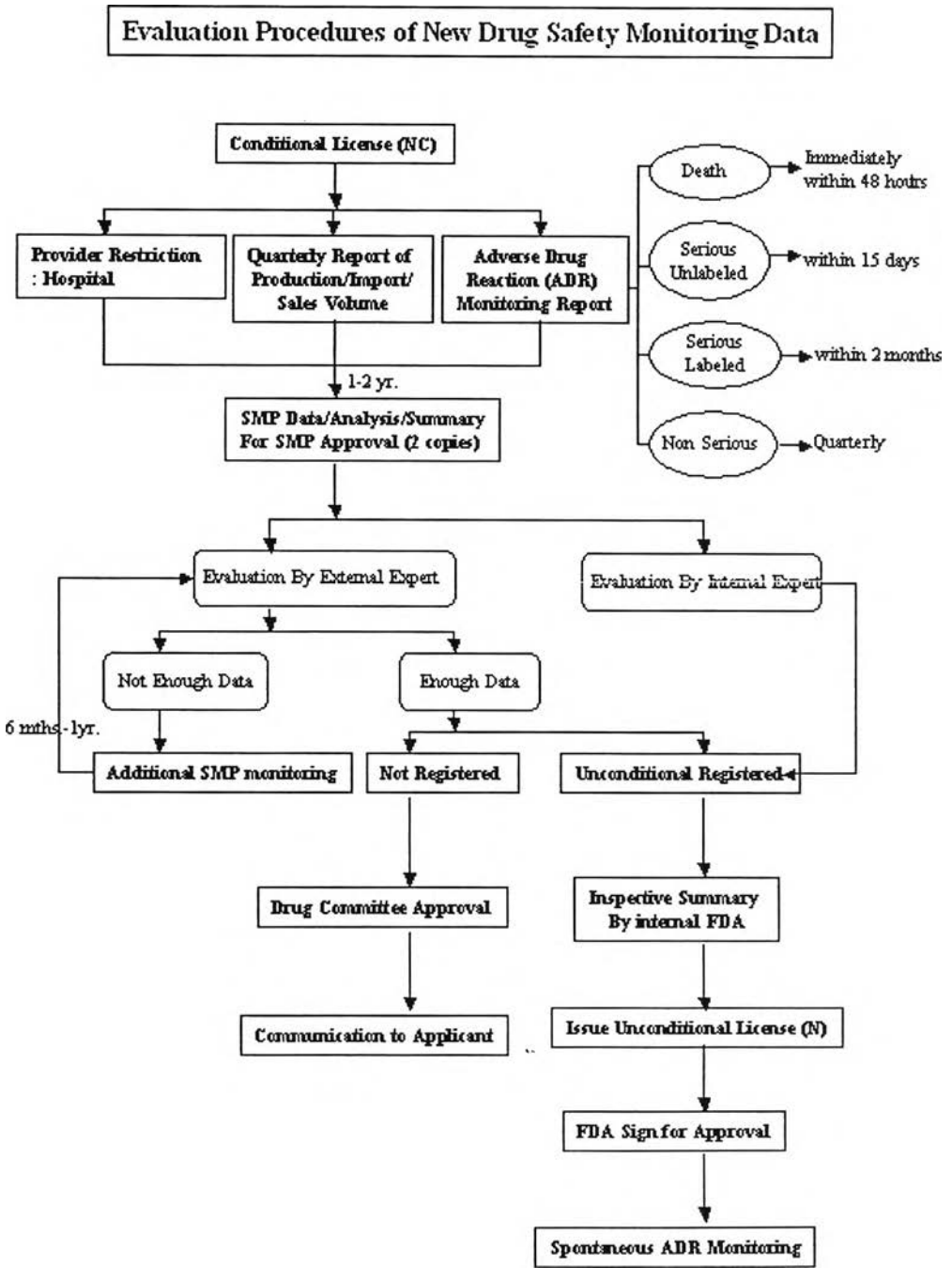

Figure 6.3 New Drug Registration Process

In assessing the evaluation process for new drug application to the SMP, analyses on the experts and criteria for evaluation of new drug application to the SMP were focused.

Experts in the Evaluation Process

There was no document available to public indicating which individuals were these new drug experts and how to recruit them. In practice, the New Drug Unit made an official request from various medical specialties at those royal colleges of medical specialties. In addition to the royal colleges of medical specialties, experts in schools of pharmacy and schools of medicine were also sought of. Names with resume indicating expertise were then submitted to the New Drug Unit. These candidates were selected and appointed as members to work under the Subcommittee on New Drug Approval Registration. However, the interviews also revealed that the FDA officers asked for an agreement from the expert before sending the new drug profile to the expert as in the statement agreed both from the FDA officer and expert that " *Before sending the new drug profile, FDA officer will call me and ask for my agreement first, if I'm not available in that time or not keen in those drugs, I can object.*" (Interview 17) " The specialties with difficulty to recruit were those in oncology and hematology as two FDA officers said " *the experts in oncology and hematology is scarcely recruited*" (Interview 14-15). Overall, about 500 experts were recruited to form 3 core components of the Subcommittee including experts panels in 1) chemical, pharmaceutical, pharmacology and toxicology, 2) pre-clinical study, and 3) clinical study (Interview 2,9,10,11,14 and also confirmed in the SOP in new drug Registration).

For each drug applying for SMP, it was reviewed by 5 to 6 experts, 2 from each expert panel. These experts were paid for their reviews. Payment rates were 4,000 bahts/review for experts in the panel of chemical, pharmaceutical, pharmacology and toxicology, and 5,000 bahts/review for experts in the other two panels (Interview 9).

In terms of the conduct of reviews, after completion of document from drug companies, the experts were given 2 months for review the profile. However, as stated

by a few experts and FDA officers, it was almost impossible to complete the reviews due to a huge workload at these experts' institutions (Interview 3, 12, 14, 41). The evidences gave a clear support for this as in the statement " I review each new drug profile very slow because my workload in my office here is so huge." (Interview 60) Therefore, some drugs took as long as 8 months for the review (Interview 41). Serving time in the expert panel ranged from 2 to 12 years from 5 expert interviewees.

Each expert took a different number of reviews as said *" Normally, I review 10-12 of new drug applications in each year."* (Interview 60) and *" Due to my delay review, the FDA send me only 2 applications in each year."* (Interview 66)

Regarding experts' qualification, it was evaluated by both the FDA officers and the experts themselves. FDA officers considered "expert's qualification" based on the soundness of the critique from the experts (Interview 9, 11, 18) as in one example in this statement

" from the critique of each expert to the FDA, I could know the magnitude of the expertise in those experts." (Interview 18)

For evaluation among the experts, they considered that having a good record of research or academic work relating to drugs being reviewed was the best indicator for expert qualification (Interview 3, 41). A good expert should be concerned about information confidentiality (Interview 41). Based on drug company's views, quality of experts depended upon how they requested and used the information. For example, experts reviewing drug in chemical part, but requested information in clinical parts, which was considered irrelevant. It was sometimes found that this irrelevant information was later used by the experts in their own teaching or research or as the company's consultant (Interview 7, 67). Another example of low quality experts were those requesting the information of cost of treatment as stated by one expert

" I think that expert should consider only safety issue not in the cost of drug since this is the responsible of drug companies themselves." (Interview 60)

Criteria for Evaluation of New Drug Application to the SMP

There were no documented criteria available to public. However, a list of issues to be concerned raised by the FDA was given to the experts. This so-called criteria for evaluation had no specific cut-point for making decision. Therefore, the decision made was based almost entirely on experts' experiences. With this lack of specific criteria, most experts made their own criteria based on the quality of information compiled by the drug companies. These criteria include 3 major concerns.

1) The drug application with the most updated scientific evidences was more likely to receive better reviews (Interview 12, 41) Evidence from the company's view was rather confirmed as said *" I found that new drug with some articles printed in scientific journal is easier be accepted than the less one."* (Interview 45)

2) Applications from drug companies with well-known research and development department were usually considered a good product (Interview 12) as stated *" From my experiences, I found that the information from R& D company is better than not R&D company."*

3) Applications of new chemical entities were more likely subject to an intensive review as the experts said *" There are variety intensive evaluation of new drug applications especially for the new chemical entity, the review must performed in comprehensive manner."*

Surprisingly, one expert created his own criteria to evaluate drugs from certain countries with questionable drug quality, for example, India and Pertorigo (Interview 12).

Recently, the FDA has developed criteria for evaluation of new drug application based on information from ASEAN countries (Interview 9, 12).

In conclusion, in evaluation process, the quality of experts and a specific and sound criteria are needed for a high quality evaluation of new drug application to the SMP.

6.2.2 ADR Management System of New Drugs

In the effort to understand ADR management system of new drugs, 4 steps in ADR management including ADR detection, assessment, minimization, and communication were analyzed.

ADR Detection

Based on document analysis, Thailand established the Spontaneous ADR Reporting System (SRS), the basis of most drug safety evaluation programs in post-marketing drug surveillance. It has been used as a major tool for drug safety of existing drugs in Thailand. The Adverse Product Reaction Monitoring Center (APRMC) under the Technical and Policy Administration Division of the FDA holds this responsibility. Generally, there were two steps of assessment of case reports in SRS; the assessment of individual cases and the interpretation of the aggregated data. The latter step is only completed for a small portion of case reports, such as when actions or measures deemed necessary (APRMC, 2001).

The system in safety monitoring in the SMP was similar to that in the SRS regarding the procedure and reporting persons. Under the SMP, all reports of new drug ADR were to submitted to the FDA, while those under the SRS were subject to voluntary report (APRMC, 2001).

Despite the fact that the two safety monitoring systems, the SMP and SRS, were quite similar, there existed the difference in the intention. While the SRS obtained ADR data with no known denominators for estimating incidence, the current SMP with known sale volume, could provide a close incidence of given ADR events (Patanawong, 1995 and from interview 11, 44).

Under the SMP, ADR reports both from hospitals and pharmaceutical companies were submitted to the APRMC, FDA. Completeness and accuracy of data by the APRMC were verified by the APRMC. The ADR profiles were summarized by the ADR subcommittee with the Head of APRMC acting as the subcommittee secretary. Recommendations or decisions were passed by the authority of the Subcommittee on Approval of New Drug Registration. The recommendations were

varied including acceptance after proving that the benefits outweigh the safety risks, extensions for more safety data, and requirement for more advance studies (Food and Drug Administration 1999).

The above findings were based on document analysis. The following results were from interview, contextual feedbacks from Delphi rounds, and ADR database analysis. These results were presented in the sequences of ADR detection, assessment, minimization and communication.

In terms of risk detection, monitoring and reporting ADR under the SMP was the responsibility of drug companies, not the hospitals. With this fact, physicians were encouraged to report the ADRs using various kinds of promotional strategies.

1) Sale representatives from drug companies would give a certain amount of ADR report form to physicians as shown in the statement from the interview with a physician that *" the company gave me 30 ADR report forms, some companies gave 300 forms depending on type of drugs."* (Interview 60)
2) Based on the interviews, some companies had sale representatives help the physicians to fill out the ADR report so that it would not become extra burden for physicians as found in the interview that " ..in some companies, sale representatives have to fill in the ADR report form because physicians and nurses are struggling with a huge number of patients." (Interview 7, 67)
3) Compensation sometimes occurred in cash payment as the company said *"The company would give around 200 to 500 Bahts as an incentive for a complete ADR report and I also heard that some companies give at 1,000."* (Interview 24)

The FDA officers also knew theses occurrence as they said *" I heard that companies had to pay some money to physicians for reporting the ADR in the SMP."* (Interview 1, 2, 9) While some physicians had never received the payment from the company as shown in the statement below.

" I have never received any incentive from the company but ever heard that company pay physician 200 Bahts for each ADR report of new drug." (Interview 48)

4) For the hospitals where cash payment was not allowed, the companies gave gifts to the physicians, or the hospitals, for example, toaster and coffee set (Interview 56, 67-68) as evident in the statement *" the nurses who fill in the data in the ADR report informed me to give a toaster instead of money."* (Interview 38)

In addition to the works of physicians and nurses, some reports were done by hospital pharmacists (Interview 20, 36-38, 40). In some hospitals, a committee on ADR detection was used to perform intensive monitoring on some new drugs used in the hospitals. These selected new drugs were, for instance, statin or coxib drugs. These drugs were selected based on the safety warnings that were prevalent at the time (Interview 6, 20-21, 25, 34-36).

Regarding quality of the report of the ADR detected, there were two conflicting opinions based on sufficiency of the data quality. From drug company's views, data quality was sufficient and acceptable. However number of reports to represent the real incidence in a hospital may not be sufficient. This was because sometimes it was difficult for company representatives to ask physicians or nurses to report the ADR as found in Delphi feedback and interviews (Interview 24, 56, 67). In addition, drug companies also stated that *" reporting ADR may be, in turn, a drawbacks for the drug safety profile."* (Interview 7) This means that the more ADR reports, the worse safety profile of the drug. This might cause difficulty in trying to get off of the SMP restriction (Interview 56). According to drug companies, being off the SMP earlier means a higher chance to be enlisted in the National List of Essential Medicines sooner (Interview 24, 56, 68).

Another view of quality of ADR under the SMP was from FDA officers and experts. It could be suspicious that a small number of ADR reports was obtained from given hospitals where big volume of sales occurred (Interview 9, 11, 17). Another reason of underreporting were from the fact that physicians wished not to report since

it might be considered as their mistake and no system to protect physicians from lawsuit was not in place. However, at least two physicians argue that it was not the fear of being sued that stopped physicians to report the ADR. Instead, the unavailability and complexity of the report form, and an already huge regular workload at the hospital that discouraged ADR reporting (Interview 34, 38-39) as shown in the statement that

" *I think physicians are not feared from being sued but reporting is a protection tool for them.*" (Interview 39)

Another reason for underreporting from drug company point of view was that sale representatives paid much more attention on sale volume, and less on ADR reporting, therefore, fewer number of reports were collected (Interview 7, 56).

There were recommendations to improve ADR reporting including team working, setting a system to facilitate ADR reporting, and reshaping physicians' attitude towards ADR reporting. In **setting a teamwork** for ADR reporting, results from interviews suggested that pharmacists should be adaptive to team working before a network can be established (Interview 5-6, 20, 52, 57) as shown in the statement " hospital pharmacists are key persons in ADR monitoring team" said by the physician from one medical school (Interview 62). To **facilitate the reporting system**, two aspects were focused; administrative and tools in reporting system. In terms of administration, a policy from the hospital administration board should be defined and put into effect as found from the interview that " Hospital accreditation can provide the administrative policy from hospital director to ease the procedures in ADR reporting." (Interview 39) For tool development, there was a need of convenient and easy ways to fill the form for physicians and nurses. The final completion of the form should be done by pharmacists (Interview 6, 20, 25-26, 29) as in one example statement that " clinical pharmacists can help report all ADR in hospital " (Interview 62) Regarding **the attitudes of physicians**, there was a need to help physicians understand that reporting ADR is the way to improve health care, not for inspecting mistakes. One of key informants who was a physician in medical school reported not knowing that there was drugs under the SMP, i.e., those bearing triangular label (Interview 48). This suggested that changing physician attitude might be needed to

start from medical school. All these opinions were agreed by all pharmacists and physicians interviewed (Interview 6-7, 20-21, 25, 31-32, 46, 48, 67-69) as in one interviewee said

" *Physician should be trained to be a good ADR recorder with positive attitude"* (Interview 64)

ADR Assessment

Once detected, ADR was further assessed by physicians. Working cooperatively, pharmacists rechecked for completeness and accuracy of important information before submitting to the FDA. For the ADR case reported to drug company by physician, product manager, sale representative, or persons from research and development depart was sent t to hospital for report completion (Interview 8, 42, 44). In ADR assessment, in view of drug company, there was usually a problem in obtaining necessary information since company representatives were not allowed to fully access the information in hospitals (Interview 8, 42, 43). Other argument was revealed from the interview with one company that *" The difficulty is not information accessing but the complexity of each drug is more crucial."* (Interview 24)

In terms of criteria for ADR assessment, the Practice Guideline for Adverse Drug Reaction Monitoring from the FDA was used (APRMC, 2001). Scientific journals and information from websites of US FDA and EU were also used for assessment among health professionals in hospital (Interview 1, 35-36, 38, 44).

Another problem in ADR assessment was that physicians had limited knowledge in ADR diagnoses. Many ADRs were those rare cases so they were hardly recognized. This problem was found more among young physicians (Interview 32, 35, 38). The example was from one physician response that " For me, some ADRs were hard for me to assess since I've no experience with them before." (Interview 40)

ADR Minimization

To solve problems in ADR episodes, based on ADR report database, 89.71% of all ADR cases were discontinuing the use of suspected drug, while a much smaller

portion (9.28%) was continuing the use. Based on a case study drug, coxibs, almost all of cases stopped using the drug (96.16%), and only 3.84% continued using. For statins, 86.53% of cases stopped and 10.97% continued using. Therefore, in most cases, discontinuation of the use of suspected drug was the first thing to minimize the risks. This was confirmed by interview results (Interview 8, 16) as stated " most of patients suffered from ADR were firstly off the drug." (Interview 8) After drug discontinuation, medical management was later given.

ADR Communication

ADR communication had two purposes; to minimize and prevent further damage at the place of event and to report to the FDA and occasionally to drug companies (Interview 8, 35-56, 44, 48). Based on interviews regarding the case study drugs, rofecoxib withdrawal according to serious ADR, various communications means had been done for preventing new cases of ADR. The prioritized means of communication included personal communication either in-person or telephone about the withdrawal and circulating warning letters to all health professionals. In the mean time, drug companies communicated in two levels; communication with regulatory agents and practitioners (Interview 25, 34-35). At regulatory level, the companies informed the FDA about the ADR and cooperated with official withdrawal decision. At practitioner level, the companies informed leading specialists about the reasons for drug withdrawal. In case of Rofecoxib, Merck company announced withdrawal worldwide on September 30, 2004. The next day, department of Regulatory Affairs of Merck (Thai) contacted the FDA for voluntary withdrawal in Thailand. Finally on October 5, 2004, an official withdrawal was announced by Thai FDA, and the official letters were distributed to all hospitals.

A drawback of communicating ADR with Thai FDA was evident. Both health professionals at the hospitals and drug companies reported that there was an insufficient responses or feedbacks from the FDA regarding quality of their reports, summary of ADR events from all over the country. In terms of report quality, there was a need to know whether the ADR detected and information filled was complete and accurate. For summary of ADR events, they would like to know if the ADR they reported were also found in other settings or regions, and similarity and differences of

ADR reported among hospitals (Interview 7-8, 16, 25, 35, 67-68) as in the statement *" the FDA should respond back to hospital in a certain period, we only got an annual SRS report that not in time for us."* (Interview 36)

6.2.3 Evaluation Process for Releasing New Drug from the SMP

The findings of evaluation process for releasing new drug from the SMP were grouped into the issues relating to experts opinion in evaluation process and criteria for evaluation. Advantages and disadvantages found in the process were detailed as follows.

In terms of experts' opinion, several problems were evident. At the evaluation for application to the SMP, 6 experts were used. On the other hand, only 2 experts were employed in the evaluation for releasing; one specialist physician in clinical study and one FDA officer (Interview 9, 11-12, 14, 18-19, 44-45, 56, 67-69). This was questioned for the " soundness" as the interviewee said that " If the FDA officer opposed to the expert's decision, he (she) can does nothing only accepts the expert's." (Interview 9)

Regarding the criteria for releasing new drugs from the SMP, the exact and detailed criteria were provided for the experts. Only a list of issues for consideration was given. Therefore the decision was solely based on the expert's personal experiences. Information for making the decision in this step was mostly from reports of other countries. Only about 10% of the safety information was from ADR reports of Thai population (Interview 18, 34, 60). The number of ADR reports submitted to the FDA was varied as in one expert said that *" No exact number of ADRs is set in the SMP, I used to assess 300 ADR report from one new drug depending on the incidence of the disease too."* (Interview 65) In addition, one company said *" I submitted 700 ADR reports for releasing new drug from the SMP."* (Interview 24)

In summary, in the process of the SMP, there was an inadequate expertise and well defined criteria for evaluation of new drug for the SMP. Under reporting was evident and needs improvement in ADR detection knowledge, cooperation, and attitudinal changes among health professionals.

6.2.4 The Assessment of the Process Component in the SMP System Using the Core Structure Indicators from Modified Delphi Method

Using indicators obtained from the Delphi method, based on results from various analyses described previously, there was only one element measured by the indicator of risk management system that existed (Table 6.3).

For the indicator "validity in ADR reporting from health professional", "Strictly performing in collecting ADR of drug company", "Certain criteria for the SMP releasing process", and " Transparency and accountability procedures in the SMP" were assessed as "No existence in the SMP". While the indicator "relevant criteria for each type of new drugs" could be assessed as "?" which referred to "the evidence from this study is not clear to assess."

Table 6.3 Assessment of the SMP System Based on Indicators from Delphi: Process Indicators

Type of indicators	No. in round 3	Final Safety Indicators of the SMP	Existence in SMP system
Evaluation process for application to the SMP (1)	1	Relevant criteria for each type of new drugs	?
ADRs management system (3)	2	Validity in ADR reporting from health professional	No
	3	Strictly performing in collecting ADR of drug company	No
	4	Risk management system: risk detection, risk assessment, risk minimization and risk communication	Yes
Evaluation process for releasing from the SMP (2)	5	Certain criteria for the SMP releasing process	No
	6	Transparency and accountability procedures in the SMP	No

Note: ? = the evidence is not clear to assess

6.3 Outcome Component

The elements in the outcome component were the results of both structure and process components. The outcomes were divided into three groups namely, administrative outcome, safety outcome and regulatory outcome.

6.3.1 Administrative Outcome

Two aspects of administration outcome were detailed. These included number and type of new drugs enter/released from the SMP, and average time in the SMP.

A) Number and type of new drugs enter/ released from the SMP (rate of releasing)

The findings on number and type of new drugs in the SMP reflected the effectiveness of the SMP process. From Delphi rounds, experts usually did not regard the number of new drug as important since it did not indicate the actual safety of drug use, but rather suggested the administrative efficiency.

To assess the effectiveness of the SMP administrative system, the data supposed to give such information should be from the New Drug Unit. Unfortunately, the data from the Unit was not ready for analysis. It took a long period of time to prepare such data for analysis. The topics presented below included the ratio of number of drugs on SMP to that off SMP, number of new drugs in SMP by production modes (locally manufactured, repacked, imported), companies of these drugs, and number of generics and trade names in the SMP.

Number of New Drug Licenses in the SMP Registration Profile

As of December 2004, there were 1,387 new drug licenses including 414 on and 973 off the SMP. Compared with the previous profiles, number of licenses of new drugs increased from 705 in 1998 to1224 in 2003 (Table 6.4). During 1998- 2004, the average number of new drug license per year was 1,056; 370 on and 649 off the SMP license. With the fact that a given trade name or generic name could be more than one license, therefore, of the total 1,224 licenses in 2003, 577 generic names and 569 trade names were found. Owner of these drug licenses were 104 drug companies from 31 countries including Thailand.

Ratios of number of new drug licenses on SMP to that off SMP decreased from 1:0.67 1998, to 1:2.35 in 2004. This meant that rate of releasing new drug licenses from the SMP was greater than that of new entries. Overall, with an average of ratio of number of new drug license on SMP to that off SMP was 1:1.75. Therefore, every one new license entry into the SMP, 1.75 releases happened.

Table 6.4 Ratio and Number of New Drug License (1996-2004)

Year	Total	On-SMP	Off-SMP	On : Off SMP
1996	n/a	334	n/a	n/a
1997	n/a	151	n/a	n/a
1998	705	423	282	1:0.67
1999	847	435	412	1:0.95
2000	925	373	552	1:1.48
2001	1,092	389	703	1:1.81
2002	1,210	409	801	1:1.96
2003	1,224	402	822	1:2.05
2004	1,387	414	973	1:2.35
Average per year	**1,056**	**370**	**649**	**1:1.75**

n/a = Not available
Source: 1996-2002 from the book of New Drug Registration published in each year: 2003-2004

Number of New Drug Licenses in the SMP by Production Modes

From 1998 to 2004, accumulative number of new drug licenses of drugs imported was far higher than that of local made or repacked drugs (Table 6.5). It also suggested that over time, accumulative number of license of imported drugs (both on and off SMP licenses) increased but with a lower rate than those of locally manufactured drugs and those repacked, as seen in ratios of 1:3.5:59.5 in 1998, to 1:2.3:36.3 in 2004 (Table 6.5).

Table 6.5 Ratio of Number of New Drug Licenses by Manufacturing Modes*

Year	Production Modes			Total	A:B:C
	Local Made (A)	Repacked (B)	Imported (C)		
1998	11	39	655	705	**1: 3.5: 59.5**
1999	14	40	793	847	**1: 2.9: 56.6**
2000	17	47	861	925	**1: 2.8: 50.6**
2001	20	55	1,017	1092	**1: 2.8: 50.8**
2002	26	69	1,115	1210	**1: 2.6: 42.9**
2003	30	66	1,128	1224	**1: 2.2: 37.6**
2004	35	80	1,272	1387	**1: 2.3: 36.3**

* Numbers in each production mode were cumulative

Comparing between number of new drug licenses on and off the SMP restriction, it was found that those still under the SMP had no significant change in number from 1998 to 2004 (Figure 6.4). On the other hand, number of new drugs licenses has been increasing for all production modes from 1998 to 2004 (Figure 6.5).

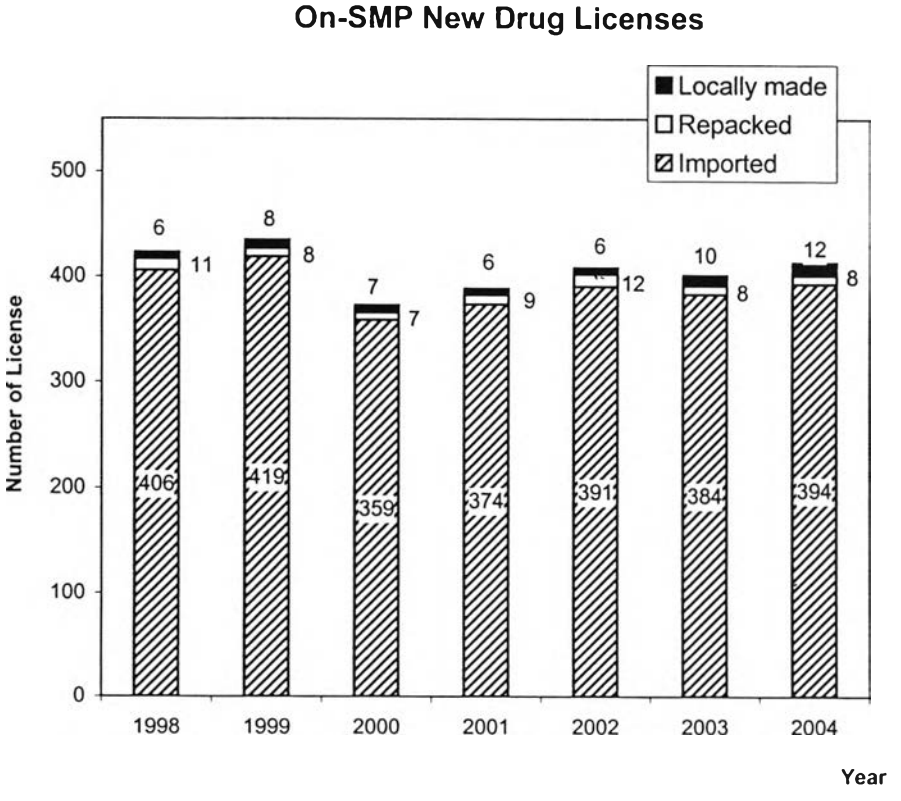

Figure 6.4 Number of New Drug Licenses by Production Modes of Drugs On SMP

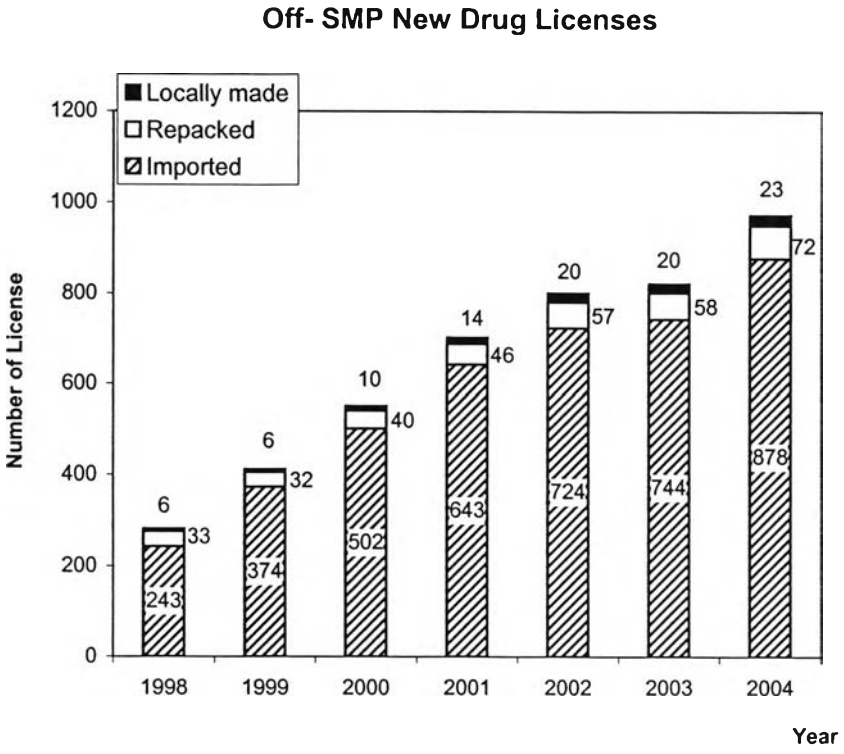

Figure 6.5 Number of New Drug Licenses by Production Modes of Drugs Off SMP

B) Average time of the SMP period (rate of releasing)

Of these 1,224 licenses in 2003, only 183 licenses could be traced back to their date of entry to the SMP (Table 6.4). These 183 licenses consisted of 2 locally made, 7 repacked and 174 imported drug licenses. Compared with a 2-year SMP period, average time under the SMP of these 183 licenses was longer (mean 3.18, S.D 1.12 and median 2.99 years). The range was found highly wide, from 0.70 to 5.73 years.

It was found that two thirds of the licenses were under the SMP period for 2-3 years (37.71%, 69 of 183), followed those under 3-4 year (31.15%, 57 of 183) (Figure 6.6). A somewhat big number of licenses under the SMP for 5 years or longer was found (12.57%, 23 of 183).

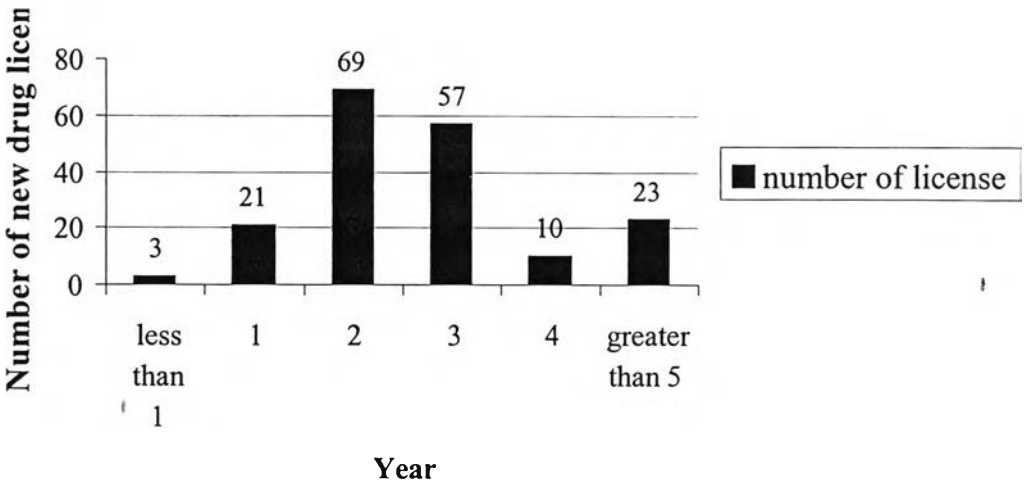

Figure 6.6 Number of Licenses by Duration under the SMP

Data from interviews showed various rage of the SMP period, as stated from one drug company that *" From my experiences, the SMP period ranged from 6 months to 2 years depending on experts consideration or the activeness of the FDA officers."* (Interview 45) Another company also confirmed the evidence of short period in the SMP as she said *" One of my new drug used to be in the SMP only 1.8 years."* (Interview 56)

For the biological products, data from the interview with the FDA officer showed the average time in the SMP greater than 2 years as in the statement *" The biological products normally take 3 years in the SMP since the experts in this area are insufficient and there is a complexity in .evaluation of this kind of product."* (Interview 14) For new chemical entity, the SMP period took more than 2 years as one company said *" If new drug is new chemical entity, it took more than 2 years in the SMP. While the new strength or dosage form, the SMP period took less than 2 years."* (Interview 58)

6.3.2 Safety Outcome

The findings in safety outcomes were focused into issues of ADR incidence, number/quality of ADR reports, ADR type and seriousness, and time to detect ADR.

A) ADR incidence

Based on the information in database of ADR reports, it was impossible to estimate the incidence of ADRs. The FDA was also unable to provide such number of incidence and ways to estimate them. However, some interviews and feedbacks from Delphi rounds provided some insights on the methods to identify the ADR incidence. They proposed that the most practical approach to estimate the ADR incidence of new drugs was probably by using sale volume as the denominator. Some companies used sale volume to estimate number of exposed patients based on given dosages for specific indications. This method was found to be consistent with the one suggested by results from the last round of Delphi that the incidence could be derived from number of ADR divided by number of exposed patients (Interview 42, 44).

B) Number and quality of ADR reports

It was found that from a total of 84,870 ADR reports, 4,862 (5.73%) were those of new drugs (referred to Table 4.1). By average, in each year, 10.19% were reports of new drugs.

Based on 82,787 licenses of all drugs (FDA, 2004), there was 1.02 reports per one drug license. For new drugs of with an accumulated 1,224 licenses as of 2003 (, it there was 3.97 reports per license. However, the number of ADR used as numerator was from the year 2002. Therefore, if the year of data matched, a higher proportion of ADR report to number of license would be higher.

From these numbers of reports per drug license, it roughly suggested that ADR of new drugs were more likely to be detected and reported.

In terms of quality, based on findings from the interviews, quality of ADR reports under the SMP was somehow questionable. This was due to the fact monetary payment might have induced biased reporting of ADR events by health professionals. This could have been done in the way that some information filled into the form may not be fully accurate. But the argument to this was found as said by one company that *" It was claimed that inaccurate ADR report might happen so I have to spend some*

money to health professionals at the hospital to fill the data by their own not by the sale representatives." (Interview 56) Under reporting of the target drug could also happened (Interview 9,11,17,56,68 and feedback from Delphi) as confirmed in the statement " It is impossible to report all ADR of new drug since the physicians are overloaded from a huge number of patients now." (Interview 7) From the analysis of ADR report database, some important information was lost. For example, there were 101 and 133 ADR events with "serious" ADR of Coxibs and Statins, but when exploring level of seriousness, only 99 and 119 events were complete, with a loss of 1.98% and 10.53% loss of information (see Table 4.2 and 4.11 for more detail).

C) ADR types and seriousness

In this study, analysis on Coxibs and Statins drugs were done as case study drugs. It was found that ratio of serious to non-serious ADR was 1:5.7 for Coxibs, and 1:3.9 for Statins (referred to Table 4.2 and 4.11). However, it was difficult to determine since ADRs of all new drugs cannot be analyzed. Even though an exact number of ADR type and severity of new drugs could not be obtained to summarize the trend, results from interviews suggested that most ADRs of new drugs were non-serious (Interview 8, 13, 24) as in the statement from a physician *" I usually found non-serious ADR such as rash, nausea and vomitting."* (Interview 13) Results from Delphi further suggested that number of serious ADRs for a given drug name would be a good indicator of safety of new drugs.

ADR types of these case study drugs were found quite similar to all other drugs in terms of body systems affected (Referred to Tables 4.8, 4.17). The most common ADRs were found in dermatologic system like other drugs.

D) Time to detect ADR

Based on case study drugs, during the SMP period, less ADRs were reported. Once off the SMP, reports of ADR were rising. This was true for both Coxibs and Statins (referred to Figures 4.1, 4.2).

In terms of time till the first ADR detected, based on the two case study drugs, the duration to detect the first ADR varied ranging from 126 days (Rofecoxib), and 797 days (Simvastatin) but all occurred during the SMP period (Table 6.6). Time to

first ADR detected was also dependent upon type of drugs. In this case, Coxibs ADRs were more likely to be detected with a shorter period of time.

Table 6.6 Time till the First ADR Detected of Coxibs and Statins

Drug	Date entered the SMP	Date the first ADR detected	Time till the first ADR detected (Days)
Coxibs			
Celecoxib	April 30, 1999	September 17, 1999	140
Rofecoxib	November 15, 1999	March 21, 2000	126
Statins			
Simvastatin	April 23, 1991	July 1, 1993	797
Pravastatin	March 2, 1992	September 25, 1997	1,651
Fluvastatin	October 24, 1995	April 20, 1997	545
Atorvastatin	November 5, 1997	October 21, 1998	352
Cerivastatin	April 30, 1998	October 13, 1999	531

6.3.3 Regulatory Outcome

The regulatory measures are the important indicators to reflect new drug safety. The component was there result of all other previous structure and process components of the SMP. Various regulatory measures to new drugs in the SMP included drug withdrawal, labeling change, re-classification, warning and intensive study.

Based on the data from FDA, there were 394 new drugs (item) accumulated from 1991 to June 28, 2003, applied to the SMP, resulting in 766 new drugs licenses. About two thirds of these 394 drugs (62.9%) were released from the SMP and received unconditional approval (Table 6.7).

In terms of withdrawal, most drug withdrawal were either voluntary or forced because no manufacturing, repacking or importing within the 2-year period under the Drug Act law (Table 6.7).

Table 6.7 Number of New Drugs and New Drug Licenses by Status*

Status new drugs	Numbers of new drugs	Numbers of drug licenses
Total new drugs applied	394	766
Received unconditional approval	248 (62.94%)	509 (66.45%)
Withdrawal	112 (28.43%)	189 (24.67%)
Voluntary withdrawal	51	96
Regulatory forcing for withdrawal	1	2
Withdrawal due to not manufactured/imported during 2 years	60	91

Source: Data from Thai FDA as of June 28, 2003

* There was a loss of data.

In terms of labeling change, re-classification and warning, there was a scarce in information. However, results from interviews suggested that these measures did exist (Interview 7, 222, 44). The document analysis also found that in 2002 some regulatory measures were carried out into effect. There were labeling changes in 4 groups of drugs including antihistamines, anti-tuberculosis, combined oral contraceptives, HMG-Co Reductase Inhibitors. In addition, drugs under the intensive study were forced to monitor of safety in all hospitals. These drugs included Equine rabies immunoglobulin (ERIF) and Sibutramine (Reductil®) From the minute of the meeting of Subcommittee of ADR (31 March 2005), it was found that there were labeling changes due to class effects of Coxibs drugs.

Finally, it was found that warning letters were the most used measures to communicate drug safety issues to health professionals (Interview 1, 22).

In conclusion, most new drugs were under the SMP for 2 years as expected. However, quality of ADR reports was still problematic. The duration to detection of the first ADR varied greatly from half a year to 5 years. Drug withdrawals were usually voluntary in nature, and the forced one due to no product production within 2 years. The most common regulatory measure was warning letters.

6.3.4 The Assessment of the Outcome Component in the SMP System Using the Core Structure Indicators from Modified Delphi Method

Using indicators obtained from the Delphi method, based on results from various analyses described previously, there were two elements measured by the indicator of " case report of ADR from world wide" and " detection of serious ADR" that existed (Table 6.8).

For the indicator "incidence of ADR (per number of patient use) with sufficient number of new drug exposed patients" and efficiency in ADR reporting in Thailand" were assessed as "No existence in the SMP".

Table 6.8 Assessment of the SMP System Based on Indicators from Delphi: Outcome Indicators

Type of indicators	No. in round 3	Final Safety Indicators of the SMP	Existence in SMP system
Safety indicator (4)	1	Incidence of ADR (per number of patient use) with sufficient number of new drug exposed patients	No
	2	Case report of ADR from world wide	Yes
	3	Efficiency in ADR reporting in Thailand	No
	4	Detection of serious ADR: ADR type A, ADR type B, unlabelled ADR, permanent ADR, death from ADR	Yes

In conclusion, the answer of the research question "how effective is the SMP in ensuring safety of new drugs in Thailand?" is inconclusive. However, some evidence suggested that the process component, especially ADR detection was the main factor to the success in establishing new drug safety profile in the country. In achieving so, an improvement in structure and process in the SMP is needed to facilitate better ADR detection.