CHAPTER III

METHODOLOGY

This chapter describes the rationale for study framework and design based on relevant concepts and theories, and methodological considerations including, study samples, data source and collection, and data analysis.

3.1 Study Framework and Study Design

To answer the research question "How effective is the SMP in ensuring safety of new drugs?" it was necessary to primarily identify new drug safety profile and to trace back their origins in the process of the SMP or any related systems affecting the new drug safety profiles. Exploring the relationship of the structure, process, and outcome among the SMP system could help explain how new drug safety profile was performed. Strengths and weaknesses of these relationships to safety profile were also discovered. Therefore, mixed methods were designed in this study.

Due to the complexity of the SMP, this study took the observational approaches using both quantitative and qualitative methods. Both techniques are distinctive in what a researcher looks at, how a researcher sees, and what a researcher can learn. In qualitative methods, an "Emic" view is a key feature to provide rich or thick descriptions and well-founded rationale for explaining the underlying reason for certain behavior. The principle of qualitative research, therefore, is understanding the context in which decisions, actions and events occur (Yoddumnern-Attig, Attig, & Boonchalaksi, 1991).

Like other methods, qualitative method also possesses disadvantages. Misleading is a major precaution for all researcher(Yoddumnern-Attig et al., 1991). There is a conflicting role of researcher while performing qualitative research: participant-observer's role and researcher's role. Good rapport emerged from the participation-observation transaction can lead to an emotional involvement which could be a source of bias in the data. In contrast, in researcher's role, the researcher uses very possible means to gain a variety of in-depth information with no emotional

involvement. Nonetheless, balancing these two roles is the way to solve such problem (Podhisita, 1991).

In quantitative method, it advocates inquiry of rigorous, reliable and verifiable data, aggregation of data, and readily systematic conduct of statistical and empirical hypothesis testing (Berg, 1998). With the purpose to understand the facts by means of systematic empirical observation and to generate empirical evidence from such observation, these two techniques, qualitative and quantitative methods, were employed. The different but complementary natures of the two methods made this study possible (Giacomini, 2001).

To improve reliability and validity of data, triangulation was performed using a variety of methodology and multiple sources of data. Various methods including documentation study, modified Delphi method, semi-structure interviews, and a case study strategy were performed for analyzing the SMP system. A comprehensive summary of methods used for answering the specific study objectives are shown in Table 3.1.

Table 3.1 Methods used for study specific objectives

General objectives	Specific objectives	Documentation study	Modified Delphi method	Semi-structured interview	Case study strategy
To analyze Thai new drug SMP and to identify safety indicators of the SMP system.	To perform a situational analysis of the SMP system regarding structure, process and outcome.	yes	-	yes	yes
	To identify safety indicators of the SMP.	yes	yes	-	-
	To elaborate process affecting safety profile and regulatory measures of new drugs.	yes	yes	yes	yes

3.2 Study Samples

Study samples in this study were from different sources.

For documentation study, studied samples were from 8 major sources; 1) Spontaneous report of ADR, (annually) Thai FDA, 2) Adverse Product Reaction Bulletins, APRMC, 3) The Adverse Drug Reaction minutes, 4) New Drug Listing Book during 1991 to 2003 from the Thai FDA, 5) Annual reports of Department of Medical Sciences, 6) Standard Operating Procedure: Safety Monitoring Programme, 2001, 7) Annual Report of Food and Drug Administration, 8) Related research.

For modified Delphi method and semi-structure interview, samples were key informants from stakeholders in the SMP system. These informants included the Thai FDA officers in New Drug Unit and in the APRMC, experts of new drug of the Thai FDA, persons responsible for safety monitoring from pharmaceutical companies and hospitals, and academicians in related fields. Total number of informant contacts in semi-structure interview was 73 of which 8 declined, finally got 65 informants. For the Delphi experts, of 45 informants, 32 also served as key informants in semi-structure interview. Thirteen were declined; finally 32 experts remained in the study expert panels.

For case study strategy, Coxibs and Statins drug were studied samples. There were 4 drugs in Coxibs; 1) celecoxib, 2) rofecoxib, 3) parecoxib, and 4) etoricoxib. For Statins, 6 drugs were studied samples including 1) simvastatin, 2) pravastatin, 3 fluvastatin, 4) atorvastatin, 5) cerivastatin, and 6) lovastatin.

3.3 Methods of Data Collection

To gain an in-depth and systematic understanding on the constraints and problems affecting structure, process, outcome and relations among these components in the SMP, various methods of data collections were conducted. Details of each method used in this study are described as follows.

3.3.1 Documentation study

This technique obtained a variety of data from different sources including annual reports of the Thai FDA, Adverse Product Reaction Bulletins, Adverse Drug Reaction Minutes, New Drug Registration Listing Book (1996 to 2003) from Thai FDA, annual reports of the Department of Medical Sciences, related research, and related files from available sources. In addition, data from website of the Thai FDA were also investigated.

The majority of new drug registration data compiled in this study was in electronic format (MS-Excel spreadsheet files) from 1991 to 2003. Furthermore, data from the previous annual versions of New Drug Registration Listing Book (1996-2002) were also retrieved.

The majority of ADR profiles were retrieved from the Book of Annual Reports of Spontaneous Reporting System (SRS) from 1991 to 2002, from APRMC, Thai FDA. All ADR and related components from ADR reports in Thailand were studied.

According to data confidentiality in few organizations, some essential data could not be retrieved. All studied documentations were officially established.

3.3.2 Modified Delphi Method

A modified Delphi method was employed in this study to obtain safety indicators of the SMP. Delphi method has been used in various fields such as education, business, information and management, and health care (Rowe & Wright, 1999). The aim of Delphi method is to obtain the most reliable consensus based on opinion of a group of experts. These experts are given a series of intensive rating questionnaires. The experts are expected to rate each question (or item) on a rating scale with an elaborate feedback comments/opinion on the question. Key features of the Delphi are anonymity, repeated iterations of knowledge elicitation, resolution of differences and advocate of refined opinion and group feed back. In other words,

Delphi does not aim to elicit a single answer or arrive at a consensus but to obtain as many high-quality responses and opinions as possible on given issues from the panel of experts to enhance decision-making.

The advantages of this method are obvious. These include overcoming of undesirable effects of group interaction, retaining the positive effects of interactive group judgments, and avoiding the pitfalls of face-to-face interaction such as group conflict and individual dominance (Rowe & Wright, 1999)The use of Delphi method in this study deems appropriate for identifying safety indicators of the SMP since no safety indicators have been established and no historical data are available in Thailand (Drug Control Division, 2001; Patanawong, 2001)

Even with its obvious advantages, limitations of Delphi method are not uncommon. These include conceptual and methodological inadequacies, potential for sloppy execution, insufficiency of detail in questionnaires, and limited choices for the experts. Furthermore, since the results depend largely on a group opinion, applying such results to general population may be limited. Occasionally limited value of feedback and consensus, and instability of responses among consecutive Delphi rounds are also found (Dijk, 1990; Rowe & Wright, 1999)

With all these pros and cons of the use of Delphi method, a research suggests a combination of techniques could help achieving a better consensus (Dijk, 1990). A good combination for a three-round Delphi study may consist of 1) the individual interview in the first round to motivate participations to join a Delphi panel, 2) a group interview for the second round to support discussion and self-confidence and 3) mailed questionnaire for the final round to obtain final votes or conclusive decisions. Thus, to better fit to Thai context, this study used a combination of Modified Delphi techniques. The study was conducted an individual interview in the first round and mailed out the questionnaires in the second and third rounds in order to avoid panel conflicts from face-to-face interaction.

A member of Delphi experts had to work in the area related to the SMP for more than 2 years. Forty-five experts were invited to be experts panel from all stakeholders related to the SMP i.e. Thai FDA, department of Medical Sciences, drug

company, academic both from pharmacy school and medical school, and hospitals. Thirteen were declined, 32 experts were remained as expert panels.

3.3.3 Semi-structured Interviews

This method aims to obtain an in-depth understanding on the situation and nature of the SMP system and to determine relationships among structure, process and outcome in the SMP through the perspective of interviewee rather than the interviewer's. Most interviews were conducted in Bangkok. Some were conducted in a province in the northeast region of Thailand.

Key informants from stakeholders in the SMP system were interviewed. These informants include the Thai FDA officers in New Drug Unit and in APRMC, experts of new drug of the Thai FDA, persons responsible for safety monitoring from pharmaceutical companies and hospitals, and academicians in related fields. Snowball techniques were performed to get key informants in each stakeholder. Some interviews were performed as in-depth interview on a specific issue to obtain both broader and more in-depth information.

Contents were a slightly different from interview to interview little due to the different roles of interviewees in the SMP. Each interviewee was asked for a permission to be interviewed and anonymous identify was applied when appropriate. Voice recording and note taking were used when permitted.

In the search of key informants, the informants were firstly asked to share their experience to this study by telephone or face-to face contacts. Of 73 informants contacted, eight declined to participate with given reasons including not working in SMP related job for more than 4 years (1 person), having no time for the interview (2 persons), not being keen in this area (1 person), not involving in the SMP process (3 persons) and no response after the third attempt to contact (1 person).

Semi-structured interview questions developed by the researcher based upon prior research and documentation review. Interview questions were firstly tested by 3 informants. During interviews, new issues emerged and have been used in the subsequent interviews.

The details of major contents explored by means of a semi-structured interview were in Appendix B.

3.3.4 A Case Study Strategy

This method aims to analyze safety profile of a specific new drug or a group of drug, both drugs still under the SMP and those already released from the SMP. A case study strategy explained what exactly happened to new drugs in terms of how safety profile of new drugs was implemented, roles and actions of stakeholders and what is the key step most affecting the success or failure of SMP process. Based on case study strategy, one collects sufficient information systematically from particular persons, social settings, events or groups. A variety of methodological approaches such as documentation review, interview, or participant observation may be employed (Berg, 1998). Previous studies had succeeded in a use of a case study method to obtain in-depth understanding on various processes, especially processes in an organization with limited time and resources. In addition, this method provides an analysis of phenomenon within the existing context and process (Hongsamoot, 2002; Kiatying-Angsulee, 2000)

In this study, Coxibs and Statins drugs were selected as case study drugs. The reasons for selecting these two drug groups were as follows;

1. There was one drug in each group already withdrawn from the market due to its serious ADRs. Rofecoxib, a coxib drug, was withdrawn on September 30, 2004. Cerivastatin, a statin drug, was withdrawn in 2001.
2. At withdrawal, the SMP status of these two drugs was different. Rofecoxib was already off the SMP while cerivastatin was still on the SMP.
3. The use of these two groups of drugs was increasing in Thailand.
4. The voluntary withdrawal by the companies were done in an urgent manner.

In case study strategy, the main focus was on the safety profiles of Coxibs and Statins, for example, number of ADRs, time to detect the first ADRs, type of ADRs,

seriousness of ADRs, ADRs management system, etc. Furthermore, other drugs in Statin and Coxib groups were also explored to compare the decisions and actions on the safety issues emerged in real practice. With a vast amount of data from interviews, documentation study and ADR profile from APRMC, more realistic decisions and actions to better handle safety of new drugs could be drawn.

3.4. Data Collection Procedures

4.1 The study protocol was approved by the Ethical Committee of Faculty of Pharmaceutical Sciences, Chulalonkorn University, on June 2004. Official letters with brief summary of the protocol were then sent to the Secretary General of the Thai FDA and Director general of the Department of Medical Sciences, asking for their permissions to collect data.

4.2 Data collection was conducted by a) documentation review, b) Modified Delphi method, 3) semi-structured interview, and 4) case study strategy.

4.3 During June 2004 to August 2005, documentation review was conducted on data from organizations including the Thai FDA, Department of Medical Sciences, hospitals, academics and pharmaceutical industry. Information from websites of the Thai FDA was also obtained.

4.4 Semi-structured interviews were conducted among key informants from each stakeholder. The first interview was carried out on September 7, 2004 and the last one was on April 7, 2005.

4.5 The first round of Modified Delphi method was performed from September 7, 2004 to February 8, 2005. The second round was conducted from April 18, 2005 to June 13, 2005. From June 23, 2005 to August 14, 2005 the final round of Modified Delphi method was performed. Safety indicators of the SMP were completely identified on July, 2005.

4.6 Related data of Coxibs and Statin drugs, as case study drugs, were retrieved and analyzed at the same time the other data collections were performed.

3.5 Method of Data Analysis

With a qualitative nature of the data, this study undertook a systematic, formalized and comparable way of analysis to achieve valid findings (Podhisita, 1991). The data were analyzed using both qualitative and quantitative techniques. Data analysis was performed in each type of methods as follows.

5.1 Essential **documentation** was analyzed before the semi-structured interview to give fundamental and theoretical information to facilitate further step of the study, the interviews. Thus, content analysis was performed for these textual data by categorizing particular items in documentation. With this technique, reliability and validity of the findings through precise counts of words was established (Silverman, 1993). In addition, quantitative data such as number of ADRs, number of new drugs, time to detect the first ADRs, etc., were analyzed using descriptive statistics. Information on safety indicators was used in the following Delphi method.

5.2 **Modified Delphi method**. The first round of Delphi was interviewing to list all possible safety indicators. These indicators were then categorized into structure, process and outcome indicators according to the conceptual framework. Data from the second and third rounds were analyzed by frequency, percentage of agreement and median in each feedback item of the safety indicators. Content analysis was performed on these textual feedback data.

5.3. All **semi-interview data** were analyzed using content analysis. Key words were set and organized. Core contents of the interview data were categorized from interview transcriptions and notes after each interview.

5.4 Data from the **case study drugs**, Coxibs and Statins, were both qualitative and quantitative. Analysis was performed as in previous methods.

5.5 Findings from all analyses were concluded and triangulated to obtain certain relationships among structure, process and outcome components of the SMP system to the new drug safety profile.

In conclusion, qualitative and quantitative data analyses were used in this study; content analysis for qualitative data and descriptive and analytical statistics for

quantitative data. Data from each method, sources of data and data analysis were summarized in Table 3.2.

Table 3.2 Sources of data and data analysis

No	Types of Data collection	Documentation study and Case study strategy								Semi-interview and case study strategy	Modified Delphi	Data analysis
		1	2	3	4	5	6	7	8	9	10	
1	Actual goal of the SMP	√					√			√		Content analysis
2	Organization and personnel of New Drug unit and APRMC, in Thai FDA	√					√			√	√	
3	Organization and personnel of departments dealing with the SMP, in Drug Company									√	√	
4	Organization and personnel of Health care facility	√							√	√		
5	Policy, law, regulation and guideline related to the SMP	√					√	√				
6	Evaluation process and criteria for application to the SMP	√					√			√	√	
7	Number of drugs assessed regarding chemical and physical properties					√				√		frequency
8	ADR reporting system	√					√			√		Content analysis
9	ADR (risk) management system	√								√	√	
10	Evaluation process and criteria in releasing new drug from the SMP						√			√	√	
11	Number of new drugs enter/release from the SMP				√				√			Frequency Mean
12	Types of new drugs enter/release from the SMP				√				√			Frequency Percentage Ratio
13	Trade name and chemical name of new drugs				√							
14	Manufacturer and distributor of new drugs				√							

Table 3.2 Sources of data and data analysis (Continue.)

No	Types of Data collection	Documentation study and Case study strategy								Semi-interview and case study strategy	Modified Delphi	Data analysis
		1	2	3	4	5	6	7	8	9	10	
15	Date get conditional/ unconditional approval of new drugs				√					√		Frequency Mean Median
16	Average time of the SMP period				√				√			Mean Median
17	Number of ADRs	√										Frequency Percentage
18	Type and seriousness of ADRs	√										
19	Name of drugs causing ADRs	√										Frequency
20	ADR case report		√						√			Content analysis Frequency
21	Ratio of ADRs of new drugs per existing drugs	√							√			Ratio
22	Ratio of serious ADRs per non-serious ADRs of new drugs	√							√			
23	Time to detect ADRs of new drug	√							√			Mean Median
24	Number and type of ADRs of new drugs on the SMP and off the SMP	√							√			Frequency Percentage
25	ADRs incidence								√			Incidence rate
26	Quality of ADRs report								√			Content analysis Frequency
27	Number and type of regulatory measure or activity related to new drug		√	√				√				Content analysis Frequency Ratio
28	Types of new drugs that having different regulatory measures		√	√				√				Frequency

Table 3.2 Sources of data and data analysis (Continue.)

No	Types of Data collection	Documentation study and Case study strategy								Semi-interview and case study strategy	Modified Delphi	Data analysis
		1	2	3	4	5	6	7	8	9	10	
29	Safety indicators of the SMP								√		√	Content analysis Median Percentage
30	Factors contributing to achieve "safety new drugs"	√	√	√	√	√	√	√	√	√	√	Content analysis
31	Weakness and strength in the SMP system	√	√	√	√	√	√	√	√	√	√	Content analysis
32	Suggestions to improve the SMP	√	√	√	√	√	√	√	√	√	√	Content analysis
33	Experiences of each interviewee in the SMP									√		Content analysis

Sources of data

1 = Spontaneous report of ADR, (annually) Thai FDA

2 = Adverse Product Reaction Bulletins, APRMC

3 = The Adverse Drug Reaction minutes

4 = New Drug Listing Book during 1991 to 2003 from the Thai FDA

5 = Annual reports of Department of Medical Sciences

6 = Standard Operating Procedure: Safety Monitoring Programme, 2001

7 = Annual Report of Food and Drug Administration

8 = Related research

9 = Interview Data

10= Feedback data from Delphi