CHAPTER VII

DISCUSSION

This chapter contains a comprehensive discussion of the SMP by firstly discussing on the major findings in each component in the SMP and illustrating the origins of safety profile of new drug in the SMP. The strengths and limitations in this study were criticized.

7.1 Situation of the SMP System

7.1.1 Structure Component

It was found that even though the first intention for **policy** in implementing the SMP was not fully meant for drug safety monitoring, functioning as "administrative tool" of the Thai FDA, the system itself evolved over time for a better approach to ensure a safe drug use in health care system. This was different from other countries. Comparing to other countries like Japan and the New Zealand, all of matters related to new drug from the entry of submission for drug registration to the post-marketing surveillance are assigned from the law and there are standard procedures in all necessary issues, such as manual or guidelines and performance standards particular in processing time of each procedure (New Zealand Medicines and Medical Devices Safety Authority 2001; Japan Pharmaceutical Manufacturers Association 2002). This obligatory deviation may be come from the seriousness of the policy and policy makers among countries.

For the existence of a clear **guideline** for monitoring ADR of new drug in hospital, this study found the evidence but not fully linked to the real practice. Health personnel at hospitals performed the new drug safety monitoring in partial procedure of existing SRS ADR monitoring, not in intensive manner. This was also supported by Tantives et al. (2003) that there was no clear policy guidance of safety monitoring mechanisms especially at the hospital level that might result in insufficient and variety of the ADR monitoring system (Tantives, Tangcharoensatien et al. 2003).

In agreement with Kiatying-Angsulee (2000), this study found that there was inadequate **information** system in the SMP especially in the Thai FDA organization. This might due to insufficient co-operations among the divisions and unclear practical policy as confirmed in the interview

" The FDA should design a system to link all information among the divisions in the FDA it self." (Interview 22) And also evident by another interview as stated that *" The FDA performs the activity in each division in separately manners and no one could link all information together."* (Interview 61)

There were crucial examples to confirm this situation. The "mixed field" format of the data files of new drug registration was not designed for further usability both in the New drug Unit and others units among the Thai FDA. Therefore, this was not surprising if this database has never been used for any advanced and comprehensive analysis. For the ADR database, the level of perceived importance of analysis and summary various aspects of ADR events depended on the leading person in the APRMC. In addition, the standard procedures or policy to guide what aspects of ADR events to analyze and disseminate to health professional and public has not been put in an established policy.

With the occurrences as " administrative tool" of the SMP, there were some consequences in the latter components, processes and outcomes, of which needed further improvements.

7.1.2 Process Component

Regarding process of the SMP, the **evaluation process** faced the difficulties due to inadequate expertise and sound criteria for evaluation of new drugs in the SMP. Although some experts were seen as "not exactly keen in the area" or " being questioned about the conflict of interest", the evaluation process in the SMP both in new drug application and releasing new drug from the SMP still depended on the external experts. The Thai FDA was claimed as *" impossible to build the internal expertise"* due to there was no intentional policy as one interviewee said

" With the current organization structure and the politic influences on all activities of the FDA, it is impossible to establish the internal expert in the Thai FDA." (Interview 55)

It was clear that there were no **criteria** in the evaluation process both for new drug application and for releasing new drug from the SMP. As for the example, it was found "no criteria" in every interview with the experts and also in the FDA officers as shown in the statement that

" From my 10-year experiences working as the external expert, there are no criteria for evaluating al all. This is a basic problem in dealing with the FDA." (Interview 50)

There were some suggestions from the interviewees that *" The FDA should perform a standard criteria in evaluating for both in the application and the releasing process."* Some evidences showed the **differences** in evaluation for each type of new drugs as revealed in the interviews from the companies *" New chemical entity took longer period than new strength or new dosage form"*. And also being confirmed by the FDA officers and the data analysis that *" biological products usually took longer period than other drugs."* With this finding, comparing to the New Zealand, they perform different actions to different types of new drug (New Zealand Medicines and Medical Devices Safety Authority, 2001). They classify new drug into 3 types depending on the level of risk: 1) new higher-risk medicine, 2) new intermediate-risk medicine, and 30 new lower-risk medicine. The procedures from evaluation process to post-marketing phase are specifically designed for each type of new drugs. This may be applied to the SMP for reshaping current procedures for all new drugs to the more appropriate ones.

Under reporting of ADR was evident. No exact number or rate of under reporting was discovered in this study and the ADR reporting of new drugs were performed with voluntary. The ADR reports of new drugs in the SMP were gathered by company's requests to physicians with doubtful of quality of the reports. Furthermore, the limitations of ADR knowledge and cooperation among health professionals were found. Therefore there are needs of improvement in ADR

detection knowledge, cooperation among health professionals, and attitudinal changes among health professionals. These were not only found in this study but also found in the others'. From the study of Kaewpaneukransee (2000) found that only 8.8 % of ADR reports of new drugs were complete and accurate. Tantives, Tangcharoensatien et al. (2003) also confirmed the evidences of under report that health professionals reported ADR at very low rate due to the perception that reporting the ADR was not beneficial to them. In addition, it was worth comparing with those of other countries. Comparing to Japan, all drug companies have to comply with the Good Post-marketing Surveillance Practice. Besides, it is mandatory to have personnel in department of Post-marketing to effectively implement and perform all tasks of post-marketing including new drug intensive monitoring (Japan Pharmaceutical Manufacturers Association 2002).

Another reason for low performance in ADR detection in the SMP system might be from the fact that the monitoring system has been parallel with, or even within the SRS system. This caused problems since reporting ADR under the SRS is voluntary. Therefore it is easy for responsible persons to get used to the voluntary manner, and have not performed the intensive reporting as expected by the SMP.

Regarding cooperation between drug companies and hospital, it was a conflict about the responsibility of gathering the ADR report. Based on the SMP, persons in drug companies are assigned for data gathering. However, it was found that persons from companies had hard time collecting data at the hospitals. They were not considered one of the hospital team. Even worse, regarded as the mere drug seller, there were not allowed to access some confidential patient data. This situation was quite different from Japan. Persons from drug companies were able to conduct the official intensive monitoring activity of new drugs with health professional team in hospital for 6 months. This activity can generate signal of new drug safety (Japan Pharmaceutical Manufacturers Association (JPMA), 2003).

Suggestions for Improving the ADR Management in the SMP

The evidences suggested that safety profile of new drug in the SMP has not been accomplished. This was because the most important element in the SMP process,

ADR detection, was not performed in an effective manner. When considering back at the problem of the whole system of the SMP, it was found that the crucial element of the SMP structure, or the policy regarding the SMP, was not officially enacted as laws. Therefore, personnel involving in ADR detection process have not put adequate effort for a complete and accurate outcome.

To effectively make the policy work, other countries have established standard procedures, guidelines and protocols for all necessary procedures involving post-marketing activities. These documents are readily available to public (Japan Pharmaceutical Manufacturers Association, 2002; New Zealand Medicines and Medical Devices Safety Authority, 2001).

Information from the interviews and Delphi also provided fruitful suggestions for the SMP improvement. The improvements were suggested in 4 aspects as presented below.

a) Good ADR monitoring system in hospital. The suggestion of "the pop-up ADR warning in computerized system" would help health professionals especially physicians aware of safety of new drugs at the time they prescribe. Another mechanism for the improvement was "providing the ADR report form every possible detection unit" such as in the ward, diagnostic room, or using online reporting system.

b) Responsible Persons. Clinical pharmacist or pharmacist in hospital had been stated most often from the interviews that they could provide more effective ADR monitoring activity. The national body, performing the safety monitoring activity, funded by some fees from drug companies was also proposed.

c) ADR report form. The interviews and feedbacks from Delphi revealed that it would be better if the ADR report forms were designed into 2 types. The first one, simplified form, for physician or nurse to detect suspected ADR. The second one was the complicated form for pharmacist to assess and report the suspected ADR to the FDA.

d) The incentive for new drug ADR reporting. The incentives might be provided to health professionals in various strategies as a tool to motivate the

reporting. Some persons suggested that a small gift or some monetary payment would be a good motivation. Some suggested setting a protection system from being sued to the reporter was an important tool.

7.1.3 Outcome Component

In terms of outcome component, administrative outcome, duration under the SMP varied greatly but the causes of such differences was not fully understood. Of 183 example new drugs, the mean of the SMP period was 3.18 years with the S.D. at 1.12. The range was found highly wide, from 0.70 to 5.73 years. These were confirmed by the interviews, the SMP ranged from 0.50 to more than 3 years. The appropriate monitoring period of new drug was not achieved through this study. But existing period in other countries are varied from 6 moths in Japan to 3 years in the US (Japan Pharmaceutical Manufacturers Association, 2002; Japan Pharmaceutical Manufacturers Association (JPMA), 2003).

The number of ADR reports was low during the SMP period and increased after the new drugs were off the SMP restriction. In the opposite to the study of

ADR incidence could not be achieved but found the evidence in some companies. Regarding regulatory measures, the most effective way of communication about ADR was warning letters. With this channel, this may be applied to the FDA feedbacks to all ADR reporters as they needed.

7.2 The Safety Indicators of the SMP System

In terms of safety indicators, the success of using the safety indicators to assess the safety in the SMP system was limited. The assessment were performed in a qualitative approach could only detect the existence of the indicator. More explanations are still necessary to the indicators that could detect as "?" or "No." Some safety indicators were also studied in other studies as (Abraham & Davis, 2005) demonstrated the evidences of safety information causing a drug withdrawal and suggested more concerns in this particular issue for new drug regulations. Some crucial indicators as evident in other studies were excluded in the first and second rounds of Delphi, for example, number drug withdrawal, time for detecting ADR after

drug marketed. It was found in other studies that there was a relationship between number of drug withdrawal and an approval time of new drug. The less approval time, the more number of ADR occurred (Faich, 1996; Nordenberg, 1999; Rawson, 2000)

For the indicator " number of new drug off the SMP", was excluded in the first round this might because there were several factors affecting the SMP releasing process as one FDA officer said *" To release 248 new drug from the SMP within 6 months in 1998-1999, I had to use various strategies such as decreasing unnecessary procedures in the SMP, decreasing some unimportant documents for license submission and finding extra budget for some payments to the experts."* (Interview 2)

To strengthen the reliability of these core indicators, further developments are needed not only for the completeness of the set of indicators but also for the more practical use. With these, the rating scales may be applied to safety indicators of the SMP.

7.3 The Strengths and Limitations of the Study

7.3.1 Strengths of the Study

Using different methods in this study both qualitative and quantitative methods were relevant to the complexity of the SMP system. The same as Giacomini (2001) said, this study confirmed "the different but complementary natures of these two methods could be achieved "

The modified Delphi method was applicable to define safety indicators of the SMP in this study. **The panel** remained at 27 people in agreement with previous studies that most studies in Delphi used panels of 15 to 35 people (Gordon, 1994). Although it consumed a long time, the combination of methods in Delphi in this study could help achieve a better consensus as previous study showed (Dijk, 1990). The evidence for this was no declined experts in the finally round. In-persons contact may be useful for conducting the Delphi method in Thai context since after using in-person contacts, many experts responded in a very short period.

7.3.2 Limitations of the Study

Due to some data confidentiality in the Thai FDA, there were un-resolved questions in this study. The ADR incidence was an example. Findings from both the Delphi and the interviews were confirmed the ADR incidence as one of the important indicator for safety issue.

The magnitude of under reporting of new drug ADR was another example. Due to the function as " administrative tool of the SMP with no real enforcement", the practices in reporting were quite under performed. Further strengthen strategies might be needed to solved this situation.