CHAPTER IV

ANALYSIS OF NEW DRUG ADR DATABASE

This chapter describes characteristics and safety profiles of new drug ADR database. ADR database from the Thai FDA was analyzed based on issues in the outcome components in the SMP namely, type of ADRs, seriousness of ADRs and other related ADRs issues of new drugs. Database of the Coxibs and Statins drugs were analyzed as case study drugs. Rationales for selecting these two drug groups were not only the fact that one drug in each group (Rofecoxib and Cerivastatin) was already voluntarily withdrawn from the market but also an increased use of both drug groups. Different SMP status of the two drugs at withdrawal was also the reason of this in-depth analysis. While Rofecoxib was already off, Cerivastatin was still under the SMP. Exact patterns of safety profile of these two drugs were detailed.

4.1 Sources of New Drug ADR Database

Major source of ADR profiles used in this study was from the annual Spontaneous Report of Adverse Drug Reaction from 1991 to 2002.

As of 2002, there were 84,870 ADR reports. The ADR events of new drugs were report the first time in 1996. Number of ADR reports of new drugs significantly increased especially during 1998 to 2000. The proportion of ADR reports of new drugs increased from 3.25% in 1996 to the highest number proportion of 10.85% in 2000. An unexpected decrease of number of new drug ADR reports (2.32%) was observed in 2001. In general, the ADR reports of new drugs accounted for a relatively small percentage of the total number of ADR reports. This was evident with an annual average of 7,072 reports including 6,667 reports of existing drugs and 694 of new drugs, as shown in Table 4.1.

Table 4.1 Number of Adverse Drug Reaction (ADR) reports (1984-September 2004)

Year	Spontaneous Report of Adverse Drug Reaction*		
	All ADRs report*	ADRs report of existing drugs*	ADRs report of new drugs (% to all reports)
1991	963	963	SMP started
1992	1,250	1,250	n/a
1993	2,303	2,303	n/a
1994	3,360	3,360	n/a
1995	3,901	3,901	n/a
1996	4,490	4,344	146 **(3.25%)**
1997	4,667	4,421	246 (5.27%)
1998	7,210	6,433	777 (10.78%)
1999	10,720	9,719	1,001 (9.34%)
2000	12,040	10,733	1,307 **(10.85%)**
2001	16,455	16,074	381 **(2.32%)**
2002	17,511	16,507	1,004 (5.73%)
Total	**84,870**	**80,008**	**4,862(5.73%)**
Annual average	**7,072**	**6,667**	**694**

* Data from the annual Spontaneous Report of Adverse Drug Reaction from 1991 to 2002.

n/a not available

4.2 Analysis of ADRs Database

4.2.1 Safety Profile of Case Study Drugs: A case of Coxibs

In Thailand, since 1999, there has been 4 Coxibs registered as drugs for the treatment of inflammation and acute pain. Based on data from New Drug Registration Book (1996 to 2003), there were Coxibs as follows;

1. Celecoxib was the first Coxib held under the SMP restriction from April 30, 1999 to June 29, 2000, with a total of 14 months under SMP restriction.
2. The second Coxib, Rofecoxib entered the SMP on November 15, 1999, and was released from the SMP on December 14, 2000. The

drug was held under the SMP for only 11 months. On September 30, 2003, Rofecoxib was voluntarily withdrawn by its company. Since the withdrawal of rofecoxib, the duration new Coxibs have been held under SMP monitoring seemed to be longer.

3. Parecoxib, the third coxib, has been held under the SMP since August 22, 2003.
4. The latest coxib, etoricoxib, entered the SMP on October 28, 2003. At the present (October 2005), monitoring on these two drugs is ongoing.

Table 4.2 to 4.10 presented data of Coxib drug from 1999 to September 2004. It was found that from 1999 to September 2004, 685 ADR events arose from 3 Coxibs including Celecoxib, Rofecoxib and Etoricoxib. ADR events associating with Celecoxib was the most reported (69.74%) followed by that of Rofecoxib (29.64%) and Etoricoxib (0.58%) (Table 4.2). Ratio of number of serious to non-serious ADR events of Celecoxib and Rofecoxib was similar (1:5.5 and 1:6.5 respectively). A ratio of 1:3.0 found in Etoricoxib seemed to indicate a high likelihood of serious events, but a total of 1 serious event and 3 non-serious events made the ration much less meaningful.

Of 99 serious ADR events, hospitalization, either initial or prolonged, was the most reported outcome (53 events). Death was the least reported events (3 events). All 3 events of death were associated with Celecoxib.

Table 4.2 ADRS events of Coxibs in Thailand

ADRs issues	Celecoxib	Rofecoxib	Etoricoxib	Total
Number of all ADRs (%)	478 (69.74)	203 (29.64)	4 (0.58)	685
Number of ADRs with seriousness N=682 (%)				
- Serious ADRs	73 (10.70)	27 (3.96)	1 (0.001)	101(14.81)
- Non-serious ADRs	402 (58.94)	176 (25.81)	3 (0.004)	581 (85.19)
- Ratio of serious: non-serious	**1:5.5**	**1:6.5**	**1: 3.0**	**1:5.7**
Category of seriousness of ADRs (n=99)				
- Death	3	0	0	3
- Life-threatening	4	0	1	5
- Hospitalization-initial/prolonged	53	19	0	72
- Required intervention to prevent permanent impairment or damage	11	8	0	19

When considering the reports by year, from 1999 to 2004, ADR events associating with Celecoxib were found the most frequently reported followed by those relating to Rofecoxib (Table 4.3). There was no ADR of Etoricoxib reported in the year it entered the SMP (2003). In the subsequent year, only 4 vents (in 3 patients) were reported to have ADR relating to the drug. Number of ADR events increased with time where the number of reported events reached the peak in 2003. By average, 1.7 ADR events occurred in one patient.

Table 4.3 ADR Events (Patients) Associating with Coxib use

Year	Celecoxib	Rofecoxib	Etoricoxib	Total
1999	4 (4)	0 (0)	-	4 (4)
2000	38 (21)	10 (6)	-	48 (27)
2001	91 (54)	29 (17)	-	120 (71)
2002	135 (74)	51 (28)	-	186 (102)
2003	172 (105)	98 (57)	0 (0)	270 (162)
2004	38 (22)	15 (9)	4 (3)	57 (34)
Total	478 (280)	203 (117)	4 (3)	685 (400)
ADR events: patient	**1.7: 1**	**1.7: 1**	**1.3: 1**	**1.7: 1**

Most ADR led to discontinuation of Coxib use (376 out of 391 patients). However, continuing drug use was found in a very few number of patients (15 out of 391 patients).

Table 4.4 Action after ADR of Coxibs

Issues	Celecoxib	Rofecoxib	Etoricoxib
Action After ADR (Patient) (N=391 events)	275	113	3
Stopped using (n=376)	265	108	3
Continued using (n=15)	10	5	0

Most patients experiencing ADR associating with Coxibs recovered from the ADR (426 events or 65.14%). There were a relatively high number of cases that did not recover (17.13%) and were lost to follow-up (9.48%). All together, death from any causes accounted for 1.38% of all events where "death from ADR" took a major portion of the outcome (5 events or 0.76%) (Table 4.5).

Table 4.5 Patient Outcomes after ADR Event

Patient Outcomes	Celecoxib	Rofecoxib	Etoricoxib	Total (%)
Recovered	294	129	3	426 (65.14)
Recovered but with lesions	29	16	0	45 (6.88)
ADR not resolved	84	27	1	112 (17.13)
Death from ADR	2	3	0	5 (0.76)
Death probably from the suspected drug	1	0	0	1 (0.15)
Death from other drugs/treatments	1	2	0	3 (0.46)
Lost to follow-up	45	17	0	62 (9.48)
Total	456	19	4	654

Of 685 ADR events relating to Coxib use, the majority of likelihood of drugs causing the ADR was "probable" (57.81%), followed by "possible" (37.81%). The definite decision indicating that the drug was the cause of the ADR, or "certain" response, was found in only 4.09% of the events. The response of "unlikely" was found with a very low proportion (0.29%). The likelihood of causing ADR by Celecoxib and Rofecoxib was similar, and accounted for the pattern of the whole Coxib group.

Table 4.6 Probability of Coxibs on ADR Events (Based on Naranjo's)

Probability of ADR	Celecoxib	Rofecoxib	Etoricoxib	Total (%)
Certain	17	11	0	28 (4.09)
Probable	295	101	0	396 (57.81)
Possible	166	89	4	259 (37.81)
Unlikely	0	2	0	2 (0.29)
Total	478	203	4	685

In most events, Coxibs were assessed as the suspected drug (481 out of 681 events, or 70.63%) followed by other drugs used concomitantly with Coxibs (194 out of 681 events, or 28.49%) (Table 4.11). When considering individual Coxibs, causality similar that of the whole group was evident.

Table 4.7 Causality of ADR Events Associating with Coxibs

Causality of ADRs	Celecoxib	Rofecoxib	Etoricoxib	Total (%)
Drug interaction	6	0	0	6 (0.88)
Other drugs used concomitantly	138	56	0	194 (28.49)
Coxib as suspected drug	330	147	4	481 (70.63)
Total	474	203	4	681

Coxib use was associated with various ADR events (Table 4.8). The five most frequent serious ADR events were; 1) Stevens Johnson Syndrome (9 events), pruritis (7 events), 2) rash and rash erythematous (6 events for each type), 3) rash maculo-papular and face oedema (4 events for each type), 4) dizziness, dyspnoea and GI haemorrage (3 events for each type) and 5) headache, hypotension and uticaria (3 events for each type). Non-serious ADR events occurred more frequently and the most reported ADR events were; 1) pruritis (87 events), 2) rash (79 events), 3) rash erythematous (42 events), 4) rash maculo-papular (34 events), and 5) face oedema (32 events).

There was a similarity of the most reported serious ADR events between Celecoxib and Rofecoxib. The most frequently reported serious ADR of Celecoxib

were 1) Stevens Johnson Sysdrome and 2) pruritis and rash erythematous (6 events for each type), while that of Rofecoxib was also Stevens Johnson Syndrome (3 events). Furthermore, the most reported ADR for Celecoxib and Rofecoxib was pruritis (66 and 21 events, respectively) (details in Appendix C).

In terms of heart-related ADRs, bradycardia, chest pain and palpitation were found. Celecoxib was associated with one serious event of bradycardia and chest pain. Palpitation was reported quite often with 2 serious and 4 non-serious events associating with Rofecoxib and 8 non-serious events with Celecoxib (Appendix C).

Table 4.8 ADR Types and Seriousness Associating with Coxibs

ADR Type	(n=101) Serious	(n=581) Non-serious	(N=682) Total
STEVENS JOHNSON SYNDROME	**9**	2	11
PRURITUS	**7**	**87**	**94**
RASH	**6**	**79**	**85**
RASH ERYTHEMATOUS	**6**	**42**	**48**
RASH MACULO-PAPULAR	**4**	**34**	**38**
FACE OEDEMA	**4**	**32**	**36**
URTICARIA	**3**	30	33
DYSPNOEA	**3**	23	26
DIZZINESS	**3**	17	20
HEADACHE	**3**	4	7
HYPOTENSION	**3**	1	4
GI HAEMORRHAGE	**3**	-	3
Heart-related ADRs			
PALPITATION	2	12	14
CHEST PAIN	1	1	2
BRADYCARDIA	1	-	1

Ratios of ADR events reported during and after SMP restrictions were somewhat different between Celecoxib (ratio of 1:42.4) and Rofecoxib (ratio of 1:19.3) (Table 4.9). This indicated that ADR events of celecoxib were more likely to be reported after the SMP monitoring than were those of rofecoxib.

Table 4.9 ADR Events of Coxibs by the SMP status (on/off)

SMP Status	Celecoxib	Rofecoxib	Etoricoxib	Total
On the SMP	11	10	4	25
Off the SMP	467	193	-	660
Total	478	203	4	685
Ratio On: Off SMP (Event)	**1: 42.4**	**1: 19.3**	**-**	**1: 26.4**

A dramatic increase of ADR events by Celecoxib and Rofecoxib since the year 2000 was visually demonstrated (Figure 4.1). Such increase categorized by the SMP status could also be numerically detailed (Table 4.10). The highest number of ADR events of both drugs was seen in 2003. In each year, number of ADR events of Celecoxib was higher than that of Rofecoxib.

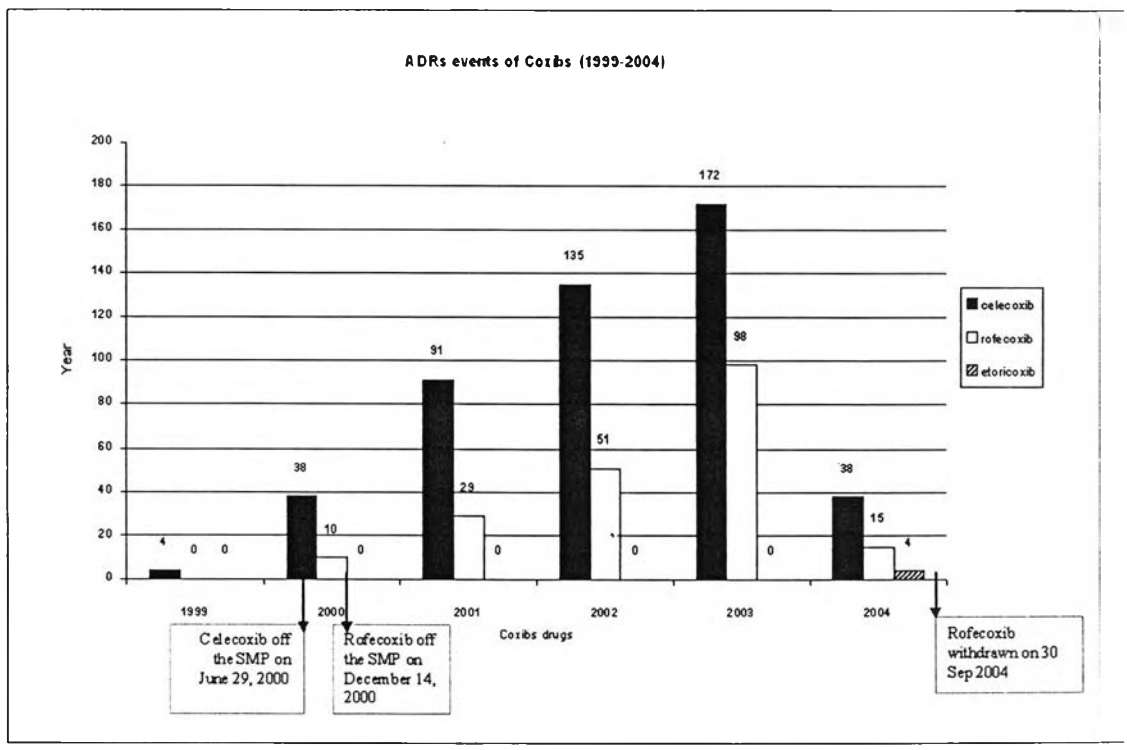

Figure 4.1 ADR Events of Coxibs by Year (1999- September 2004)

Table 4.10 ADR Events of Coxibs By the SMP Status (On/Off) and Year

Year	celecoxib		rofecoxib		etoricoxib		Total
	On	Off	On	Off	On	Off	
1999	4	-	-	-	-	-	4
2000	7	**31**	10	0	-	-	48
2001	-	91	-	**29**	-	-	120
2002	-	135	-	51	-	-	186
2003	-	172	-	98	-	-	270
2004	-	38	-	15	4	-	57
Total	**11**	**467**	**10**	**193**	**4**	**-**	**685**

4.2.2 Safety Profile of Case Study Drugs: A case of Statins

Since 1999, there has been 5 Statins registered as anti-hyperlipidemic drug in Thailand. These drugs, in chronological order, include;

1. Simvastatin: entered the SMP on April 23, 1991 and was off the SMP on 13 January 1998, with a total of 81 months under SMP restriction.
2. Pravastatin: entered the SMP on March 2, 1992, and was off the SMP on January 16, 1998, with a total of 70 months under SMP restriction.
3. Fluavastatin: entered the SMP on October 24, 1995, and was off the SMP on July 17, 1998, with a total of 33 months under SMP restriction.
4. Atorvastatin: entered the SMP on November 5, 1997, and was off the SMP on August 3, 1999, with a total of 21 months under SMP restriction.
5. Cerivastatin: entered to SMP on April 30, 1998, and was off the SMP on March 9, 2000 with voluntary withdrawal. The drug therefore was under SMP restriction for 22 months.

ADR profiles of those 5 Statins were found in the ADR database including those of Lovastatin, a Statin not registered in Thailand.

It was found that from 1993 to September 2004, the 650 ADRs events arose from these 6 Statins including Simvastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, and Lovastatin (Table 4.11). ADR events associating with Simvastatin were the most reported (68.00%), followed by Atorvastatin (26.15%) and Fluvastatin (3.69%). The least reported Statin was Lovastatin (0.31%).

Of these 650 ADR events, 133 events were serious ones. Therefore a ratio of number of serious to non-serious ADR events all Statins together was 133: 514 or 1:1.39. The likelihood of serious ADR events among Statins seemed different where Ratios of ADR events ranging from the highest likelihood found in Simvastatin (1:3.4), followed by that in Atorvastatin (1:4.6) and Fluvastatin (1:7).

Of 119 serious ADR events, hospitalization, either initial or prolonged, was the most reported outcome (84 events). Death was the least reported events (2 events). All 2 events of death were associated with Simvastatin.

Table 4.11 ADRS events of Statins in Thailand

ADRs issues	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total
Number of all ADRs (%)	442	9	24	170	3	2	650
	(68.00)	(1.38)	(3.69)	(26.15)	(0.46)	(0.31)	(100)
Number of ADRs,by seriousness N=647 (%)							
-Serious ADRs	100	0	3	30	0	0	133
	(15.46)	(0.00)	(0.46)	(4.64)	(0.00)	(0.00)	(20.56)
-Non-serious ADRs	341	9	21	138	3	2	514
	(52.70)	(1.39)	(3.25)	(21.33)	(0.46)	(0.31)	(79.44)
-Ratio of serious: non-serious	**1: 3.4**	-	**1: 7**	**1: 4.6**	-	-	**1: 3.9**
Category of seriousness of ADRs (n=119)							
- Death	2	-	0	0	-	-	2
- Life-threatening	5	-	0	3	-	-	8
- Hospitalization-initial/prolonged	61	-	2	21	-	-	84
- Disability	11	-	1	0	-	-	12
- Required intervention to prevent permanent impairment or damage	7	-	0	6	-	-	13

When considering reports by year, from 1993 to 2004, ADR events associating with Simvastatin were found the most frequently reported followed by those relating to Atorvastatin (Table 4.12). Number of ADR events increased with time where the number of reported events reached the peak in 2003. By average, 1.6 ADR events occurred in one patient. In each drug, number of ADR events per one patient was not much different from one another. These numbers ranged from 1.4 in Fluvastatin to 2.0 in Lovastatin.

Table 4.12 ADR Events (Patients) Associating with Statin Use

Year	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total
1993	3 (2)	0	-	-	-	-	3 (2)
1994	6 (3)	0	-	-	-	-	6 (3)
1995	5 (3)	0	0	-	-	-	5 (3)
1996	2 (2)	0	0	-	-	-	2 (2)
1997	0 (0)	0	1 (1)	0	-	-	1 (1)
1998	6 (5)	1(1)	4 (3)	3 (2)	0	-	14 (11)
1999	17 (14)	0 (0)	6 (3)	16 (9)	2 (1)	-	41 (27)
2000	52 (30)	1(1)	1 (1)	21 (12)	0 (0)	-	75 (44)
2001	67 (43)	2 (1)	3 (3)	65 (35)	1 (1)	-	138 (83)
2002	97 (63)	3 (1)	5 (3)	38 (20)	-	-	143 (87)
2003	142 (91)	2 (1)	4 (3)	23 (15)	-	2 (1)	173 (111)
2004	45 (32)	0 (0)	0 (0)	4 (4)	-	0	49 (36)
Total	442 (288)	9 (5)	24 (17)	170 (97)	3 (2)	2 (1)	650 (410)
ADR events: patient	**1.9: 1**	**1.8: 1**	**1.4: 1**	**1.8: 1**	**1.5: 1**	**2.0: 1**	**1.6: 1**

Like findings in Coxib drugs, most ADR events led to discontinuation of Statin use (347 out of 401 events). However, in a small number of events, the use of Statins was continued (44 out off 401 events) and the dose was reduced in a very few events (10 out of 401 events)(Table 4.13).

Table 4.13 Action after ADR of Statins

Action after ADR	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin
Action After ADR of Coxibs						
(Patient) (N=401 events)	**279**	**5**	**17**	**97**	**2**	**1**
Stopped using (n=347)	238	5	15	87	1	1
Continued using (n=44)	32	0	2	9	1	0
Decreased dose (n=10)	9	0	0	1	0	0

As shown in Table 4.14, most of patients recovered from ADRs (452 vents), 98 ADRs events continued, 34 ADRs events recovered but with lesions. There was 35 events lost to follow up.

Most patients experiencing ADR associating with Statins recovered from the ADR (452 events or 72.67%). There were a relatively high number of cases that did not recover (98 events or 15.75%), recovered but with lesions (5.47%) and were lost to follow-up (5.63%). All together, death from any causes accounted for 0.48% of all events where only one case occurred in each subcategory of death. The outcome of death was reported associating with only Simvastatin.

Table 4.14 Patient Status (Outcomes) after ADR Event

Outcomes after ADR	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total (%)
Recover	310	5	17	116	2	2	452 (72.67)
Recover but had lesion	20	0	4	10	0	0	34 (5.47)
ADR continued	65	0	3	29	1	0	98 (15.75)
Death from ADR	1	0	0	0	0	0	1 (0.16)
Death may from related to drug	1	0	0	0	0	0	1 (0.16)
Death from others	1	0	0	0	0	0	1 (0.16)
Lost follow up	28	1	0	6	0	0	35 (5.63)
Total	426	6	24	161	3	2	622

Of 650 ADR events relating to Statin use, the majority of likelihood of drugs causing the ADR was "probable" (383 or 58.92%), followed by "possible" (36.0%). The definite decision indicating that the drug was the cause of the ADR, or "certain" response, was found in only 4.46% of the events. The response of "unlikely" was found with a very low proportion (0.62%). The likelihood of causing ADR by

Simvastatin and Atorvastatin was quite similar, and accounted for the pattern of the whole Statin group.

Table 4.15 Probability of Statins on ADR Events

Probability of ADRs	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total (%)
Certain	15	0	0	14	0	0	29 (4.46)
Probable	284	4	12	80	1	2	383 (58.92)
Possible	142	4	12	74	2	0	234 (36.00)
Unlikely	1	1	0	2	0	0	4 (0.62)
Total	442	9	24	170	3	2	650

Unlike Coxibs that in most cases, they were assessed as the suspected drug, other drugs used concomitantly with Statins were the most rated the cause of ADRs (385 out of 650 events, or 59.23%) followed by the use of Statins (262 out of 650 events, or 40.31%) (Table 4.16). The pattern that the use of other drugs concomitantly with Statins rather than the use of Statins was the cause of the ADRs was seen in each Statin, except Lovastatin.

Table 4.16 Causality of ADR Events Associating with Statins

Causality of ADRs	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total (%)
Drug interaction	3	0	0	0	0	0	3 (0.46)
Other drug used concomitantly	242	7	17	116	3	0	385 (59.23)
Statin as suspected drug	197	2	7	54	0	2	262 (40.31)
Total	442	9	24	170	3	2	650

Statin use was associated with various ADR events (Table 4.17). The five most serious ADR events were; 1) Stevens Johnson Syndrome (10 events), 2) Hypoglycemia, myalgia and pruritis (7 events for each), 3) nausea, myopathy, and hepatitis (5 events for each), 4) rash and acute renal failure acute (4 events for each) and 5) anigioedema, coughing, diarrhoea, dysnoea, fatique, headache, rash maculo-papular, vomiting (3 events for each). In addition, various non-serious ADRs were

found. The five most reported were; 1) pruritis (31 events), 2) coughing (28 events), 3) rash (27 events), 4) nausea (24 events) and 5) headache (22 events).

The most frequently reported serious ADRs relating individual Statins were also elaborated. It was found that the most frequently reported ADRs relating to Simvastatin were hypoglycemia, myalgia and pruritis (6 events for each), while those of Fluvastatin and Atorvastatin were Stevens Johnson Syndrome (2 and 3 events respectively) (Detail in Appendix D).

In terms of non-serious ADRs of individual Statins, Simvastatin was associated with pruritis (23 events), Atorvastatin with coughing and rash erythematous (7 events for each) (Appendix D).

Since Statins can cause muscle-related ADR, the presence of these ADRs was mandatory. These ADRs were found quite often and included myalgia, rhabdomyolysis, myopathy, fatigue, muscle weakness, myositis, and generalized weakness. (Appendix D).

Table 4.17 ADRs of Statins by Seriousness of ADRS (1993-September 2004)

ADR Type	(n=133) Sericus	(n=514) Non-serious	(N=647) Total
STEVENS JOHNSON SYNDROME	**10**	2	12
PRURITUS	**7**	**31**	**38**
MYALGIA	**7**	15	22
HYPOGLYCAEMIA	**7**	2	9
RHABDOMYOLYSIS	**7**	-	7
NAUSEA	**5**	**24**	**29**
MYOPATHY	**5**	6	11
HEPATITIS	**5**	1	6
RASH	**4**	**27**	**31**
RENAL FAILURE ACUTE	**4**	-	**4**
COUGHING	3	**28**	**31**
HEADACHE	3	**22**	25
Muscle related ADR			
MYALGIA	**7**	15	22
RHABDOMYOLYSIS	**7**	-	7
MYOPATHY	**5**	6	11
FATIGUE	**3**	13	16
MUSCLE WEAKNESS	**2**	6	8
MYOSITIS	-	2	2
WEAKNESS GENERALIZED	-	1	1

Ratios of ADR events reported during and after SMP restrictions were different between Simvastatin (ratio of 1:26.6) and Fluvastatin (ratio of 1:2.4) (Table 4.18). This indicated that ADR events of Simvastatin were more likely to be reported after the SMP monitoring than were those of Fluvastatin.

Table 4.18 ADR Events of Statins by the SMP Status*

SMP Status	Simvastatin	Pravastatin	Fluvastatin	Atorvastatin	Cerivastatin	Lovastatin	Total
On the SMP	16 (10)	0 (0)	7 (6)	170 (97)	3 (2)	0 (0)	196 (115)
Off the SMP	426 (278)	9 (5)	17 (11)	0 (0)	0 (0)	0 (0)	452 (294)
Unspecified	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)
Total	442 (288)	9 (5)	24 (17)	170 (97)	3 (2)	2 (1)	650 (410)
Ratio On:Off SMP (Event)	**1: 26.6**	-	**1: 2.4**	-	-	-	**1: 2.3**

* Number presented as events (patients)

A dramatic increase of ADR events by Simvastatin and Atorvastatin after the years they were off the SMP (1998 and 199 respectively) was visually demonstrated (Figure 4.2.) The highest number of ADR events of Simvastatin was seen in year 2003 (142 events), while that of Atorvastatin in 2001 (65 events). Interestingly, number of reports on Atorvastatin has been declining since then.

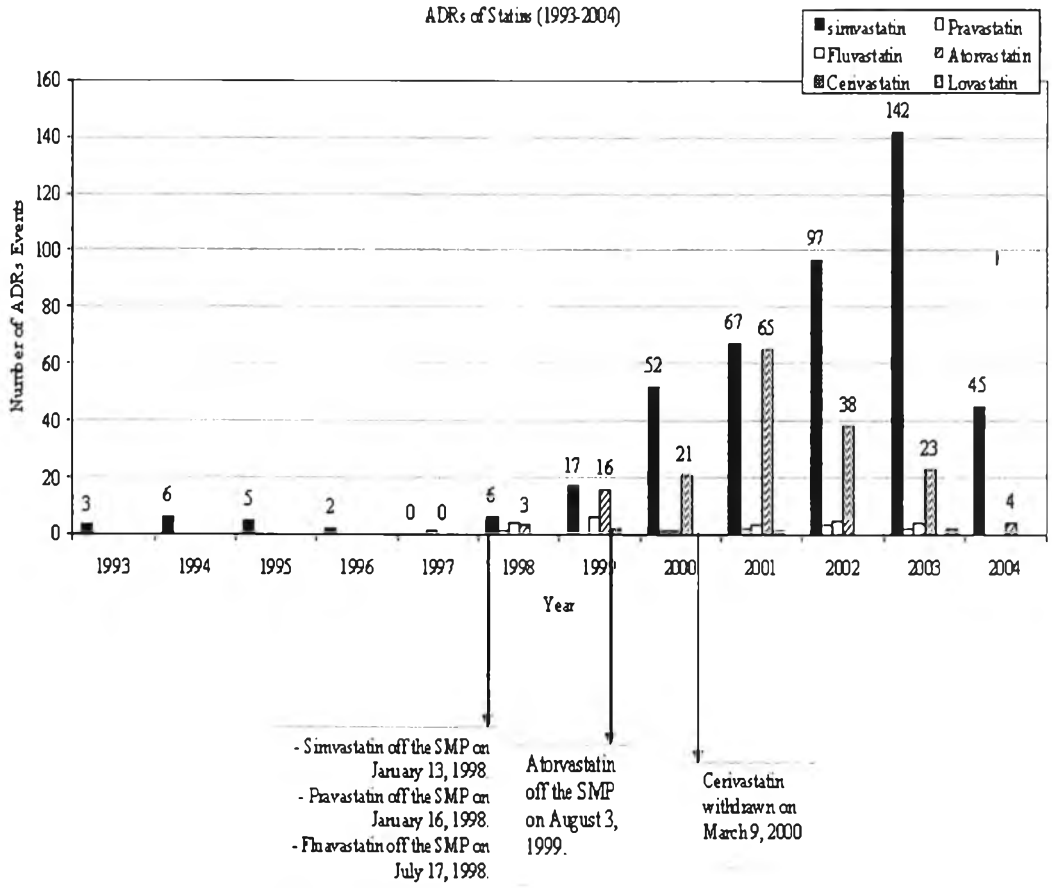

Figure 4.2 ADRs Events of Statins by the SMP Status (1993- September 2004)