

Sequence of Events with VIOXX, since opening of IND

1. **December 20, 1994** -- Merck opens Investigational New Drug (IND) **46,894** for osteoarthritis and acute pain in the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products. This was the first IND submitted for FDA review for human use.
2. **February 13, 1998** – IND 55,269 is submitted for the treatment of Alzheimer’s Disease to the Division of Neuropharmacological Drug Products.
3. **March 24, 1998**. Arthritis Advisory Committee meeting discussed safety issues surrounding COX-2 inhibitors.
4. **November 23, 1998**, Merck submitted a New Drug Application (NDA 21-042) for Vioxx™ (rofecoxib) for the treatment of acute pain in adults, dysmenorrhea and osteoarthritis (data to support this NDA included in **IND 46,894**).

The Vioxx™ NDA included approximately 60 studies, which provided approximately five thousand subjects exposed to rofecoxib from one day to 86 weeks, of whom 371 and 381 patients received 12.5 and 25 mg daily (the recommended doses for chronic use) for one year or longer and 272 patients received ≥ 50 mg daily for ≥ 6 months (50 mg daily was the dose approved for acute pain).

The NDA included two six-week placebo and ibuprofen-controlled studies; one six-week placebo and nabumetone controlled study in the elderly and one 6-week dose-ranging study. Some of the patients participating in these studies were involved in extension studies up to 86 weeks. Additionally, there were two six-month diclofenac-controlled studies, with extensions up to one year and two 6-month placebo and ibuprofen-controlled endoscopic studies (See Medical Officer review dated May 19, 1999).

No cardiovascular signal was observed in the original NDA application.

5. **April, 20 1999** – Arthritis Advisory Committee (AAC) convened to consider the efficacy of 12.5 and 25 mg dose for osteoarthritis as well as gastrointestinal, renal, and hepatic safety of this new molecular entity. The AAC recommended approval.
6. **May 20, 1999** – Vioxx™ (NDA 21-042) was approved for acute pain, dysmenorrhea and OA.
7. **November 08, 1999** – IND 59,222 was submitted to the Division of Oncology Drug Products (DODP) to pursue colon cancer prevention claim. This IND included Protocol 122 entitled, “A Multicenter, Randomized, Parallel Group, Placebo-Controlled, Double-Blind Study with In-House Blinding to Determine the Effect of 156 Weeks of Treatment with MK-0966 on the Recurrence of Neoplastic Polyps of the Large Bowel in Patients with a History of Colorectal Adenomas”. DODP

offered comments and requested clarification regarding the study design before the protocol was implemented. The original protocol had several deficiencies that need to be resolved before the study would be allowed to proceed (see FAX of December 07, 1999 and the follow-up ADVICE Letter of December 29, 1999).

- 8. January 05, 2000** – An PreIND/End-of-Phase II meeting was held for IND 59,222 (Protocol 122 APPROVe) in response to the Agency comments and recommendations in the December 07, 1999 fax.
- 9. March 30, 2000** -- Preliminary information regarding an imbalance in serious cardiovascular thrombotic events had been submitted to the **original IND 46,894** for osteoarthritis and acute pain in March 30, 2000, along with analyses of serious cardiovascular events in all studies previously submitted to NDA 21-042, ongoing placebo-controlled prevention of Alzheimer's studies, the ADVANTAGE study (which was almost completed) and post-marketing adverse experience surveillance, all of which did not show a cardiovascular signal. Merck's explanation was that naproxen had protective effects. A letter was sent to all investigators informing these results. The informed consent was amended to include this information. All protocols were amended to allow the use of low dose aspirin for those patients who may be at risk for cardiovascular events.
- 10. June 23, 2000** – IND 59,222 Protocol 122 (APPROVe) was amended to allow the use of low dose aspirin for patients who might be at high cardiovascular risk and remove a treatment arm with the 50 mg dose
- 11. June 29, 2000** – VIGOR (Vioxx Gastrointestinal Outcome studies) was submitted for review (NDA 21-042/supplement 007). The VIGOR study demonstrated significant decrease in the risk of gastroduodenal perforations, ulcers and bleedings (56) in VioxxTM as compared to (121) on naproxen, but also an increased risk of cardiovascular thrombotic events, mostly driven heart attacks (0.5 and 0.1% for VioxxTM and naproxen, respectively). Important limitations to the study included the use of VioxxTM 50 mg dose (twice the highest recommended dose for chronic use), the use in a population with rheumatoid arthritis, the exclusion of patients taking aspirin (which left out patients at high cardiovascular risk requiring low dose aspirin for cardiovascular prophylaxis) and the use of a single comparator with putative antiplatelet effects.
- 12. February 8, 2001** – Arthritis Advisory Committee met to discuss the results of VIGOR, a large (8,000-patient) post-marketing study designed to evaluate the gastrointestinal safety of VioxxTM as compared to naproxen, submitted under NDA 21-042/S-007. The study succeeded in demonstrating superior gastrointestinal safety but also showed an increased risk of cardiovascular thrombotic events for VioxxTM as compared to naproxen. The Advisory Committee noted that the VIGOR trial had limitations as to the generalizability of the cardiovascular findings which needed further investigation. These limitations included study design using one comparator and no placebo, a higher dose (50mg) not recommended for chronic use, a population

limited to rheumatoid arthritis patients, and the exclusion of patients on low dose aspirin. The Committee agreed on the important benefit of reduced gastrointestinal bleeding that rofecoxib had demonstrated, a benefit no other NSAID had, and encouraged the FDA to keep that benefit in mind when evaluating the safety issues in the VIGOR trial (see attached FDA and Merck briefing documents, slide presentations, and transcripts of the AAC).

- 13. February 28, 2001** – Sponsor submitted supplemental application for the Rheumatoid Arthritis indication (NDA 21-042/S-012 supported studies submitted under **IND 46,894**). This submission included a 1,100-patient database in patients with RA that involved Vioxx™ 25 and 50 mg and naproxen 500 mg bid in trials of 3 months to one year duration.
- 14. April 6, 2001 - Approvable** action for NDA 21-042 supplement 007 (VIGOR study). Additional information was requested before labeling changes could be made.
- 15. April 11, 2001** – DAAODP met with Merck to discuss the additional information request in the April 06, 2001 approvable letter.
- 16. April 30, 2001** – Merck fulfills request of February 14, 2001 for complete case study report of ADVANTAGE study. Safety Update Report still needed for complete response to approvable letter issued on April 06, 2001.
- 17.** [Redacted]
- 18. July 12, 2001 – Sponsor submitted Complete Response** to the April 06, 2001 Approvable letter the VIGOR study (NDA 21-042/S-007). This submission included:
 - The ADVANTAGE study, a 6,000-patient study comparing Vioxx™ 25 mg and naproxen in patients with osteoarthritis. Information from this study was submitted in March 30, 2001, April 13, 2001, and April 16, 2001.
 - A Safety Update Report (SUR) which included serious adverse events from studies that had been submitted to the original NDA application and from new, ongoing studies that included preliminary information from studies 078 and 091 (studies for the prevention of Alzheimer's).
 - Cardiovascular safety data from studies rheumatoid arthritis submitted in February 28, 2001, as part of an efficacy supplement to NDA 21-042.
 - Sponsor responses to FDA specific requests for clarification and information related to cardiovascular and overall safety of Vioxx™, submitted to the FDA in July 26, and 30, August 4, and 17, September 20, October 1, 3, 5, and 8, November 5, and 26, 2001.
- 19. August 14, 2001** – Memorandum of need to obtain a purchase order with Kaiser to conduct a project title: Comparison Rates of Myocardial Infarction (MI) between Patients Treated with Cyclo-Oxygenase 2 Inhibitors (COX-2) and Traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

20. September 01, 2001 – IND 59,222 was transferred to the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) following recommendations and comments from the Division of Oncology Drug Products in a letter dated December 30, 1999 and January 05, 2000 End of Phase II meeting with (DODP).

21. September 21, 2001 -- FDA internal regulatory briefing on Vioxx™. It was recommended to include balanced information regarding safety results of Vioxx™ and de-emphasize the GI safety advantage in Vioxx™ label.

22. October 04, 2001 – An urgent message was received from Bob Silverman of Merck. Bonnie Goldmann, (Merck) had been instructed by upper management to probe Dr. Woodcock about Agency thinking on Vioxx™ label.

23. October 15, 2001 – Label negotiations were initiated by the FDA with the transmission of FDA proposed labeling for NDA 21-042/S-007 VIGOR to Merck.

24. November 01, 2001 – DGCDP met with Merck to discuss the recommendations and comments in the April 13, 2001 advice letter for the prevention of colon polyps claim indication. DGCDP emphasized that cardiovascular safety issues needed to be addressed in this study. The division stated:

“With regards to the interim safety analysis, it is understood that you will include an analysis of cardiovascular, edema, hypertension, thromboembolic, renal, hepatic and upper GI adverse events as well as an analysis of overall safety outcomes, SAEs and deaths. In addition to obtaining a recommendation from the independent safety monitoring board concerning continuation of the study, please clarify parameters that would prompt discontinuation of the study.”

“The agency has further concerns regarding the safety profile of prolonged VIOXX administration in this population, given the recent analysis of the cardiovascular/thrombotic/edema/hypertension and overall safety profiles and mortality outcomes associated with Rofecoxib treatment studies (VIGOR, ADVANTAGE, database of investigator reported events of study subjects with rheumatoid arthritis, and Alzheimer's studies).”

25. November 06, 2001 – Merck provides a response to FDA label proposal of October 15, 2001. The sponsor rejected FDA proposed labeling. There was little change from the original proposed label that accompanied NDA 21-042/S-007. In view of the extent of the lack of agreement a telecom was arranged with the sponsor and the division (DAAODP) explained our position regarding the sponsor's annotations to their counterproposal of November 06, 2001. This telecom took place on November 21, 2001. The division (DAAODP) requested that the sponsors reconsider their proposal in light of our comments and resubmit a new proposal.

- 26. November 21, 2001** – DAAODP initiated a telecom with Merck. Bob Silverman was present for Merck. DAAODP discussed issues raised in November 06, 2001 cover letter. The DAAODP requested that the sponsor reconsider their proposal in the light of our comments and resubmit a new proposed label. It was also suggested that Merck meet with the DAAODP prior to the holiday break to discuss the label.
- 27. November 28, 2001** -- Except for studies 078 and 091 – was completed on November 28, 2001 (see November 28, 2001, Medical Officer's review of the Complete Response to the April 06, 2001 Approvable letter) and showed a trend for increased risk of myocardial infarctions for VioxxTM as compared to naproxen. However no such difference was noted in clinical trial data submitted with VioxxTM compared placebo or other NSAIDs
- 28. December 05, 2001** – Merck submitted a revised label proposal for VIGOR as suggested in the November 21, 2001.
- 29. December 12, 2001** – Regulatory briefing was held to update Drs. Woodcock and Temple on the labeling negotiation.
- 30. December 19, 2001** – A face-to-face meeting was scheduled and confirmed to continue discussion of VioxxTM proposed label for January 09, 2002.
- 31. December 21, 2001** – Approvable action for NDA 21-042/S-012 (rheumatoid arthritis) pending additional cardiovascular safety information.
- 32. January 03, 2002** – Bob Silverman requested confirmation of Dr. Temple's attendance for the scheduled January 09, 2002 meeting. He was informed that Dr. Temple would not be available.
- 33. January 07, 2002** – Merck cancelled the January 09, 2002 meeting. Merck requested the meeting to be rescheduled with Dr. Temple attending. Merck submitted revised labeling which now included NDA 21-042/S-007 VIGOR and S-012 RA. There was still substantial distance between the sponsor and DAAODP.
- 34. January 11, 2002** -- Approvable action for NDA 21-042/S-007, pending labeling negotiations regarding the cardiovascular safety of VioxxTM.
- 35. January 25, 2002** -- As there was substantial distance between the sponsor's and the division's (DAAODP) positions, the division presented an update of labeling negotiations at a pre-decisional meeting at the Center level. This venue allowed for open discussion for difficult issues with experienced leaders in the Center. There was a consensus that the data from the various large databases was of concern and that labeling should include information related to cardiovascular findings associated with VioxxTM. This was similar to comments made by multiple advisory committee members at the February 2001 meeting.

36. January 30, 2002 – A telecom with the sponsor was held on January 30, 2002 for NDA 21-042/S-007 VIGOR and S-012 RA. Labeling negotiations continued with teleconferences being held on February 08, and 20, and March 07, and 20, 2002 until a final label was issued (see attached MINUTES and proposed FDA label).

37. March 12, 2002 – A detailed review of cardiovascular thrombotic events in ongoing studies 078 and 091 for the prevention of Alzheimer’s disease was conducted separately. These studies provided a 2,800-patient placebo-controlled database for Vioxx™ 25 mg as compared to placebo, with a median exposure of 14 months. Analyses of cardiovascular thrombotic events in these studies showed no difference in the risk of myocardial infarctions or stroke between Vioxx™ 25 mg and placebo (see MO review dated March 12, 2002 under NDA 21-042/S-007).

“The Alzheimer’s studies described in this memo were not specifically designed or powered to address CV outcomes. However, they provide a relatively large placebo-controlled database (rofecoxib N= 1267, placebo N= 1464), with a median exposure of 14 months and a substantial number of MI and cerebrovascular events for analysis. In this database, there was no excess for *all* cardiovascular thrombotic events (cardiac, cerebrovascular and peripheral together) and particularly, no excess of MI in the rofecoxib 25 mg group, as compared to placebo. However, total cause mortality (29 vs. 15) and cardiovascular thrombotic deaths (8 and 3) trended against rofecoxib.

These data support the hypothesis that the excess of MI found with rofecoxib 50 mg in the VIGOR study - as well as the trends observed in the ADVANTAGE and the RA databases with the 25 mg dose relative to naproxen - may in part be explained by the lack of an anti-platelet effect of rofecoxib relative to naproxen. However, in addition, the biologically plausible pro-thrombotic effect and the known effects on fluid retention, edema and hypertension may play a role in the different cardiovascular safety profile of rofecoxib as compared to naproxen.

Adequately powered and prospectively designed studies are necessary to definitively address cardiovascular safety issues with VIOXX.”

38. March 14, 2002 – FDA does an additional statistical analysis of cardiovascular thrombotic events in VIGOR. This analysis suggested there was an increase with Vioxx™ 50 mg compared to naproxen over time.

39. March 19, 2002 – The Gastrointestinal Drugs Advisory Committee met to discuss study design issues for chemopreventive agents studied for the prevention for sporadic adenomatous polyposis. On June 7, 2002 Merck submitted an amendment to IND 59,222 containing a review of the advisory committee meeting and a proposal to resolve outstanding issues regarding Protocol 122.

40. April 11, 2002, The Agency approved the rheumatoid arthritis indication along with labeling changes that included the results of the VIGOR study and changes to the PRECAUTIONS, Drug Interactions, and Dosage and Administration sections of the

label to reflect all that was known at that time about potential risk for cardiovascular thrombotic events with Vioxx™.

Excerpts from the April 2002 label are as follows:

Special Studies

The following special studies were conducted to evaluate the comparative safety of VIOXX.

VIOXX GI Clinical Outcomes Research (VIGOR Study)

Study Design

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX 50 mg once daily versus naproxen 500 mg twice daily was also studied. VIGOR was a randomized, double-blind study (median duration of 9 months) in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy (mean age 58 years). Patients were not permitted to use concomitant aspirin or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose aspirin for cardiovascular prophylaxis were to be excluded from the study. Fifty-six percent of patients used concomitant oral corticosteroids. The GI safety endpoints (confirmed by a blinded adjudication committee) included: PUBs-symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding.

Study Results

Gastrointestinal Safety in VIGOR

The VIGOR study showed a significant reduction in the risk of development of PUBs, including complicated PUBs in patients taking VIOXX compared to naproxen (see Table 2).

[Table 2. VIGOR-Summary of Patients with Gastrointestinal Safety Events¹ COMPARISON TO NAPROXEN]

Other Safety Findings: Cardiovascular Safety

The VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily (see Table 3). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 4.) (See PRECAUTIONS, Cardiovascular Effects.) Adjudicated serious cardiovascular events (confirmed by a blinded adjudication committee) included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

Table 3
VIGOR-Summary of Patients with Serious Cardiovascular
Thrombotic Adverse Events¹ Over Time
COMPARISON TO NAPROXEN

Treatment Group	Patients Randomized		4 Months ²	8 Months ³	10 ½ months ⁴
VIOXX 50 mg	4047	Total number of events	17	29	45
		Cumulative Rate [†]	0.46%	0.82%	1.81%*
Naproxen 1000 mg	4029	Total number of events	9	15	19
		Cumulative Rate [†]	0.23%	0.43%	0.60%

¹Confirmed by blinded adjudication committee, ²Number of patients remaining after 4 months were 3405 and 3395 for VIOXX and naproxen respectively, ³Number of patients remaining after 8 months were 2806 and 2798 for VIOXX and naproxen respectively, ⁴Number of patients remaining were 531 and 514 for VIOXX and naproxen respectively.

†Kaplan-Meier cumulative rate.

* p-value <0.002 for the overall relative risk compared to naproxen by Cox proportional hazard model

Table 4
VIGOR- Serious Cardiovascular
Thrombotic Adverse Events¹

	VIOXX 50 mg N ² =4047 n ³	Naproxen 1000 mg N ² =4029 n ³
Any CV thrombotic event	45 *	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

¹Confirmed by blinded adjudication committee, ²N=Patients randomized, ³n=Patients with events

* p-value <0.002 and ** p-value ≤0.006 for relative risk compared to naproxen by Cox proportional hazard model

For cardiovascular data from 2 long-term placebo-controlled studies, see PRECAUTIONS, Cardiovascular Effects.

PRECAUTIONS

Cardiovascular Effects

The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between the treatment groups. (See CLINICAL STUDIES, Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.) In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs. 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs. 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, Special Studies, Platelets; PRECAUTIONS, Drug Interactions, Aspirin.) Prospective, long-term studies on concomitant administration of VIOXX and aspirin evaluating cardiovascular outcomes have not been conducted.

Drug Interactions:

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. In a 12-week endoscopy study conducted in OA patients there was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose (81 mg) enteric coated aspirin plus VIOXX 25 mg daily, as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See CLINICAL STUDIES, Special Studies, Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis.)

At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB₂ generation in clotting blood. Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, Special Studies, Platelets and PRECAUTIONS, Cardiovascular Effects.) Prospective, long-term studies on concomitant administration of VIOXX and aspirin have not been conducted.

41. August 13, 2002 – MON – Request for purchase order to fund Kaiser for a project titled: Design of a Survey Questionnaire to be Used in the Study of Comparison Rates of Myocardial Infarction (MI) between Patients Treated with Cyclo-Oxygenase-2 Inhibitors (COX-2) and Traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

42. October 07, 2002 – [Redacted]

43. November 01, 2002 – Under IND 59, 222 recommendations and comments were provided regarding Merck’s proposal to address outstanding issues related to Protocol 122 from the March 19, 2002 Gastrointestinal Advisory Committee meeting. This letter emphasized the need for long-term clinical data to fully address cardiovascular safety issues with VioxxTM. This letter states:

“We do not agree that 3-year data are sufficient for approval of your drug for this indication. VIOXX has an evolving safety profile that is new since discussions with you on January 5, 2000. In April, 2001, the division IND 59,222 Page 2 recommended 8 years of follow up. Your label now acknowledges that a previously unanticipated risk, cardiac events, has been associated with rofecoxib and this is the subject of on-going scientific assessment. The risk of cardiac and other adverse events, including mortality, over time must be fully studied and we believe that 3 years is insufficient because it is likely that longer administration will occur. Given the changing nature of rofecoxib’s safety profile, we now feel that a patient’s duration of treatment should be 5 years. Colonoscopies should be performed at baseline, at year 1, at year 3, and at the end of treatment. In addition, a follow-up colonoscopy a minimum of 1 year after treatment discontinuation is needed to evaluate the potential for polyp rebound (i.e., a total of 6 years). Labeling recommendations in the Dosage and Administration section will specify a duration of administration based on the clinical trial data.”

44. November 13, 2002 -- Merck proposed an analysis of CV thrombotic events in placebo-controlled studies (Protocol 203). The protocol was entitled “A prospective combined analysis of thrombotic cardiovascular events in three randomized, double-blind, placebo-controlled studies of rofecoxib in patients at risk of developing recurrent sporadic adenomatous colon polyps (APPROVe, protocol 122), recurrent colon cancer (VICTOR, protocol 145, which was being conducted outside the USA) or prostate cancer (Prostate cancer chemoprevention study, protocol 201).” The objective of protocol 203 was to compare the cardiovascular safety of rofecoxib 25 mg to placebo using a combined analysis of data from the three studies which had been submitted to the Divisions of Gastro-Intestinal and Coagulation Drug Products and the Division of Reproductive Drug Products.

All three studies were multi-center, double-blind, randomized, placebo-controlled studies. They each had their own Data Safety Monitoring Board and one Cardiovascular Adjudication Committee that determined whether the cases were in fact confirmed cardiovascular thrombotic events. The CV Adjudication committee

had its Standard Operating Procedures and used the same definitions as used for the VIGOR study.

45. December 09, 2002 – Under IND 46,894 FDA asked Merck to provide a follow up safety update analysis of cardiovascular thrombotic events in the placebo-controlled Alzheimer's studies that had been included in the April 11, 2002 label.

46. December 19, 2002 – Under IND 46,894 the FDA sent an advice letter to Merck acknowledging that Protocol 203 (the pooled analysis of cardiovascular events) would provide substantial clinical information greatly needed for Vioxx™, but emphasized that it might not be sufficient to address the ongoing cardiovascular safety concerns surrounding Vioxx™.

Subsequently, several teleconferences took place between FDA and Merck to further discuss this pooled analysis (see MINUTES dated February 04, and March 09, 2004, and an ADVICE Letter dated August 16, 2004). Of note to date we had not reached agreement on this pooled analysis, and no results from this have been made available to the FDA.

47. February 28, 2003 – A meeting was held with Merck to further discuss the proposed safety database in support of the colon polyp prevention (see MINUTES). The FDA reiterated the risk of cardiac and other adverse events, including mortality, overtime must be fully studied, and that three years was insufficient because it was likely that longer administration would occur. The FDA was also concerned about possibility of rebound of polyps after stopping the drug.

48. December 5, 2003 – Sponsor submitted supplemental application for the treatment of Juvenile Rheumatoid Arthritis (NDA 21-042/S-026). This filing was preceded by extensive discussion about design/duration of pediatric studies.

49. December 17, 2003 -- In response to the request for information of December 9, 2002 by the Division of Anti-inflammatory Drug Products, the sponsor provided a safety update analysis of cardiovascular thrombotic events in the placebo-controlled Alzheimer studies.

50. January 28, 2004 – Review of the December 17, 2003 submission is completed. At that time an excess in total cause mortality was noted as well as a trend towards worsening cognitive function in one of the Alzheimer's studies. No regulatory action was indicated at that time, pending complete review of the submission by the Division of Neuropharmacologic Drug Products and a full safety update that was expected for 4Q 2004.

51. March 30, 2004 – Merck submitted supplemental NDA 21-042/S-030 to support change to Vioxx™ label with the final thrombotic cardiovascular safety data from Alzheimer's protocols 078 and 091.

- 52. March 26, 2004** – NDA 21,647 approved for the treatment of migraine headache supported by studies conducted under IND 55,269. Signatory authority, Dr. Russell Katz, (Division of Neuropharmacological Drug Products)
- 53. April 13, 2004** – Merck is invited to give a presentation on their interpretation of efficacy data from studies 078 and 091 Alzheimer's disease. Merck is also invited to present gout data from pending NDA 21-389 Arcoxia™ (etoricoxib) Tablets at the June 2, and 3, 2004 Arthritis Advisory Committee meeting.
- 54. June 4, 2004** – NDA 21-042/S-026 an Approvable action was taken for the JRA indication. Although agreement was reached that the study submitted in support of efficacy demonstrated non-inferiority to the comparator (naproxen), agreement was not reached on the language to be added to the package insert describing the pediatric clinical trial.
- 55. June 09, 2004** – 74-Day letter for NDA 21-042/S-030 is issued with the following comments regarding the efficacy of Protocols 078 and 091:
- “The results of Study 078 do appear to indicate that patients with Mild Cognitive Impairment, who take rofecoxib in a dose of 25 mg/day, have an increased risk of developing overt Alzheimer's Disease compared with those who receive placebo. The lack of a significant effect on cognition and on measures of global function in either of two further studies of rofecoxib in overt Alzheimer's Disease [Study 091, and the study conducted by Aisen et al] do contrast with the results of Study 078. The study by Aisen et al, did show a trend toward greater worsening on the cognitive primary efficacy measure, the ADAS-Cog, in patients treated with rofecoxib than in those treated with placebo.”
- 56. August 11, 2004** – DAAODP learns that Dr. Graham is going to present a poster related to cardiovascular risks with Vioxx™ at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Upon review of the poster abstract, the Division felt that the data did not support the author's conclusions. A complete study report was not provided to the DAAODP until October 7, 2004. The study is under review.
- 57. August 19, 2004** – NDA 21-042/S-026 approval of the JRA indication supported by studies conducted under IND 46,894.
- 58. September 27, 2004** - Merck is schedule to brief FDA on the cognition efficacy data from Protocols 078 and 091 submitted under IND 55,269 and NDA 21-042/S-030 currently under review. At 8:32 a.m. Merck conveys to FDA that DSMB recommended stopping APPROVe study under IND 59,222. The APPROVe study showed increased risk of myocardial infarction and stroke for the 12.5 and 25 mg dose as compared to placebo after 18 months of treatment.

- 59. September 28, 2004** – Merck request an emergency meeting with FDA upper management. At the meeting Merck shares data from the APPROVe trial conducted under IND 59,222 and announces the product withdrawal of VioxxTM from the market.
- 60. September 30, 2004** – Public announcement of worldwide product withdrawal of VioxxTM.