Table 13
Analysis of Time to Taking Rescue Medication
(Intention-to-Treat Approach)

Treatment	N	Number (% †) of Patients Taking Rescue Medication	Time (Hour) to Rescue Medication by Percentile		
			25th	Median-50th (95% CI)	75th
Placebo	53	51 (96.2)	1.3	2.8 (1.8, 3.8)	5.0
MK- 0966 50 mg	110	72 (66.5)	2.3	5.3 (4.0, 8.1)	NE
Naproxen Sodium	55	40 (73.6)	3.0	5.3 (3.3, 7.5)	NE

Pairwise Comparison	Cox Proportional Hazards Regression (Primary Analysis)		Log-Rank Test ‡
	Risk Ratio (95% CI)	p- Value	p- Value
MK- 0966 50 mg vs. Placebo	0.46 (0.30, 0.68)	<0.001	<0.001
Naproxen Sodium vs. Placebo	0.50 (0.32, 0.80)	0.004	<0.001
Naproxen Sodium vs. 50/ 25 mg	1.10 (0.72, 1.68)	0.653	0.600

Effect		
Treatment	p- Value	p-Value
Baseline Pain Intensity (PI)	<0.001	<0.001
Surgical Procedure	0.006	0.003
Center (Study Site)	0.413	0.294
Treatment- by- PI Interaction	0.043	<0.001
Treatment- by- Surgery Interaction	0.739	NA
Treatment- by- Center Interaction	0.009	NA
	0.281	NA

† Kaplan-Meier estimate of incidence rate (This may be different from the crude rate).
‡ Secondary supportive results from non-parametric test.
NE: Not estimable. Percentile NE due to low percentage (<= x% for the x'th percentile).
NA: Not available from non-parametric log-rank.

2) Percent of Patients Who Took Rescue Medication Within 12 Hours

There were 96.2, 65.5, and 72.7% of patients who took rescue medication within 12 hours postdose in the placebo, rofecoxib 50-mg, and naproxen sodium 550-mg groups, respectively.

The Percent of Patients Who Took Rescue Medication within 12 hours of study drug administration was significantly ($p<0.001$) lower in the rofecoxib 50-mg group compared with the placebo group.

A significantly ($p=0.003$) smaller percentage of patients in the naproxen sodium 550-mg group who took rescue medication compared to the placebo group. The percentages of patients who took rescue medication within 12 hours postdose in the rofecoxib 50-mg and naproxen sodium 550-mg groups were not significantly different.

Overall Analgesic Effect on Days 2 to 5

1) Use of Supplemental Rescue Medication Over Days 2 to 5

Ninety-five, 92, 81, and 94% of patients in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg, and naproxen sodium/placebo groups, respectively, required at least 1 dose of supplemental rescue medication on Days 2 to 5. LSMean tablets per day were 2.6, 2.1, 1.6, and 2.4 tablets/day in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg, and naproxen sodium/placebo groups, respectively.

The LSMean in the rofecoxib 50-mg/50-mg group was significantly lower than that in the placebo group (p=0.005); however, the differences between the LSMeans for the rofecoxib 50-mg/25-mg and placebo groups was not statistically significant (p=0.127).

The LSMean tablets per day for the rofecoxib dose groups were not significantly different (p=0.159)

2) Patient's Global Evaluation Over Days 2 to 5

The LSMean Patient's Global Evaluation scores averaged over Days 2 to 5 in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg, and naproxen sodium/placebo groups were 1.8, 2.0, 2.3, and 2.1, respectively.

The LSMean in the rofecoxib 50-mg/50-mg group was significantly greater than that in the placebo/placebo group (p=0.041); however, the difference between the LSMeans for the rofecoxib 50-mg/25-mg and placebo groups was not statistically significant (p=0.267). The LSMean Patient Global Evaluation score averaged over Days 2 to 5 for the two rofecoxib dose groups were not significantly different (p=0.327).

The daily LSMean patient global evaluation scores were similar in the different treatment groups across Days 2 to 5. Only at bedtime of study day 3 the rofecoxib 50/50 mg treatment group was statisticall significant better than placebo.

3) Pain Intensity Score Over Days 2 to 5

The LSMean pain intensity score averaged over Days 2 to 5 were 1.3, 1.2, 1.2, and 1.3 in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg, and naproxen sodium/placebo groups, respectively. The LSMean Pain Intensity scores averaged over Days 2 to 5 in the rofecoxib 50-mg/25-mg and rofecoxib 50-mg/50-mg groups were not significantly different from that in the placebo group. The LSMean Pain Intensity scores averaged over Days 2 to 5 between the two rofecoxib dose groups were not significantly different

Safety Results

The incidence of adverse experiences was generally similar across all treatment groups and was not significantly greater in the rofecoxib groups compared with placebo. One or more adverse experiences were reported by 77.4, 57.1, 77.8, and 67.3% of patients in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg, and naproxen sodium/placebo groups, respectively (Table 14).

Table 14
Clinical Adverse Experience Summary

	Placebo /Placebo (N= 53)		Rofecoxib 50/25 mg (N= 56)		Rofecoxib 50/50 mg (N= 54)		Naproxen 550 mg/Placebo (N= 55)	
	n	(%)	N	(%)	n	(%)	n	(%)
Number of patients evaluated	53		56		54		55	
Number (%) of patients:								
with one or more adverse experiences	41	(77.4)	32	(57.1)	42	(77.8)	37	(67.3)
with no adverse experience	12	(22.6)	24	(42. 9)	12	(22.2)	18	(32.7)
with drug- related adverse experiences †	7	(13.2)	8	(14.3)	7	(13.0)	8	(14.5)
with serious adverse experiences	4	(7.5)	3	(5.4)	1	(1.9)	2	(3.6)
with serious drug- related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.8)
Discontinued due to adverse experiences	8	(15.1)	3	(5.4)	4	(7.4)	3	(5.5)
Discontinued due to drug-related adverse experiences †	2	(3.8)	2	(3.6)	1	(1.9)	1	(1.8)
Discontinued due to serious adverse experiences	2	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to serious drug- related adverse experiences †	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

No significant differences between treatments were observed.
† Determined by the investigator to be possibly, probably, or definitely drug related.

Clinical Adverse Experiences by Body System

The incidence of adverse experiences in each body system was not significantly greater in the rofecoxib treatment groups compared with the placebo group. Statistically significant differences between treatment groups in body systems were noted (Table 15), but the findings were not considered clinically meaningful.

Table 15

Number (%) of Patients With Clinical Adverse Experiences by Body System

	Placebo (N= 53)		Rofecoxib 50/25 mg (N=56)		Rofecoxib 50/50 mg (N= 54)		Naproxen 550 mg /Placebo (N=55)	
	n	(%)	N	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	41	(77.4)	32	(57.1)	42	(77.8)	37	(67.3)
Patients with no adverse experience	12	(22.6)	24	(42.9)	12	(22.2)	18	(32.7)
Body as a whole/ site unspecified	24	(45.3)	10	(17. 9) *	11	(20.4)*	16	(29.1)
Cardiovascular system	3	(5.7)	2	(3.6)	2	(3.7)	2	(3.6)
Digestive system	22	(41.5)	14	(25.0)	22	(40.7)	21	(38.2)
Ears, eyes, nose, and throat	4	(7.5)	0	(0.0)	1	(1.9)	3	(5.5)
Hemic and lymphatic	2	(3.8)	4	(7.1)	3	(5.6)	2	(3.6)
Metabolites and nutrition	1	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal system	7	(13.2)	5	(8.9)	6	(11.1)	6	(10.9)
Nervous and psychiatric	11	(20.8)	9	(16.1)	12	(22.2)	11	(20.0)
Psychiatric disorder	6	(11.3)	1	(1.8)	4	(7.4)	2	(3.6)
Respiratory system	5	(9.4)	2	(3.6)	3	(5.6)	2	(3.6)
Skin and skin appendages	11	(20.8) **	5	(8.9)	10	(18.5)**	2	(3.6)
Urogenital system	6	(11.3)	6	(10.7)	3	(5.6)	2	(3.6)

* p<0.05 vs. placebo.
** p<0.05 vs. naproxen sodium/placebo.

The most commonly reported adverse experiences were constipation (28.3, 10.7, 20.4, and 21.8%), fever (20.8, 5.4, 9.3, and 5.5 %), and nausea (11.3, 10.7, 20.4, and 16.4%) in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50-mg/50-mg and naproxen sodium/placebo groups, respectively.

The incidence of dyspepsia was significantly greater in the rofecoxib 50-mg/50-mg group compared with the placebo/placebo group (p=0.018); 0 (0.0%), 2 (3.6%), 5 (9.3%), and 2 (3.6%) of the patients in the placebo/placebo, rofecoxib 50-mg/25-mg, rofecoxib 50 mg/50-mg and naproxen sodium/placebo groups, respectively. Only two of the dyspepsia adverse experiences in the
rofecoxib groups were considered by the investigator to be drug related (one in each of the rofecoxib treatment group).

Discussion and Overall Conclusions for Study # 072

Rofecoxib 50-mg dose demonstrated significantly greater analgesic effect compared with placebo in all measures of analgesic effect (i.e., the overall, onset, peak, and duration of analgesic effects) in the treatment of postoperative dental pain.

Efficacy—Day 1

Rofecoxib at a dose of 50-mg demonstrated significantly greater analgesic effect compared with placebo in most measures of analgesic effect derived from pain intensity and pain relief scores following the first dose administration and up to 12 hours. Onset of analgesia was observed at 1 hour post dose and it seems that efficacy has been sustained for 12 hours. The active comparator Naproxen Sodium 550 mg showed onset of analgesia at 1 hour and continuing through 12 hours and thus validating the study.

Efficacy—Days 2 to 5

Rofecoxib at a dose of 50 mg daily demonstrated statistically significant improvements compared with placebo in the measures of overall analgesic efficacy derived from the amount of supplemental rescue medication used and average daily global evaluations. Rofecoxib at a dose of 50 mg on Day 1 followed by 25 mg daily did not demonstrate statistically significant improvements compared with placebo in these measures. Rofecoxib 50 mg/25 mg was not significantly different in these measures than rofecoxib 50 mg/50 mg, there was however a trend of increasing improvement with increasing dose.

Rofecoxib 50 mg/50 mg daily was numerically but not statistically better than placebo in the mean pain intensity scores on Days 2 to 5. The mean scores for all treatment groups were relatively low both prior to and after dosing with study medication, reflecting overall mild pain in the entire patient population. This is not surprising given that there were no restrictions on when rescue medication could be taken in relation to the pain intensity evaluations.

Safety

The incidence of drug-related adverse experiences was similar in all treatment groups. There were no significant rofecoxib treatment related effects on weight, blood pressure, creatinine clearance, proteinuria, or wound healing. However, this was a short-term study and most safety conclusions should be made after reviewing the longer-term OA studies included in this submission.

In conclusion, results of this study were consistent with the results of previous studies in postoperative dental pain and dysmenorrhea and confirmed that a single dose of rofecoxib 50 mg is efficacious in the treatment of postoperative pain. As for the multiple-dose 2 to 5-day administration, efficacy has been demonstrated in less supplemental rescue medication use and in average daily global evaluation but not in pain intensity scores. This efficacy was exhibited only for the 50 mg dose on day 1 followed by 50 mg on days 2 to 5.

Division of gastrointestinal and Coagulation Drug Products
Medical Officer's Consult Review

Date 5/5/99

NDA:	**21-042 tablets** **21-052 suspension**
Sponsor:	**Merck Research Laboratories**
Requested by:	**Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products HFD-550**
Date of Request:	**December 18, 1998**
Drug :	**Rofecoxib (MK-0966 or VIOXX)**
Proposed Indication:	**Acute and chronic treatment of the signs and symptoms of osteoarthritis** **Relief of pain** **Treatment of primary dysmenorrhea**
Materials reviewed:	**NDA 21-042 studies 041,050,044,045,069**
Consultant:	**Lawrence Goldkind M.D.**

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Executive Summary

The sponsor of this NDA, Merck and Co. has presented an extensive clinical GI safety development program in NDA 21-042. Two endoscopic ulcer studies compared Vioxx at two proposed dosages of 25 and 50 mg/day to ibuprofen at a comparable antiarthritic efficacy dosage of 2400 mg/day in three divided doses and placebo at 6and 12 weeks. The active drugs were continued for an additional 12 weeks. Endoscopy was performed at 24 weeks as well. A robust statistically significant difference was shown between Vioxx 25 and 50mg daily compared to ibuprofen 2400 mg in three divided doses daily. Conclusions based on placebo comparisons made by the sponsor are more difficult to assess. The individual studies revealed opposite trends in placebo ulcer rates compared to Vioxx. Furthermore, the placebo ulcer rates were 5% versus 10% in study 045 and 044 respectively. In study 044 placebo rates were higher than Vioxx 25 mg at 6 and 12 weeks and higher than Vioxx 50 mg at 12 weeks. In study 045 the ulcer rates were 0, 3.2 and 6.6% at 6 weeks in the placebo, Vioxx 25 and 50mg groups respectively. At 12 weeks the ulcer rate was 2.75, 4.8 and 8.2% respectively for placebo, Vioxx 25 and 50 mg. Baseline characteristics were different between the two studies in respect to the important characteristics of NSAID use prior to starting the study and prior history of clinical ulcers (PUB). Study 044 had a 75% higher rate of history of PUBs and 67% higher rate of NSAID use within 30 days prior to baseline visit compared to study 045. These important differences in baseline characteristics between the two groups may account for the differences in placebo ulcer rates between the two studies and raise questions about the validity of combining such studies for statistical analysis. When the two endoscopic studies with over 1400 enrollees are combined for analysis, the ulcer rates at 6 weeks were 1.6, 3.1 and 5.8 % respectively for placebo Vioxx 25 and 50mg respectively. At 12 weeks the ulcer rates were 7.3, 4.7 and 8.1 respectively. At 12 weeks there are similar ulcer rates between placebo and Vioxx 25mg as defined by the sponsor (less than a 4% difference in comparability bounds with a confidence interval of 90%). However, a dose-related rise in ulcer rates was noted in the Vioxx groups at all time intervals (6, 12 and 24 weeks), such that there was a strong trend ($p= 0.066$) at 12 weeks and a statistically significantly higher ulcer rate in the Vioxx 50 mg group compared to the Vioxx 25 mg group at 24 weeks ($p=0.043$). These significant differences between the two therapeutic dosages of Vioxx make placebo comparisons difficult to interpret. Furthermore, significant differences between placebo and Vioxx in esophageal injury scores were also seen. The statistical comparisons between one dose of Vioxx and placebo at one time interval of study in the one study endpoint of endoscopic gastroduodenal ulcers may be misleading because the more global UGI safety profile of the drug is of most clinical relevance.

The sponsor performed an analysis of combined data from 8 controlled trials within the submission to assess the comparative rates of clinically relevant ulcers (PUBs) as well as the comparative rates of GI adverse events and "NSAID-type" GI adverse events and withdrawals due to such events. When combining results from all three dosages of Vioxx (12.5, 25, and 50mg) and comparing this group to the combined NSAIDs (ibuprofen, diclofenac and nabumetone) there was a statistically significantly lower incidence of discontinuations due to overall GI adverse events in the Vioxx group compared to the NSAID group at 4, 6 and 12 months. Discontinuation or withdrawal from the study due to a composite adverse event endpoint of NSAID-type symptoms (epigastric tenderness, dyspepsia, nausea, vomiting and heartburn and acid regurgitation)was evaluated. There was a trend towards a lower rate in the Vioxx group however, the difference between the groups was not statistically significant. There was a near two-fold higher rate of such withdrawals in the Vioxx group compared to placebo at 4 months, the last time point for placebo data. Overall, NSAID-type symptoms were experienced by a similar percentage of Vioxx and NSAID users over 12 months. At 4 months placebo, Vioxx and NSAID groups experienced similar rates of NSAID-type symptoms. The incidence of clinically relevant ulcers (PUBs) was lower in the Vioxx group than the NSAID group with a relative risk of 0.45 ($p= 0.006$) When the groups were broken down into individual doses of Vioxx and separate NSAIDs several points emerged:

1. The exposure to nabumetone was limited to one small 6-week study in the elderly (over 80 y/o). This limits the use of nabumetone as a comparator.
2. The incidence of adverse events in the Vioxx 50 mg group was higher than in the lower dosages of Vioxx as well as the diclofenac group for all four endpoints of withdrawal due to GI adverse events, withdrawal due to NSAID-type adverse events and total NSAID-type adverse events and PUBs. The differences were not statistically significant however the trends prevent valid class comparisons suggest that there may be dose related differences in GI adverse events when using Vioxx.
3. The incidence of heartburn and nausea and vomiting as individual endpoints was in the range of 7-9% in the Vioxx 50 mg group at 12 weeks and was slightly higher numerically than in the ibuprofen group. This is consistent with the esophageal injury scores generated in the endoscopic studies where ibuprofen and Vioxx 50 mg groups displayed similar rates of esophageal erosion and ulceration.

A 4-week study of fecal occult blood loss showed statistically significantly lower rates in patients treated with Vioxx 25 and 50 mg compared to ibuprofen. Only slight differences were seen in the Vioxx group compared to placebo. The clinical significance of these differences in this bioassay is unclear.

In another bioassay, a 7-day study of intestinal permeability showed no significant differences between baseline and 7-day intestinal permeability ratios as measured by the ^{50}Cr EDTA/L-rhamnose urinary excretion ratio for the placebo and Vioxx 25 and 50 mg groups. There was a statistically significantly higher ratio after one week of indomethacin exposure.

In summary, the sponsor has shown that Vioxx is associated with a lower rate of gastroduodenal ulcers over 12 and 24 weeks at doses tested and a lower rate of occult GI

blood loss over a 4-week period than ibuprofen. Intestinal permeability as measured by the ^{50}Cr EDTA/L-rhamnose urinary excretion ratio was similar for placebo and Vioxx. In terms of gastrointestinal symptoms and clinically relevant ulcers, Vioxx could not be as well differentiated from NSAIDs as a class given the differences between ibuprofen and diclofenac and the differences between Vioxx 50 mg compared to Vioxx 12.5 and 25 mg. A true clinical endpoint study comparing Vioxx and NSAID comparators would clarify the UGI safety profile better than is possible in the studies presented in NDA 21-042. It will be difficult however to extrapolate individual comparisons to the entire class.

Background:

NSAID induced gastrointestinal side effects are the most frequently reported adverse drug related events in the United States. Although most of these are minor, adverse events such as symptomatic ulcer, perforation and bleeding are reported to occur in 2-4% of patients on chronic therapy. Use of this category of drugs is associated with gastrointestinal adverse events from the esophagus down to the colon and rectum. The most clinically relevant adverse events occur in the stomach and duodenum in the form of complicated ulcers that result in bleeding obstruction or perforation. These complications occur in less than 1% of patients on chronic NSAID therapy over 6 months.[1]
Asymptomatic erosions and ulceration are not uncommon (and according to some studies occur in up to 30% of rheumatologic patients on chronic NSAID therapy)[2,3].
Symptomatic ulcers are less common; occurring in approximately 30% of patients with documented ulcers: leaving 70 % of ulcers asymptomatic. Conversely, dyspeptic symptoms unassociated with ulcers or even erosions occur in 10-15% of arthritic patients taking NSAIDs [4,5]. This relative disassociation between ulcer-like symptoms and ulcers in NSAID users complicates the study of adverse events associated with the use of this group of drugs. Likewise, the definition of an ulcer used in various endoscopic studies varies. Endoscopic skills and subjective interpretation of "depth" which is required for any definition of ulcer vary from observer to observer. Based on a comparison of autopsy and clinical trial data one author suggests that if a clinical study of NSAID related gastric ulcers yields a rate of significantly more than 15%, the endoscopist is likely to be detecting erosions[6]. The above noted factors create difficulty in relying on endoscopic ulcer studies as the sole basis of assessing GI the safety of known GI toxic medications such as NSAIDs. Given the significant symptomatic adverse event profile in the absence of ulcers as discussed above should symptoms be included in defining GI toxicity? Discontinuation due to GI symptoms is relevant to the effectiveness of an NSAID. Certainly serious complications such as GI bleeding, perforation and obstruction are vital to the definition of any GI safety profile.
The broad based usage of NSAIDs for acute and chronic pain in the general population as well as in the large population of arthritis patients translates into a large absolute number of serious complications. It has been estimated that at least 2600 deaths and 20,000 hospitalizations per year in the United State scan be attributed to NSAID use in rheumatoid arthritis patients alone[7]. Put another way, the chance of hospitalization or death from a gastrointestinal adverse event is 1.3-1.6% per year in-patients with rheumatoid arthritis known to be taking NSAIDs. Some authors estimate over 7000 deaths per year are attributable at least in part to the use of NSAIDs in the general

population in the U.S. alone. Estimates from the United Kingdom suggest 1200 patients a year die there as a result of NSAID adverse events[8].

NSAID gastroduodenal injury is multifactorial. The most commonly cited pathogenic mechanism is the inhibition of cyclooxygenase (Cox) and its catalytic effect on arachadonic acid and prostaglandin G2 locally in gastroduodenal mucosa and the subsequent depletion of endogenous constitutive prostaglandins. This appears to be the major mechanism of gastroduodenal injury. Another mechanisms of NSAID gastroduodenal injury is the mucus layer penetration of unionized drug in the acidic gastric environment and subsequent mucosal epithelial cell damage. Important clinical support for the Cox inhibition mediated mechanism comes from seminal studies involving misoprostol (a synthetic analog of prostaglandin E1 available in the U.S. as Cytotec). At adequate doses and regimens this drug significantly reduces ulcer formation. Gastric ulcer rates in NSAID treated patients on misoprostol were 4% compared to almost 16% in placebo treated patients.[9] In another study serious complications such as bleeding, perforation and gastric outlet obstruction were decreased by 40% in misoprostol treated rheumatoid arthritis patients on NSAIDs[1]. This placebo controlled study required nearly 9000 patients to show statistical significance due to the low overall occurrence of these adverse outcomes in placebo treated patients (0.76% over 6 months). An important result of the large controlled studies of misoprostol was the risk stratification for ulcers. Advancing age, cardiovascular disease, a history of ulcer disease and especially a history of complicated ulcer disease are risk factors for NSAID related ulcers. An earlier population based retrospective case-control study from the United Kingdom had found increasing age, gender, prior peptic disease, alcohol consumption, smoking, anticoagulant usage and corticosteroid usage to be risk factors for peptic ulcer complications. Other studies have yielded contradictory results, especially related to tobacco and corticosteroid usage. Most studies however are weakened by small size, as well as retrospective and uncontrolled approaches.

There is no conclusive evidence that the occurrence of NSAID related ulcers will predict the risk of complicated ulcers. This intuitive assumption however is accepted by many. The primary evidence supporting this assumption is the cross study analysis of two studies involving misoprostol that is discussed in appendix I. Preliminary data from the recently approved NDA 20-998 suggests that this is true, however outcome studies are in progress to test this hypothesis specifically for ulcers associated with the use of Cox-2 specific inhibitors.

Historically, the concept of multiple forms of Cox dates back to 1972.This concept was based on observations that acetaminophen blocked prostaglandin synthesis in the central nervous system but not in peripheral tissues. In the 1980s studies showed that prostaglandin synthesis could be inhibited by sodium salicylate at sites of inflammation without affecting gastric prostaglandin synthesis. In 1991 the existence of multiple isoforms of Cox was proven through molecular characterization of the second form. This discovery has led to a flurry of theories, models and studies of the physiologic and pathophysiologic roles of the different forms as well as attempts to capitalize on the different tissue locations of the two isoforms to tailor therapy that requires inhibition of

Cox. Cyclooxygenase-1 (Cox-1) is a constitutive enzyme that has been described as having a "housekeeping" role in maintaining the integrity of the gastric mucosa and renal function; Cox-2 is more inducible and is found in association with inflammatory processes. The location on different chromosomes would support distinctly different roles for these two isoforms. Crossover in tissue location of the two forms does exist (except in platelets), and messenger RNA for both forms has been found in most human tissues tested including stomach, small intestine mammary gland, uterus, pancreas, liver, kidney, brain, thymus, prostate and lung. There is, however, a distinct differential distribution of each isoform in specific tissues. In general Cox-1 is prevalent in stomach, kidney and platelet while Cox-2 is prevalent at sites of active inflammation.

An array of selective Cox-2 inhibitors has been developed and extensively tested. Meloxicam, an anti-inflammatory drug, is just such a Cox-2 selective inhibitor and has been extensively tested and marketed in Europe. While clearly displaying the anticipated decrease in GI toxicity at lower dosage regimens, it has not been free of associated adverse events. Early trials with 30-60 mg daily dosing schedules revealed similar incidence of adverse events compared to standard NSAIDs. Even clinically accepted doses of 15 mg a day revealed some GI toxicity, although less than that seen with active comparators such as piroxicam and diclofenac. Celecoxib (Searle), a recently approved Cox-2 selective agent has been documented to be associated with markedly fewer ulcers than ibuprofen and naproxen at clinically comparable dosage levels. Unlike meloxicam, there was no dose-related rise in ulcer risk at dosages up 400mg BID or four times the recommended dose. Clearly issues of degree of Cox-2 specificity, dose, relative efficacy and safety all must be addressed when assessing the safety and efficacy of these compounds. In addition, assays for Cox isoform specificity are not well standardized. There are multiple in vivo and in vitro assays with much discrepancy among these various assay methods. Therefore, the relative merits of these drugs and their safety and efficacy profiles therefore can be accepted only with critical clinical scrutiny.

Vioxx (rofecoxib/ MK-0966) is the subject of NDA 21-042. The sponsor describes it as a selective Cox-2 inhibitor. The GI consultation is specifically requested to review GI safety claims related to this compound. The proposed label claims that:

1. Vioxx at doses of 25mg and 50mg a day is associated with significantly lower rates of gastroduodenal ulceration and significantly fewer "PUBs" than nonspecific cyclooxygenase inhibitors. (the term PUB is not defined clearly by the sponsor and does not have a standardized definition in the medical literature)
2. Vioxx usage at doses of 25mg to 50mg is comparable to placebo in terms of ulcer occurrence.
3. The incidence of discontinuation due to any GI adverse events is significantly lower in patients treated with Vioxx than in patients treated with nonspecific cyclooxygenase inhibitors.
4. The incidence of prespecified GI adverse events regardless of drug relationship is significantly lower in patients treated with Vioxx than in patients treated with nonspecific cyclooxygenase inhibitors over the first 6 months