The question of whether to pursue litigation over Cox-2 inhibitors -- which currently include, primarily, Vioxx (Rofecoxib) and Celebrex (Celecoxib) -- is a question that many firms are pondering at the present time. There has been in recent months significant activity at the Food & Drug Administration (FDA) over the safety profile of Vioxx, specifically concerning serious cardiovascular injury, as that term is defined in an article published in the Journal of the American Medical Association which will be addressed later in this article. Interestingly, this class of drugs which are being discussed and debated by many counsel are one of the hottest selling groups of drugs that the pharmaceutical industry has seen in recent years. Equally interesting is the fact that the drugs at issue are the progeny of the drug that spawned the birth of the modern pharmaceutical industry over 100 years ago -- aspirin.

Coxibs are members of a broader class of drugs known as nonsteroidal anti-inflammatory drugs; other members of this class of drugs include ibuprofen, naproxen, Naprosyn, and, as stated previously, aspirin. Throughout the development and use of nonsteroidal anti-inflammatory agents (NSAIDs) it has been widely recognized that this class of drugs are extremely effective at reducing pain through the inhibition of the cyclo-oxygenase enzyme, causing the inhibition of the production of prostaglandin and prostacyclin thus inhibiting inflammation in joints, and thereby eliminating pain. However, what has also been widely recognized about NSAID therapy is that in addition to mediating joint pain due to inflammation, it has also been responsible for significant gastrointestinal side effects, including perforations, ulcerations and bleeds (PUB’s). As a result, the pharmaceutical industry has long recognized the distinct advantages — both therapeutically and commercially — of developing a
nonsteroidal anti-inflammatory agent that could have the salutary effect of reducing pain while at the same time sparing the gut of GI upset. In 1989, Dr. Philip Needleman, then of Washington University Medical School in St. Louis, Missouri, postulated that there were in fact two (2) forms of cyclooxygenase that participate within our system: Cox-1 and Cox-2. It is believed that the Cox-2 enzyme is responsible for the release of prostaglandin at inflammatory sites, while the Cox-1 enzyme maintains the integrity of the smooth muscle surfaces of the GI tract. The theory behind Cox-2 inhibitors is that they give all the benefits of general NSAID’s while sparing patients of GI complications. And it is out of this theory that Cox-2 selective NSAIDs were born.

With this very brief background of the development of and theory behind Cox-2 inhibitors, it would be helpful to look at the recent cardiac concerns related to one of these block-buster drugs. Merck, the manufacturer and marketer of Vioxx, submitted its new drug application on November 23, 1998. (See http:\www.fda.gov\cdr\fo\nda\99\021042_52_vioxx_appltr.pdf), with 14 supplementations being received by FDA up to May 19, 1999, the day before FDA’s approval letter was penned allowing for the marketing of Vioxx.

- April 20, 1999, the Advisory Committee on Arthritis Drugs meets to review the medical profile of Vioxx.
- May 21, 1999, FDA approves Vioxx (Rofecoxib), a new drug for the treatment of osteoarthritis, menstrual pain and for the management of acute pain in adults. Shortly thereafter, Merck initiates one of the most aggressive direct-to-consumer (DTC) advertising and promotion campaigns since the inception of direct-to-consumer advertising in 1993.
- June 22, 1999, Merck enters into a speaker’s contract with Peter Holt, M.D., who subsequently conducts several live and audio conferences to educate (sic) health care professionals on the claimed benefits of Vioxx.
- October 8, 1999, less than five (5) months into the market history of Vioxx, Merck updates the
Vioxx package insert.

- June 8, 13 and 16, 2000, promotional audio conferences are held by Peter Holt, M.D., the substance of which was, at a minimum, directed by Merck for use by Dr. Holt. Portions of these presentations are the subject of a subsequent warning letter to Merck for violations of the Food, Drug & Cosmetic Act.

- December 12, 2000, FDA notifies Merck about its knowledge of the Holt promotional conferences, and seeks the company's reply.

- January 5, 2001, Merck replies to inquiries concerning the Holt promotional teleconferences.

- February 8, 2001, the FDA Arthritis Advisory Committee meets to discuss concerns over cardiovascular risks associated with the use of Vioxx. In order to understand the context of this Advisory Committee meeting, it is important to understand the purpose of the study reviewed and out of which the cardiac concerns were spawned. Merck, in an attempt to rid Vioxx of the standard NSAID gastrointestinal warnings, initiated the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) to assess the gut-sparing benefits of this medication. There were no cardiac endpoints assessed in the VIGOR study. Despite its initial claim that Vioxx would not disrupt the GI tract and complicate the care regimen with the same GI problems as general NSAIDs, the Food & Drug Administration, when faced with a lack of hard data establishing the GI protective aspects of the drug, required Merck to carry the same GI warnings as general NSAIDs; that is, Merck was compelled to include on its label precautions that 2-4% of individuals taking Vioxx would suffer GI complications. It has been, and continues to be a major selling point for Merck, both from a theoretical, scientific standpoint as well as a strong marketing standpoint, that as a Cox-2 inhibitor Vioxx does not cause the same problems in the GI tract as do other general NSAIDs. Consequently, the VIGOR study was undertaken.

- Merck advocates that, based upon GI scoping that showed fewer perforations, ulcerations,
bleeds (PUBs) in the 15-month VIGOR study that in fact Vioxx was gentler on the gut. The FDA, however, saw things a bit differently, and, based purely on what was presented following the VIGOR study, it held its position that PUBs do not necessarily equate to GI complications; the FDA maintained that the lack of scope evidence does not in fact equate to fewer incidences of GI complications. Nevertheless, for purposes of this paper, there are two important aspects of the February 8, 2001 Advisory Committee meeting. The first is that it underscores the fact that Merck, in undertaking VIGOR, was focused on the GI aspects of Vioxx and not cardiac issues. Secondly, is the memo of Shari L. Targum, M.D., the Project Manager for the Division of Anti-inflammatory Drug Products concerning cardiac issues. In Dr. Targum's memorandum it is clearly stated that as early as November 18, 1999, the Data and Safety Monitoring Board of the VIGOR study, a committee independent from the sponsor, was concerned over the "excess deaths and cardiovascular events experiences in Group A [vioxx group] compared to Group B [naproxen]." (52 v. 29 respectively). This memo establishes a date of recognition within the FDA of when serious cardiovascular events were brought to the attention of Merck, and a starting point for determining what actions were undertaken once a red flag is raised.

- From an international standpoint, in June of 2000 there was information presented before the European United League Against Rheumatism, an organization in which Merck is a member and a corporate sponsor that demonstrated a statistically significant increase in hypertension and myocardial infarction.

- May 22, 2001, in the wake of studies that clearly demonstrate concerns over the cardiovascular safety profile of Vioxx, in particular the increased incidents of cerebrovascular accidents, myocardial infarction, deep vein thrombosis, and pulmonary embolism, among other cardiovascular injuries, Merck made two (2) significant press releases. The first coming on May 22, 2001, titled "Merck, Sharp & Dohme Reconfirms Favorable Cardiovascular Safety of
Vioxx, Emphasizes Powerful Pain Relief” and a second, which was released on June 16, 2001 in Europe, which claims "Vioxx Similar to Placebo and three (3) Widely Prescribed NSAIDs Regarding Cardiovascular Events”.

- On July 11, 2001 the Vioxx package insert is updated for the second time.

- September 17, 2001, Merck receives its strongest FDA warning letter to date relative to its drugs. The warning letter specifically addresses Dr. Holt's videoconferences, Merck's press releases, and its unfounded and illegal claims of product safety. The FDA cites Merck for minimizing potentially serious cardiovascular findings and of misrepresenting the product's safety profile. Specifically, Merck is chastised for making the unfounded claim, in light of the cardiovascular risks demonstrated in the VIGOR study, that Naproxen has cardioprotective qualities similar or identical to aspirin, and that consequently there appears to be a lowering of cardiovascular events by Naproxen rather than an increase in cardiovascular events related to Vioxx. In addressing Merck's claims of a "favorable cardiovascular safety profile”, the FDA stated that it "is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to Naproxen" to state that Vioxx has a favorable cardiovascular safety profile.

- August 29, 2001, an article entitled "Risk of Cardiovascular Events Associated with Selective Cox-2 Inhibitors", was published in the Journal of the American Medical Association,¹ setting out the risks associated with Cox-2 selective inhibitors. The JAMA article was based on a Meta analysis of previously compiled data through the VIGOR, CLASS (Celebrex Long-Acting Safety Study), and two (2) smaller studies, for cardiovascular risks. Neither the CLASS nor VIGOR studies had developed end-point analyses for cardiovascular risks; instead, these risks were first identified through the previously mentioned Advisory Committee review of the

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VIGOR Data and Safety Monitoring Board Minutes. Nevertheless, the data reviewed was
conspicuously limited as neither Merck nor Pharmacia/Pfizer had undertaken the task of
identifying and studying cardiovascular risks relative to their blockbuster products. Instead, the
manufacturers and marketers of these products simply turned a blind eye to the very idea of a
cardiovascular risk and glossed over the need for further study. In response, Drs. Topol and
Nissen, both of whom were lobbied by the product sponsors to temper their criticisms prior to
the publication of the JAMA article, state that "they have tried unsuccessfully to persuade the
makers of Vioxx and Celebrex to launch new clinical studies of the possible cardiac risks." The
doctors further state “[Merck and Pharmacia's] reluctance to move forward is disturbing . . .
either they're moving at galacial speed or they're waiting to see what the fallout will be from this
and other reports. We're staring at a major public health issue.” Id.

- Further still, in response to the now-recognized potential risk, the manufacturers still maintain the
  lack of any clear indication for further studies. Instead, Merck has set about the standard plan
  for refuting concerns over its drug: its in-house medical staff, combined with paid consultants,
  have authored articles to support its spin of the medical evidence. See, “Comparison of
  Cardiovascular Thrombotic Events in Patients with Osteoarthritis treated with Robicoxib versus
  Non-Selective, Non-Steroidal Anti-Inflammatory Drugs” (Ibuprofen, diclofenac, and
  Nabumetone), A. Reicin, M.D.; D. Shapiro, Ph.D.; R. Sperling, M.D.; and E. Barr, M.D.; and
  Q. Yu, M.S.; American Journal of Cardiology, Vol. 89, January 15, 2002. Interestingly, the
  Reicin article was submitted to the Journal of Cardiology on August 29, 2001, the very week
  after JAMA published the Nissen, et al. article criticizing Vioxx. Also interesting is the fact that
  prior to the submission of the Dr. Reicin article she and two (2) other in-house, Merck-
  employed physicians met with Drs. Topol and Nissen (separately) in Cleveland and New York

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2 The Wall Street Journal, August 22, 2001, quoting Eric Topol, M.D.
in an effort to temper the effects of their criticisms.

Since the publishing of Nissen and Topol's JAMA article, Merck has steadfastly disputed the conclusions drawn by Nissen and Topol, and continues to assert the cardioprotective qualities of Naproxen.

Conversely, since the release of the JAMA article, there have been a number of articles written independent of any Cox-2 sponsor support that appear to substantiate the claims of the Cleveland Clinic Meta analysis. One such article was authored by Richard J. Bing, M.D. and Magdelena Lomnicka, titled "Why Do Cyclooxygenase-2 Inhibitors Cause Cardiovascular Events?" In evaluating whether Cox-2 inhibitors cause cardiovascular events, Bing et al. set out the relationship between the Cox-1 and Cox-2 properties of non-selective NSAIDs. This point was likewise addressed clearly and concisely by Drs. Nissen and Topol in the JAMA article as well. A second, more recent, article by researchers at Vanderbilt University Medical School sets out, again, the theory of how exactly Cox-2 inhibitors promote thromboembolic events. See, The Lancet, Non-Steroidal Anti-Inflammatory Drugs and Risk of Serious Coronary Heart Disease: An Observational Cohort Study, W. Ray, C. Stein, K. Hall, J. Daugherty, M. Griffin, (January 12, 2002) Vol. 359. Without going into an exhaustive review of the Bing and Ray articles, which are far beyond the purpose of this brief presentation, suffice it to say that both articles, and the research underlying each, demonstrate that Cox-2 selective inhibitors promote cardiovascular events by tipping the balance of prostacyclin/thromboxane in favor of thromboxane. In doing so, the imbalance promotes both platelet aggregation and vasoconstriction leading to potentially catastrophic cardiovascular events, including stroke, heart attack and pulmonary embolism among other events.

Although there clearly existed medical evidence of increased cardiovascular risk associated with Cox-2 inhibitors long before the publication of the Nissen, et al., JAMA article, clearly the JAMA

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3 Journal of the American College of Cardiology, Why Do Cyclo-Oxygenase-Inhibitors cause
article thrust into the arena of medical debate concerns over cardiovascular risks in relation Coxib therapy. However, the manufacturers of these products, which enjoy healthy market share and profits, have not initiated long-term studies geared at investigating cardiovascular risks. Instead they have chosen the road of plausible deniability, while claiming non-established medical reasons for the disparity exhibited in the cardiovascular risks demonstrated by the VIGOR study. In spite of a relative risk exceeding 2.0 for Vioxx users (2.38 & 4.89 for non-aspirin-indicated and aspirin-indicated patients, respectively, each with a 95% confidence interval), when compared to Naproxen users, Merck continues to bury its head in the sand.

- April 11, 2002, the FDA instructed Merck to include certain label precautions for cardiovascular risks.

Having reviewed, albeit briefly, the history of the developing medical knowledge of cardiovascular risks related to Vioxx, I will conclude this brief overview with some general marketing information. Since the advent of direct-to-consumer advertising of pharmaceutical products, the industry has scarcely seen two (2) more highly advertised products than Vioxx and Celebrex. Through media sources, it has been reported that Merck spends in the neighborhood of $15-16 million a month on direct-to-consumer advertising. It is further well understood that a great deal more than that amount is spent marketing to physicians. To place these figures in some perspective, it was recently reported that Anheuser-Busch spends roughly $133 million advertising its products to the public; Pepsi-Cola spends roughly $120 million. These figures and products would, by simple mathematical calculation, be approximately $50 million and $70 million less than Merck spends to advertise Vioxx alone. The two-headed marketing juggernaut of direct-to-consumer advertising and detailing of physicians with information that has clearly been recognized by the Food & Drug Administration to lack fair balance and to overstate the safety profile of Vioxx, has resulted in tremendous rewards to the corporation.

**Cardiovascular Events**, R. Bing, M. Lomniclen (Feb. 6, 2002), Vol. 39, No. 3.
In conclusion, Vioxx clearly fits within the business model of many drugs that have been litigated to a successful conclusion: a product that has a demonstrated risk which is underappreciated by its sponsor; benefits that are oversold to the public (and physicians) through an aggressive marketing campaign, while risks are purposefully hidden; and a company that has profited tremendously from its bad acts. Vioxx clearly meets this lawyer’s criteria for pursuit in litigation.