Lawrence Baruch, M.D. 111 East 85th Street
New York, NY 10028

June 2, 2008

Ellen Relkin
Weitz and Luxenberg
180 Maiden Lane
New York, NY 10038

Re: Celebrex and Myocardial Infarction

Dear Ms. Relkin:

I am certified by the American Board of Internal Medicine in the specialty of Internal Medicine and the subspecialty of Cardiovascular Disease. I have completed the specialty and subspecialty recertification process in both Internal Medicine and Cardiovascular Disease (November, 2003). After completing my cardiology fellowship training at the Mt. Sinai Hospital in New York City in 1993, I have been engaged in the full-time practice of cardiology as the Director of the Heart Failure and Echocardiography Programs at the Bronx Veteran Affairs Medical Center, and as an attending cardiologist and echocardiographer at Mt. Sinai Hospital in New York City (since 1995). For the past 6 years, I have served as the Director of Research at COECare, a company that develops software to improve the value and quality of care in cardiovascular disease and orthopedic medicine. I am licensed to practice medicine in the State of New York.

Over the past 15 years, I have been actively engaged in the training of cardiology fellows, internal medicine housestaff, and medical students. I have also had the opportunity to deliver grand rounds at a number of institutions, including Emory University, the University of Kansas, and Westchester County Medical Center, as well as present papers at various cardiology meetings. I have authored 18 publications and a number of abstracts. I serve as a reviewer for a number of medical journals, including Stroke, Archives of Internal Medicine and the Journal of Cardiac Failure.

I have been an investigator in more than 30 clinical trials across the spectrum of cardiovascular disease, including heart failure, atrial fibrillation, and acute coronary syndrome. I served as a member of the steering committee of CHARM-ES (an echocardiographic substudy of the international CHARM heart failure study). Over the past 5 years, I have served as the principal investigator on 4 grants funded by the NIH's National Heart, Lung, and Blood Institute focused on improving and monitoring the quality of cardiovascular care utilizing computer software in the areas of coronary artery disease, heart failure, cholesterol, and atrial fibrillation. In addition, I am a co-investigator on an NIH funded grant in the area of hypertension management.

I have been asked to render my expert opinion on the subjects of medicine, cardiology, myocardial infarction, the risk versus benefits of the Cox-2 inhibitor Celebrex and the adequacy of the Celebrex labeling and warnings to the medical

community. Based on my training, knowledge of the scientific literature, and experience in the diagnostic evaluation and management of cardiovascular disease, I have formulated the following opinion regarding the role of Celebrex in myocardial infarction and the related issues set forth above.

The documents and exhibits referenced in this report are materials I may refer to or rely upon at trial. I may provide testimony relating to the injuries caused by Celebrex, all of which are within the realm of my expertise as a clinical cardiologist, as well as the appropriateness of the labeling, warnings, and communications to cardiologists and prescribing physicians. In providing my opinions, I rely on my education, training, and experience, review of the relative medical and scientific literature, as well as documents from the Federal Food & Drug Administration meetings related to Cox-2 inhibitors (coxibs).

As a clinical cardiologist, I have monitored the scientific and medical literature pertaining to the cardiovascular risks associated with coxibs, including Celebrex. It is my general opinion to a degree of reasonable medical probability that the ingestion of coxibs as a class, including Celebrex, is associated with, and can actually cause, and contribute to a myocardial infarction. Myocardial infarction may cause death, heart failure, stroke, and heart rhythm disturbances.

My opinions are largely based on my review of the medical literature pertaining to the larger randomized prospective clinical trials involving the coxibs- namely VIGOR, the six long term clinical trials discussed in the Celebrex Cross Trial Safety Analysis (Solomon, *Circulation* 2008:117:2104-13), including but not limited to, APC, and PreSAP, as well as CLASS, APPROVE and the, more moderate sized, Valdecoxib/Parecoxib post coronary artery bypass surgery (CABG) studies. An early signal of increased cardiovascular risk from coxibs in a large prospective randomized trial was reported in November 2000 with the publication of the VIGOR trial, where the incidence of myocardial infarction was fourfold greater in the Vioxx cohort (n=17) than in the comparator, Naproxen (n=4). Of note, in the FDA database, the incidence of myocardial infarction in the Vioxx cohort was 20, while remaining unchanged in the Naproxen cohort. Subsequently, 12-month data from CLASS reported a numerical excess of myocardial infarctions in the Celebrex cohort (n=19) when compared to traditional NSAIDs (n=13).

Five of the larger randomized prospective clinical trials with Coxibs, namely APC, APPROVE, CABG II, ADAPT, and PreSAP, were placebo controlled. Of these, three, APC, APPROVE, and Valdecoxib-CABG, demonstrated increased cardiovascular risk with 3 different coxibs, Celebrex (2.0 vs. 0.5% p=.03), Vioxx (1.5 vs. 0.78% p=.008), and Valdecoxib/Parecoxib (2.0 vs. 0.5% p=.03), respectively. This suggests a class effect of the coxibs with respect to increased cardiovascular risk. Another placebo controlled trial, PreSAP, demonstrated a trend toward increased cardiovascular events (Celebrex 2.5% vs. placebo 1.9%).

These clinical trials are consistent with the biologic plausibility that supports the hypothesis that coxibs, including Celebrex, cause and contribute to the occurrence of myocardial infarction by augmenting the response to thrombogenic stimuli by their negative effect on prostacyclin, a compound which places a general constraint on platelet activation. This potential mechanism for vascular thrombosis, commonly referred to in the literature as the *"Fitzgerald hypothesis"*, was explicitly identified as early as July 1998, more than 2 years prior to the release of VIGOR.

It should be recognized that although myocardial infarction is the result of plaque rupture and thrombosis, a mechanism consistent with the *"Fitzgerald hypothesis,"*plaque rupture may be associated with a variety of potential clinical outcomes: 1) a plaque ruptures and the body's own antithrombotic mechanisms prevent the formation of a clinically significant thrombus and the event is unrecognized, 2) a plaque ruptures and a partially occlusive thrombus develops which may or may not result in mild myocardial infarction or symptoms and signs of myocardial ischemia; and 3) a plaque ruptures and a thrombus occludes the artery completely which results in significant myocardial necrosis. Thus while coxibs may alter the thrombotic balance, not all plaque rupture results in an acute coronary syndrome and/or myocardial infarction, and exposure to coxibs concurrent with a plaque rupture appreciably enhances the risk of infarction and/or its severity. Cox-2 inhibitors, including Celebrex, create a milieu that is more favorable toward thrombosis.

Furthermore, the rapid and elevated thrombotic risk detected in two coronary artery bypass graft surgery trials with parecoxib and valdecoxib is consistent with almost complete Cox-2 suppression, which plausibly translates into a deep suppression of prostacyclin. More recent research suggests that there is an association between polymorphisms of the human prostacyclin receptor and the development of thrombosis and atherogenesis.

There are a number of additional mechanisms by which Celebrex may also contribute to myocardial infarction; these include, but are not limited to the following: limiting late ischemic preconditioning, atherogenesis, increasing TXA_2 biosynthesis, reducing the vasodilatory response to arachidonic acid, and increasing blood pressure. These mechanisms are not mutually exclusive, and instead, can be contributory to cardiovascular injury. These mechanisms are not as well recognized or established as the Fitzgerald explanation.

Cox-2 inhibitors including Celebrex, like traditional NSAIDs, raise blood pressure, impair renal perfusion, and cause fluid retention. These adverse CV effects would generaly be through a nonthrombotic cardiovascular mechanism, namely the development of heart failure and edema., hence the mandate to monitor blood pressure and renal function in patients prescribed coxibs or traditional NSAIDs.

The randomized clinical trials, observational studies, and meta-analyses of the coxibs suggest that higher doses are associated with greater cardiovascular risk. The best example of this "dose response" is found in the APC trial with Celebrex where the 400 milligram twice a day dose was associated with a relative risk of cardiovascular events of 3.4 (95% CI, 1.4 to 7.8) compared to placebo, while the relative risk with the 200 milligram twice a day dose was lower but nevertheless substantial at 2.3 (95% CI, 0.9 to 5.5). This is supported by the results of the Celebrex Cross Trial Safety Analysis, which demonstrated an almost doubling of risk at a dose of 200 milligrams twice daily and a tripling of CV risk at a dose of 400 milligrams twice daily. As such a reduction in dose will presumably limit the number of patients exposed to the cardiovascular hazard of coxibs, however, it will not eliminate the risk on an individual level, as there is variability in how people react to these drugs.

The Celebrex Cross Trial Safety Analysis also demonstrated that the risk of Celebrex depends on the baseline cardiovascular risk of a patient. Those with the highest baseline cardiovascular risk had the greatest risk of Celebrex-related adverse events. Another interesting aspect of the study was that the interaction between the level of baseline risk and dose was significant. Simply put, not only was the dose important and the baseline risk important, but the interaction between the two was important—the effect of one influences the other. For example, in those at lowest baseline risk, the dose of the drug doesn't have as much of an effect as those at highest baseline risk.

The onset of cardiovascular risk with coxibs appeared early in the VIGOR and APC trials. Even in the APPROVE trial, where initial reports suggested a delayed onset of cardiovascular risk (18 months), when reanalyzed "correctly" using the intention to treat analysis, risk began to appear within 3-6 months (NEJM 2006;55:203-204).

I have reviewed a number of the observational studies related to coxibs. These studies offer conflicting reports as to the cardiovascular risk of the class in general and each agent individually. It must be recognized that while observational studies are important, often provocative, and potentially hypothesis generating, they generally are not definitive. This is secondary to their retrospective design, which allows for a number of deficiencies including confounding (e.g. BMI and exercise), the usage of prescription records to assess usage as opposed to actual consumption, and the inability to account for non-prescription NSAID and aspirin use. It is well documented in a number of instances that the findings of observational studies are ultimately proved wrong when actual prospective randomized trials are performed to address the question of interest (e.g. the impact of hormone replacement therapy in postmenopausal women and folic acid supplementation in patients with elevated homocysteine levels). Moreover, the availability of prospective carefully collected data from gold standard long-term double-blind prospective randomized trials, provides more reliable data from which to draw conclusions regarding the cardiovascular hazard of coxibs, including Celebrex

It should be noted that the signal of a hazard of Cox-2 inhibitors appeared soon after these agents became available. A number of large clinical trials, including VIGOR, CLASS, and SUCCESS, as well as smaller trials such as the first CABG trial supported the thrombotic mechanism hypothesized by Fitzgerald as early as 1998. These signals from the clinical trials were not only ignored, but denied in well-developed broad marketing initiatives. Accordingly, Pfizer should have provided warnings about these potential risks and certainly should not have provided false reassurance by its encouragement of Celebrex use in a patient population known to be at risk for cardiovascular events. When Pfizer marketed Celebrex as the cardiovascular safe alternative to Vioxx, unpublished data I have reviewed reveals that internally Pfizer had reason to believe Celebrex had distinct cardiovascular risks.

Certainly the data regarding Celebrex and cardiovascular risk showed "reasonable evidence of an association" with the drug for years before Pfizer warned the medical community of this important risk from use of their Cox-2 drug in a vulnerable population. In that I understand that FDA rules did not require a causal relationship to be proven before a drug company must warn of an association (set forth in the recent opinion of newsworthy note McDarby v. Merck, New Jersey Appellate Division), Pfizer's failures are troubling and prevented clinicians from having important information in the treatment of their patients.

In summary, the increased risk of myocardial infarction seen with various Cox-2 inhibitors, including Celebrex, is consistent with a mechanistic explanation that extends to all coxibs. As anti-inflammatory agents are so widely used and cardiovascular disease is the leading cause of death in the United States, even a slight increase in the incidence of myocardial infarction has the potential to significantly impact the health of the population at large. Over and above this, as a small increase in cardiovascular risk maybe difficult to detect in clinical trials of coxibs which were not designed primarily to address their cardiovascular risk, it is clear that the *absence of definitive evidence* in some of the coxib clinical trials certainly does not prove the *evidence of absence* of cardiovascular risk in those trials. In fact, the available evidence is more than adequate to conclude that coxibs, including Celebrex, actually cause, and contribute to a myocardial infarction. Based on the above considerations, I am of the opinion, that the risks of Celebrex *often* outweigh its benefits, most dramatically in patients at elevated risk for or with established cardiovascular disease.

Therefore, a rational treatment approach for the patient with inflammation would be based on the following principles, which are consistent with the recommendations of one of the leading and most respected cardiovascular organizations, the American Heart Association's "Use of Nonsteroidal Antiinflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association."

a. Prescribe the least risky treatment/medication initially;

b. When medications are required prescribe the lowest dose for the shortest; duration

c. Stratify each individual patient with respect to cardiovascular and gastrointestinal risk;

d. If an anti-inflammatory medication is required, consider the "least bad" or "good" NSAID, naproxen, as first-line therapy with or without a gastroprotective agent.

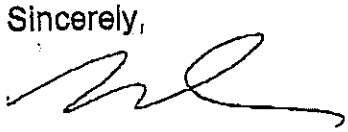
My opinions are based on the knowledge, skill, experience, training, and education that I have obtained throughout my career, including my experience as a medical doctor and researcher. Although I am not an epidemiologist or a biostatistician, through my training during medical school and beyond, along with my involvement in clinical trials, reading of the medical literature and integrating the findings of research into my clinical practice, I have acquired working knowledge of clinical trial design, its interpretation, epidemiology, and biostatistics. I have reviewed the applicable scientific literature, and my testimony is also based on my reading of the literature, including but not limited to the bibliography attached hereto as Exhibit "A".

A copy of my current curriculum vitae is attached hereto as Exhibit "B," and is incorporated by reference into this report the same as if fully set forth at length. This CV includes a list of all publications I have authored in the past ten years.

I am compensated for work done in the preparation of this report at a rate of $500 per hour.

Based upon the information that is presently available to me, the statements contained in this report are accurate. The available scientific literature may expand as science moves forward. I continually review the ever-growing body of literature on Celebrex and the Cox-2 inhibitors in general. I expect to review additional material of a scientific nature from the discovery files that are being produced by Pfizer for the attorneys involved in this litigation. I understand that Pfizer has not yet produced all of the SAS data for the long-term clinical trials and that this will be produced and reviewed by a biostatistician. I anticipate reviewing that analysis. Therefore, I reserve the right to change and/or supplement my opinions based upon this or any other additional information, should it become available.

Sincerely,



Lawrence Baruch, M.D., FACC