# In re Bextra and Celebrex

KeyCite Yellow Flag - Negative Treatment
Declined to Follow by In re Zicam Cold Remedy Marketing, Sales Practices, and Products Liability Litigation, D.Ariz., July 15, 2011

524 F.Supp.2d 1166
United States District Court,
N.D. California.

# In re BEXTRA AND CELEBREX MARKETING SALES PRACTICES AND PRODUCT LIABILITY LITIGATION.

This Order Relates to: all Cases.

No. M:05-CV-01699-CRB.
|
MDL No. 1699.
|
Nov. 19, 2007.

## Synopsis

**Background:** Consumers, among others, sued manufacturer of arthritis pain medication, alleging that they had suffered serious cardiovascular injury due to their ingestion of medication. After actions were consolidated in multi-district litigation, manufacturer moved to exclude expert testimony to the effect that medication was capable of causing heart attack or stroke when ingested at 200 milligrams a day (mg/d) or 400 mg/d, and plaintiffs moved to exclude expert testimony offered by manufacturer.

**Holdings:** The District Court, Charles R. Breyer, J., held that:

[1] proffered testimony of plaintiffs' cardiology expert on issue of whether medication was capable of causing heart attack at dose of 200 mg/d was inadmissible;

[2] neurologist's testimony on issue of whether medication was capable of causing stroke at dose of 200 mg/d was inadmissible;

[3] cardiologist's extrapolation opinion was inadmissible;

[4] exclusion of plaintiffs' expert testimony on issue of whether medication could cause heart attacks when used at dose of 400 mg/d was not warranted;

[5] neurologist's expert testimony that medication was capable of causing strokes was admissible; and

[6] exclusion of manufacturer's meta-analyses was not warranted.

Motions granted in part and denied in part.

West Headnotes (13)

[1] **Evidence**
Necessity and sufficiency

When evaluating the admissibility of expert testimony, the trial court must first determine nothing less than whether the experts' testimony reflects scientific knowledge, whether their findings are derived by the scientific method, and whether their work product amounts to good science. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

2 Cases that cite this headnote

[2] **Evidence**
Necessity and sufficiency

In evaluating reliability of proffered expert testimony, trial judge's obligation is to make certain that an expert employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

1 Cases that cite this headnote

[3] **Evidence**
Necessity and sufficiency

Many factors may be relevant to the inquiry into reliability of proffered expert testimony, including (1) whether the proffered theory or technique has been tested, (2) whether the

theory or technique has been subjected to peer review and publication, (3) the known or potential rate of error of the technique or theory when applied, and (4) the general acceptance of the theory or technique in the scientific community. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

Cases that cite this headnote

[4] **Evidence**
Matters involving scientific or other special knowledge in general

In addition to determining reliability of proffered expert testimony, court must ensure that the proposed testimony is relevant to the task at hand, in that it logically advances a material aspect of the proposing party's case; this is known as the "fit" requirement. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

1 Cases that cite this headnote

[5] **Negligence**
Dangerous instrumentalities and substances
**Products Liability**
Proximate Cause
**Products Liability**
Chemicals in general
**Products Liability**
Drugs in general

To prevail in toxic tort or pharmaceutical personal injury lawsuit, plaintiff must show both general causation, pertaining to whether substance had capacity to cause harm alleged, and individual or specific causation, referring to whether a particular individual suffers from a particular ailment as a result of exposure to a substance.

6 Cases that cite this headnote

[6] **Evidence**
Medical testimony

Proffered testimony of cardiology expert, which asserted to a reasonable degree of medical probability that 200 milligram-per-day dose of manufacturer's arthritis pain medication could increase consumers' risk of heart attacks, did not reflect scientific knowledge, was not derived by scientific method, and was not good science, and thus was inadmissible in multi-district litigation addressing consumers' pharmaceutical personal injury claims against manufacturer, inasmuch as expert, who lacked relevant experience and training, reached opinion by first identifying conclusion and then cherry-picking observational studies that supported his conclusion, including one study the results of which expert testified did not make "biological sense" and which expert fundamentally misunderstood, and rejected or ignored great weight of evidence that contradicted his conclusion. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

10 Cases that cite this headnote

[7] **Evidence**
Medical testimony

Doctor was not qualified to favor certain observational studies over great weight of epidemiologic evidence to give opinion on whether 200 milligram-per-day dose of arthritis pain medication could increase consumers' risk of heart attacks in multi-district litigation of pharmaceutical personal injury claims against drug manufacturer, in that doctor was clinical cardiologist who saw patients 95 percent of his physician time, did not have specialized epidemiology training, had not published any research for more than 10 years, and had not participated in observational study of any kind. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

2 Cases that cite this headnote

  

[8] **Evidence**
Medical testimony

Neurologist offered as stroke expert by plaintiffs in multi-district litigation addressing consumers' pharmaceutical personal injury claims against manufacturer of arthritis pain medication ignored vast majority of evidence on issue of whether 200 milligram-per-day dose of medication could increase consumers' risk of cardiovascular injury in favor of few studies that supported her conclusion, including unpublished, non-peer-reviewed study that combined all doses of medication and failed to adjust for critical compounding factors, and therefore neurologist's testimony was unreliable and inadmissible to establish general causation. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

4 Cases that cite this headnote

[9] **Evidence**
Medical testimony
**Evidence**
Experiments and results thereof

Cardiology expert's extrapolation of studies addressing risk of cardiovascular injury stemming from use of arthritis pain medication at dose of 400 milligrams per day (mg/d) did not support proffered opinion that medication could cause heart attack when taken in doses of 200 mg/d, and therefore extrapolation evidence was inadmissible in multi-district litigation addressing consumers' pharmaceutical personal injury claims against medication's manufacturer, given that expert's method of extrapolation, in which he simply took relative risk point established for 400 mg/d dosage and cut it in half, while ignoring confidence interval, lacked support in scientific literature, that expert admitted that there was no way of knowing what confidence interval was for 200 mg/d dosage under his unique methodology, and that expert agreed that there was dose effect with medication. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

7 Cases that cite this headnote

[10] **Evidence**
Experiments and results thereof

Exclusion of expert testimony that arthritis pain medication was capable of causing heart attacks and strokes when used at dose of 400 milligrams per day (mg/d) was not warranted in multi-district litigation addressing consumers' pharmaceutical personal injury claims against medication's manufacturer, even though large, long-term, randomized, placebo-controlled clinical trial on which testimony was based was terminated early and its results had not been replicated by two other randomized controlled studies, given that trial was halted early because evidence of harm was so significant, that other studies also were halted early due to results of challenged trial, and that one of other studies was not designed to detect differences in cardiovascular and cerebrovascular risks and involved study participants with risk factors which possibly differed from general population. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

2 Cases that cite this headnote

[11] **Evidence**
Medical testimony

Although, in multi-district litigation addressing consumers' pharmaceutical personal injury claims against manufacturer of arthritis pain medication, there was some epidemiologic evidence to dispute neurologist's expert testimony that medication was capable of causing strokes, by suggesting that even though heart attacks and certain strokes were caused by same mechanism, manufacturer's medication did not cause both, there also was some evidence to support neurologist's mechanism testimony, and therefore such testimony was not scientifically invalid and was admissible. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

Cases that cite this headnote

[12] **Evidence**
Medical testimony

Consumers could present expert testimony that arthritis pain medication caused heart attacks or strokes at durations of less than 33 months of continuous daily use, in multi-district litigation on consumers' pharmaceutical personal injury claims against medication's manufacturer, even though statistically significant association did not appear until after 33 months in one clinical trial. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

Cases that cite this headnote

[13] **Evidence**
Experiments and results thereof

Plaintiffs' challenges to meta-analyses performed by experts for manufacturer of arthritis pain medication went to weight of meta-analyses, and not their validity, and thus did not warrant exclusion of meta-analyses in multi-district litigation addressing pharmaceutical personal injury claims against manufacturer. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

1 Cases that cite this headnote

Named Expert: Dr. Neil Doherty, Dr. Maryilyn Rymer

**Attorneys and Law Firms**

***1168** Elizabeth Cabrazer, Scott P. Nealey, Lieff, Cabraser, Heimann & Bernstein, LLP, San Francisco, CA, Frank Mario Pitre, Cotchett Pitre & McCarthy, Burlingame, CA, J. Paul Sizemore, Beasley Allen Crow Methvin Portis & Miles, Montgomery, AL, Ellen Relkin, Weitz & Luxenburg, New York City, for Plaintiffs.

Amy W. Schulman, DLA Piper US LLP, New York City, Daniel Garland Brown, Darby and Gazak, P.S.C., Louisville, KY, Gerald B. Taylor, Jr., Beasley Allen Crow Methvin Portis & Miles, Montgomery, AL, Thomas Phillip Cartmell, Wagstaff & Cartmell LLP, Kansas City, MO, Charles Q. Socha, Socha Perczak Setter & Anderson, PC, Denver, CO, for Defendants.

## *1169 MEMORANDUM AND ORDER RE: MOTIONS TO EXCLUDE EXPERT TESTIMONY

CHARLES R. BREYER, District Judge.

In this Multi-District Litigation ("MDL") proceeding, over 3000 plaintiffs allege that they or their loved ones suffered a heart attack, stroke or other adverse cardiovascular event as a result of taking Celebrex, a pain medication manufactured by defendant Pfizer, Inc. ("Pfizer"). Pfizer has moved to exclude any expert testimony to the effect that Celebrex is capable of causing a heart attack or stroke when ingested at 200 milligrams a day or 400 milligrams a day. Plaintiffs have also moved to exclude certain expert testimony offered by Pfizer. The Court held three days of hearings which included direct and cross examination of certain experts. After carefully considering the parties' memoranda and evidence, and the testimony offered at the hearing, the Court concludes that plaintiffs have not presented scientifically reliable evidence that Celebrex causes heart attacks or strokes when ingested at the 200 milligram a day dose. In all other respects the parties' motions are denied.

## BACKGROUND

Non-steroidal anti-inflammatory drugs ("NSAIDs") have been widely used for pain relief for several years. NSAIDs, however, have certain side effects, including gastrointestinal toxicity which results in thousands of deaths every year. The pharmaceutical company Merck & Co., Inc. ("Merck") developed Vioxx, and Pfizer (or, more precisely, its predecessors) developed Celebrex and Bextra, NSAIDs known as COX-2 inhibitors, with the expectation that they would have fewer gastrointestinal side effects than traditional NSAIDs. The Food and Drug Administration ("FDA") approved Celebrex for adult

arthritis in 1998, Vioxx in 1999, and Bextra in late 2001. The recommended dose of Celebrex was and is 200 milligrams a day ("mg/d") for arthritis and 400 mg/d for rheumatoid arthritis.

In 2000 the results of a long-term randomized study of Celebrex known as CLASS ("Celecoxib Long-Term Arthritis Safety Study") were published. The study was designed to evaluate the gastrointestinal side effects of taking Celebrex at 800 mg/d. Based on investigator reported cardiovascular events, the study showed no increased risk of heart attack or stroke by taking Celebrex over diclofenac or ibuprofen. Around the same time, a similar study of Vioxx, known as VIGOR, showed a four-fold increase in cardiovascular ("cv") risk for patients taking Vioxx versus Aleve (naproxen). The FDA subsequently revised the labels of Celebrex and Vioxx to reflect the cv risk results of these studies.

Another Vioxx randomized clinical study, known as APPROVe, was published in 2004. This study demonstrated a two-fold increased risk of cv adverse events for patients taking Vioxx versus a placebo. This study contributed to Merck's voluntary removal of Vioxx from the market on September 30, 2004.

The preliminary results of APC, a randomized, placebo-controlled study of Celebrex at 200 mg twice daily (400 mg/d) and 400 mg twice daily (800 mg/d) to evaluate whether Celebrex prevents the development of colon polyps, became available in late 2004. APC showed dose-related increased cv risk for patients taking Celebrex compared to placebo: more than doubling the risk for 200 mg twice daily and tripling the risk for 400 mg twice daily. The APC steering committee discontinued the study in December 2004 because of these preliminary results.

In February 2005 the FDA convened an Advisory Committee to review the data on ***1170** cv risk and NSAIDs, including COX-2 inhibitors. The Committee concluded that all COX-2 inhibitors increase cv risk versus placebo, but it did not make any findings as to what dose is required to increase the risk. It also concluded that the data was insufficient to determine if traditional NSAIDs also increase cv risk. With respect to Celebrex, the FDA found that APC is the "strongest data in support of an increased risk of serious adverse CV events." FDA Decision Memorandum, April 6, 2005, at 4, Declaration of Loren Brown ("Brown Decl.") Exh. 16. The FDA also noted that APC's results had not been replicated by preliminary data from two other randomized controlled clinical studies: (1) PreSAP, a colon polyp prevention trial of Celebrex at 400 mg/d; and (2) ADAPT, an Alzheimer's trial of Celebrex at 200 twice daily (400 mg/d). Both studies showed no increased cv risk for Celebrex versus placebo.

The FDA subsequently asked Pfizer to remove Bextra from the market, which Pfizer did in April 2005. The FDA also determined that the benefits of Celebrex outweigh its risks and therefore it allowed Celebrex to remain on the market. Celebrex is the only COX-2 inhibitor currently on the market.

The FDA also directed all NSAIDs, including Celebrex, to include a black box warning on their labels. The black box warns of cv risk as follows:

> **Cardiovascular Risk**
>
> • CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk ....

Celebrex 2007 Label, Brown Decl. Exh. 3.

As a result of these developments, thousands of patients and patient representatives filed lawsuits against Merck and Pfizer alleging that the patient had suffered a serious cardiovascular injury, such as a heart attack or stroke, due to their ingestion of Vioxx, and/or Celebrex and/or Bextra. All of the federal court claims against Merck were consolidated in a MDL action in New Orleans. All of the federal court claims against Pfizer were consolidated into this MDL proceeding.

## THE DAUBERT MOTIONS

Pursuant to Federal Rule of Evidence 702, Pfizer moves to exclude plaintiffs' experts from offering the following six opinions:

1. That 200 mg/d of Celebrex causes heart attacks and strokes;

2. That 400 mg/d of Celebrex causes heart attacks and strokes;

3. That Celebrex causes heart attacks or strokes more than three days after a patient stops taking it;

4. That Celebrex causes strokes; and;

5. That Celebrex causes heart attacks or stokes at durations of less than 33 months of continuous daily use.

Pfizer also asks the Court to exclude any expert opinion that Celebrex caused any individual plaintiff's heart or stroke absent epidemiology evidence that demonstrates a relative risk greater than 2.0, that is, that Celebrex doubles the risk. Plaintiffs have moved to exclude certain expert testimony offered by Pfizer; specifically, they seek to exclude admission of the meta-analyses performed by plaintiffs' experts.

In connection with these motions, the parties submitted direct written testimony of their respective experts as well as legal ***1171** memoranda. The Court then held three days of hearings, which were conducted jointly with the New York Justice presiding over the New York State Celebrex and Bextra cases. Plaintiffs' experts Dr. Neil Doherty, Dr. Joel Bennett, Dr. Nicholas Jewell and Dr. Maryilyn Rymer testified on direct and cross-examination, along with defendant's expert Dr. Milton Packer. The parties also submitted post-hearing memoranda. The motions are now ripe for decision.

## LEGAL STANDARD

### A. Admissibility of Expert Testimony

[1] [2] When evaluating the admissibility of expert testimony, the trial judge "must engage in a difficult, two-part analysis." *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1315 (9th Cir.1995) (*Daubert II* ). First, the court must "determine nothing less than whether the experts' testimony reflects 'scientific knowledge,' whether their findings are 'derived by the scientific method,' and whether their work product amounts to 'good science.' " *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 589-90, 593, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993)); *see also In re Silicone Gel Breast Impl. Products Liab. Lit.,* 318 F.Supp.2d 879, 890 (C.D.Cal.2004) (" '[T]he trial judge in all cases of proffered expert testimony must find that it is properly grounded, well-reasoned, and not speculative before it can be admitted.' ") (quoting Fed.R.Evid. 702 Advisory Committee's Notes). The trial judge's obligation "is to make certain that an expert ... employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 152, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

[3] Many factors may be relevant to the reliability inquiry, including: (1) whether the proffered theory or technique has been tested, (2) whether the theory or technique has been subjected to peer review and publication, (3) the known or potential rate of error of the technique or theory when applied, and (4) the "general acceptance" of the theory or technique in the scientific community. *Daubert,* 509 U.S. at 593-94, 113 S.Ct. 2786.

> [C]ourts have also found the following factors relevant in assessing the reliability of expert testimony: (1) whether the expert is proposing to testify about matters growing directly out of independent research he or she has conducted or whether the opinion was developed expressly for purposes of testifying; (2) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion; (3) whether the expert has adequately accounted for obvious alternative explanations; (4) whether the expert is being as careful as he would be in his regular professional work; and (5) whether the field of expertise claimed by the expert is known to reach reliable results for the type of opinion offered.

*In re Silicone Gel Breast Impl. Products Liab. Lit.,* 318 F.Supp.2d at 890 (citing Fed.R.Evid. 702 Advisory Committee's Notes).

[4] In addition to determining reliability, the court "must ensure that the proposed expert testimony is 'relevant to the task at hand,' i.e., that it logically advances a material aspect of the proposing party's case." *Daubert II,* 43 F.3d at 1315 (quoting *Daubert,* 509 U.S. at 597, 113 S.Ct. 2786). This is known as the "fit" requirement. *Id.* Here, the pertinent fit inquiry is "causation." The parties' motions address expert testimony on the causation inquiry.

**B. Causation**

Causation in toxic tort or pharmaceutical personal injury cases "is typically discussed ***1172** in terms of generic and specific causation." *In Re Hanford Nuclear Reservation Lit.,* 292 F.3d 1124, 1133 (9th Cir.2002). General or generic causation means "whether the substance at issue had the capacity to cause the harm alleged." *Id.* In *Hanford,* for example, the Ninth Circuit explained that the general causation inquiry was "whether exposure to a substance for which a defendant is responsible, such as radiation at the level of exposure alleged by plaintiffs, is capable of causing a particular injury or condition in the general population." *Id.*

[5] To ultimately prevail in such a lawsuit, however, a plaintiff must show both general and "individual" or "specific" causation. *Id.* Specific causation refers to whether a particular individual suffers from a particular ailment as a result of exposure to a substance. *Id.* That is, that the challenged conduct, here, the taking of Celebrex at a certain dose for a particular amount of time, was "the cause-in-fact" of the particular plaintiff's injury. *Id.*

The parties' motions involve the use of epidemiology to prove causation. "The field of epidemiology addresses the incidence, distribution and etiology (causation) of disease in human populations by comparing individuals exposed to a particular agent to unexposed individuals to determine whether exposure increases the risk of disease." *In re Silicone Gel Breast Implants Products Liab. Lit.,* 318 F.Supp.2d at 892. Scientists use "relative risk" to identify an association between, for example, the ingestion of a drug and a disease.

> For example, if a study found that 10 out of 1000 women with breast implants were diagnosed with breast cancer and 5 out of 1000 women without implants (the "control" group) were diagnosed with breast cancer, the relative risk of implants is 2.0, or twice as great as the risk of breast cancer without implants. This is so, because the proportion of women in the implant group with breast cancer is 0.1 (10/1000) and the proportion of women in the non-implant group with breast cancer is 0.05 (5/1000). And 0.1 divided by 0.05 is 2.0.

*Id.* A relative risk of 1.0 suggests that there is no association between the product and the disease, that is, the same numbers of people using the product are diagnosed with the disease as those not using the product. Similarly, a relative risk of less than 1.0 suggests that the product is actually "protective" of the disease: fewer people using the product contract the disease than those not taking the product. *Id.* at n. 5.

In general, epidemiology studies are probative of general causation: a relative risk greater than 1.0 means the product has the capacity to cause the disease. "Where the study properly accounts for potential confounding factors and concludes that exposure to the agent is what increases the probability of contracting the disease, the study has demonstrated *general* causation-that exposure to the agent is capable of causing [the illness at issue] in the general population." *Id.* at 893 (internal quotation marks and citation omitted).

Such studies can also be probative of specific causation, but only if the relative risk is greater than 2.0, that is, the product more than doubles the risk of getting the disease.

> When the relative risk is 2.0, the alleged cause is responsible for an equal number of cases of the disease as all other background causes present in the control group. Thus, a relative risk of 2.0 implies a 50% probability that the agent at issue was responsible for a particular individual's disease. This means that a relative risk that is greater than 2.0 permits the conclusion that the agent ***1173** was more likely than not responsible for a particular individual's disease.

*Id.* at 893. The issue on these motions, however, is not specific causation; there is no particular plaintiff before the Court. Rather, the primary issue is whether the Court should permit plaintiffs' experts to testify that Celebrex is capable of causing heart attacks or strokes at certain doses.

## EPIDEMIOLOGY STUDIES AND TERMS

Before discussing the parties' motions, it is important to identify the different epidemiology studies relied upon by the experts. There are generally three types of clinical epidemiology studies at issue on the parties' motions: (1)

randomized controlled clinical trials, (2) observational studies, and (3) meta-analyses.

The "gold standard" for determining whether a drug is related to the risk of developing an adverse health outcome is a "randomized clinical trial" in which the subjects are randomly assigned to one of two groups: one group exposed to the drug of interest and the other not exposed. After a period of time the study participants in both groups are evaluated for an adverse health outcome. Federal Judicial Center, Reference Manual on Scientific Evidence 338 (2d ed.2000). "Randomization minimizes the likelihood that there are differences in relevant characteristics between those exposed to the agent and those not exposed," such as smoking, obesity, aspirin use and so on that could account for any difference in outcomes between the two groups. *Id.*

An "observational study" evaluates causation by comparing the risk of disease between patients exposed to a given substance and patients who were not exposed. The study may be prospective, identifying patients and then following them for a period of time, or restrospective, identifying patients and then performing a medical chart review to determine what happened during the period they did or did not take the drug. The downside to observational studies is that because the investigators do not control who participates in the study, it is more difficult to control for confounding factors such as smoking, obesity and the like. The investigator attempts to address the possible role of confounding factors "by considering them in the design of the study and in the analysis and interpretation of the study results." *Id.* at 339.

There are two types of observational studies: a cohort study and a case control study. A cohort study identifies patients who are taking the drug (exposed) and follows them for a certain amount of time to determine if they have the alleged bad outcome, here, such outcome is heart attack or stroke. The cohort study also identifies people not taking the drug and follows them (unexposed). The study then compares the rate of the alleged bad outcomes in group one with the rate in group two to compute the "relative risk." *Id.* at 339-40.

A case control study identifies persons who had a bad outcome (the cases), for example, patients in the United Kingdom database that had a heart attack within the last three years, and reviews their medical records to determine how many of those persons were taking the studied drug around the time of their heart attack. The study then identifies an equal number of people who did not have a heart attack (the controls) and determines how many of them were taking the drug. *Id.* From those figures an "odds ratio" is computed. For example, if the percentage of people taking Celebrex in both groups is the same, the odds ratio is 1.0; that is, taking Celebrex did not increase the risk of heart attack.

Sometimes randomized controlled studies and observational studies of the same ***1174** drug will have conflicting results; some will show a statistically significant association while others will not. A meta-analysis pools the results of various studies to arrive at a single figure to represent the totality of the studies reviewed. "In a meta-analysis, studies are given different weights in proportion to the sizes of their study populations and other characteristics." *Id.* at 380. Meta-analysis has the advantage of pooling more data so that the results are less likely to be misleading solely due to chance. On the other hand, one problem with meta-analysis, particularly in meta-analysis of observational studies, is that the pooled studies often use disparate methodologies.

When reviewing the results of a study, whether it is a randomized clinical trial, observational trial, or a meta-analysis of such trials, it is important to consider the confidence interval. The confidence interval is, in simple terms, the "margin of error." So, for example, if a given study showed a relative risk of 1.40 (a 40 percent increased risk of adverse events), but the 95 percent confidence interval is .8 to 1.9, we would say that we are 95 percent confident that the true value, that is, the actual relative risk, is between .8 and 1.9. Because the confidence interval includes results which do not show any increased risk, and indeed, show a decreased risk, that is, it includes values less than 1.0, we would say the study does not demonstrate a "statistically significant" increased risk of an adverse outcome. Confidence intervals are calculated, in part, based on the number of people and events included in the study. "The larger the sample size in a study (all other things being equal), the narrower the confidence boundaries will be (indicating greater statistical stability), thereby reflecting the decreased likelihood that the association found in the study would occur if the true association is 1.0 [no increased or decreased risk]." *Id.* at 361.

With these terms in mind, the Court now turns to the parties' motions.

## DISCUSSION

**I. Pfizer's Motion**

A threshold question raised by Pfizer's motion is whether a particular dose of Celebrex is relevant to the general causation inquiry. Pfizer seeks to exclude any opinion that Celebrex is capable of causing heart attacks and strokes at 200 mg/d as well as any opinion that Celebrex is capable of causing heart attacks and strokes at 400 mg/d. It does not move to exclude expert testimony that Celebrex is capable of causing heart attacks and strokes when a patient ingests 800 mg/d, at least when taken over many months. Thus, Pfizer's motion assumes that Celebrex at different doses can have different cardiovascular effects.

The Court finds that dose matters. All of plaintiffs' experts, with perhaps a single exception, agree that there is a dose effect with Celebrex; that is, that it is more toxic, and is therefore more likely to cause an adverse side effect, when taken at greater doses. *See* Reference Manual on Scientific Evidence at 403 ("There are three central tenets of toxicology. First, 'the dose makes the poison'; this implies that all chemical agents are intrinsically hazardous-whether they cause harm is only a question of dose. Even water, if consumed in large quantities, can be toxic."); *see also Mitchell v. Gencorp,* 165 F.3d 778, 781 (10th Cir.1999) (noting that to prevail in a toxic tort case a "a plaintiff must demonstrate 'the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure to the defendant's toxic substance before he or she may recover") (internal quotation marks and citation omitted); *Allen v. Penn. Eng'g Corp.,* 102 F.3d 194, 199 (5th Cir.1996) (explaining ***1175** that in toxic tort cases, "[s]cientific knowledge of the harmful level of exposure to a chemical plus knowledge that plaintiff was exposed to such quantities are minimal facts necessary to sustain the plaintiff's burden"); *see also Hanford Nuclear Reservation Lit.,* 292 F.3d at 1133 (explaining that the general causation inquiry is whether exposure to the challenged substance *"at the level of exposure alleged by the plaintiffs* is capable of causing the alleged injuries") (emphasis added). As plaintiffs' cardiology expert, Dr. Neil Doherty, testified: it is a "fundamental principal of medicine" and "medical causality" that the risk of adverse cardiovascular events with Celebrex is dose-related. Transcript of October 10, 2007 Hearing ("Oct. 10 TR") at 328. Thus, the Court must analyze plaintiffs' experts' opinions as to causation at 200 mg/d separate from their opinions as to 400 mg/d.

**A. 200 mg/d**

Celebrex at 200 mg/d and the risk of adverse cv events has not been studied in published, large, long-term randomized controlled trials. Nonetheless, included in the record are approximately 30 unpublished randomized controlled trials, albeit of short duration and small size. These studies do not demonstrate any association between Celebrex and adverse cv outcomes. A meta-analysis of all available published and unpublished randomized clinical trials of all COX-2 inhibitors as well as traditional NSAIDs found that while COX-2 inhibitors as a whole are associated with a moderate increase in the risk of adverse cv events, no such association is found with the available data for Celebrex at 200 mg/d or less.[1]

The record also includes observational studies with Celebrex data, mostly at 200 mg/d. These observational studies together include more than 8,000 adverse cv events, and all of the studies with the most events demonstrate no statistically significant association between Celebrex at 200 mg/d and adverse cv events. A meta-analysis performed by an independent researcher unaffiliated with Pfizer ("McGettigan") concluded that while Vioxx does increase the risk of adverse cv events, "[i]n doses of around 200 mg/d, [Celebrex] was not associated with an increased risk ...."[2] Another meta-analysis of eight observational studies showed no increased risk from Celebrex 200 mg/d compared to patients taking no medication.[3]

In sum, there are no randomized controlled trials or meta-analyses of such trials or meta-analyses of observational studies that find an association between Celebrex 200 mg/d and a risk of heart attack or stroke. And most observational studies, indeed, the observational studies that include 97 percent of the reported adverse cv events, also find no statistically significant association. It is thus unsurprising that most of plaintiffs' experts agree that the available evidence at 200 mg/d is inadequate to prove causation. *See* Deposition Testimony of Dr. Joel Bennett at p. 537, Brown Reply Decl. ***1176** Exh. 108 ("I think that if you look at all the evidence, I think at 200 milligrams it's hard to make a case that Celebrex has toxicity. It doesn't mean that, again, that in individual cases it couldn't, it could be lost in the big scheme of things, but, in fact, the data don't suggest that in a large population it increases the risk."); Deposition Testimony of Dr. Lemue Moye at p. 268, Brown Reply Decl. Exh. 109 ("[T]here's no study that convincingly demonstrates a signal of cardiovascular events at very low does such as 200 per day."); Deposition Testimony of Dr. Nicholas Jewell at p. 130, Brown Reply Decl. Exh. 110 (when asked whether there is reliable scientific evidence to establish that 200 mg/d causes heart attacks and strokes

he responded that the evidence is not sufficient "to be definitive"); Deposition of Dr. James M. Wright at pp. 83-84, 92, Brown Decl. Reply Exh. 106 (stating that it has not been proven that at 200 mg/d Celebrex increases the risk of heart attack because "we don't have enough information").

**1. Dr. Neil Doherty**

[6] Plaintiffs' cardiology expert, Dr. Neil Doherty, nonetheless asserts "to a reasonable degree of medical probability that the 200 mg dose of Celebrex can increase the risk of MI's [heart attacks]." Written Direct Examination of Dr. Neil F. Doherty III ("Doherty Written Direct") at ¶ 18. He reaches his opinion by first identifying his conclusion-causation at 200 mg/d-and then cherry-picking observational studies that support his conclusion and rejecting or ignoring the great weight of the evidence that contradicts his conclusion. Dr. Doherty's opinion does not reflect scientific knowledge, is not derived by the scientific method, and is not "good science;" it is therefore inadmissible.

[7] First, Dr. Doherty is not qualified to favor certain observational studies over the great weight of the epidemiologic evidence to give an opinion on causation. He is a clinical cardiologist who sees patients 95 percent of his physician time. He does not have any specialized epidemiology training. He has not published any research since 1992, and his 13 publications are unrelated to the subject matter of these lawsuits. He has never participated in an observational study of any kind. He is therefore not qualified to opine that one or two observational studies are correct while all the other studies (the studies that include 97 percent of the adverse cv events) are wrong. Moreover, he only became interested in Celebrex and cv risk *after* he was retained by plaintiffs in this litigation; indeed, although the issue of COX-2 inhibitors and adverse cv events has been well known since at least 2005, he did not discontinue prescribing Celebrex until after plaintiffs retained him as an expert in this case. Doherty Written Direct at ¶ 2. Dr. Doherty's opinion was developed for the purpose of this litigation. *See Daubert II,* 43 F.3d at 1317 ("One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying.").

Second, apart from his lack of relevant experience and training (or because of it), the foundation of his opinion-wholly rejecting the McGettigan meta-analysis and the other observational studies that do not support his opinion-is not a scientifically valid methodology. For example, while he justifies his wholesale rejection of McGettigan on the blanket ground that meta-analysis is inappropriate for observational studies, plaintiffs' other experts rely on such studies; indeed, Dr. Bennett testified that McGettigan is a "good study." Dr. Bennett Depo. at p. 187-88, Brown Reply ***1177** Decl. Exh. 108. And the American Heart Association Committee that developed a "Science Advisory" on the use of NSAIDs also relied on McGettigan. Finally, Dr. Doherty testified that he prefers the Oxford Centre for Evidence Based Medicine ranking of the levels of evidence that a scientist should consider. Doherty Written Direct at ¶ 21-22. That ranking identifies systematic review, including meta-analysis, as the highest level for each category of evidence. Oct. 10 TR at 350.

Third, Dr. Doherty testified that the "strongest evidence" for his 200 mg/d opinion "is the Andersohn study published in *Circulation* in 2006."[4] Doherty Written Direct at ¶ 18. He attempts to justify his heavy reliance on Andersohn by asserting that it is the "best designed" of all the observational studies. When asked why, however, Dr. Doherty responded only that the study is derived from the United Kingdom database which is among the most complete in the world. Oct. 10 TR at 309-10. He also mentioned that Andersohn is a prospective, rather than retrospective study. *Id.* at 310. But many of the other studies he rejects out of hand are also prospective, and he does not cite anything in the medical literature that suggests that it is a valid scientific method to prefer one study over many that have contradictory results simply because the study that supports the expert's conclusion utilized the United Kingdom database.

Fourth, Dr. Doherty's reliance on Andersohn as "the strongest evidence" of an increased risk at 200 mg/d is undermined by his own testimony that Andersohn's results do not make "biological sense." Oct. 10 TR at 363-64. Andersohn found the increased risk of heart attack was higher at shorter durations of use (less than three months) than at higher durations; indeed, there was no statistically significant association at durations greater than three months, a finding that directly contradicts Dr. Doherty's testimony that the risk of heart attack increases with duration of use. Oct. 10 TR at 359-61. Andersohn also found that the risk of heart attack is statistically significant in patients without cv risk factors, but is not statistically significant in patients with such risk factors. *Id.* at 364. Again, this finding directly contradicts Dr. Doherty's testimony that the risk of heart attack from Celebrex is greater in patients with heart disease. To conclude that Celebrex 200 mg/d causes heart attacks and

strokes based on a study that does not make "biological sense" is not sound science.

Fifth, Dr. Doherty's opinion is based on his fundamental misunderstanding of Andersohn. Dr. Doherty testified that Andersohn is a cohort study and he "puts a lot more weight" into cohort studies as opposed to case control studies. Oct. 10 TR at 255, 309, 350. He repeatedly testified that he relies on Andersohn out of all of the available evidence because it is a good cohort study. *See, e.g., id.* at 313, 315. When he was confronted with Andersohn's own description of the study, however, Dr. Doherty conceded that Andersohn is not a cohort study, but is instead "a case-control study nested within a cohort study." *Id.* at 352.

Dr. Doherty also insisted that Andersohn used cox proportional hazard analysis, the analysis most commonly used for cohort studies. Oct. 10 TR at 320-21, 355. On cross-examination, however, he could not identify where in the study the authors disclose that they used cox-proportional hazard analysis and Dr. Doherty pointedly did not clarify his testimony on re-direct. ***1178** The Court has reviewed Andersohn and it does not indicate that the study authors used cox-proportional hazard analysis; rather, they used logistic regression which resulted in an "odds ratio," an analysis consistent with case control studies. Dr. Doherty's fundamental misunderstanding of the study he "relied most strongly on" to support his opinion, Doherty Written Direct at ¶ 31, is perhaps explained by his inability to explain the difference between a cohort study and case control study "off the top of his head," Oct. 10 TR at 348, and his inability to define the cox proportional hazards model or explain logistic regression analysis. *Id.* In any event, as Andersohn is a case control study, Dr. Doherty's heavy reliance upon it is unreliable in light of his own blanket rejection of all of the case control studies showing no association between Celebrex 200 mg/d and cv risk on the ground that case control studies are not as reliable as cohort studies. Doherty Written Direct at ¶ 37.

While Andersohn is the "strongest evidence" supporting Dr. Doherty's opinion, he also cited an additional observational study, Gislason.[5] Gislason, however, had few events and merely evaluated COX-2 inhibitors and the risk of a heart attack in patients who had already had a heart attack. Moreover, the study failed to control for smoking, a well-known risk for heart attack, as well as aspirin use, even though another of plaintiffs' experts, Dr. Maryilyn Rymer, criticized another observational study for not adjusting for aspirin use. Dr. Maryilyn Rymer Written Direct Testimony ("Rymer Written Direct") at ¶ 34. In light of these limitations, and the totality of the available evidence, Gislason does not salvage Dr. Doherty's opinion that Celebrex at 200 mg/d can cause heart attacks.

Dr. Doherty also relied on the "imbalance hypothesis" as evidence that it is biologically plausible that Celebrex causes heart attacks. This hypothesis asserts that COX-2 inhibitors as a class, that is, Vioxx, Bextra and Celebrex, create an imbalance in the arteries by blocking prostacyclin (an anti-clotting agent). Under this theory, the imbalance caused by ingesting a COX-2 will lead to an adverse cv event if the patient already has a risk factor, such as high blood pressure, smoking, or high cholesterol. Dr. Doherty argues that this hypothesis means that it makes sense that Celebrex increases the risk of heart attacks and strokes. He did not explain, however, how he reconciles this theory with Andersohn-the strongest evidence of his causation opinion-which showed a greater risk of heart attacks in patients with no cv risk factors.

In any event, both Dr. Doherty and Dr. Joel Bennett-plaintiffs' imbalance hypothesis expert-agree that the only way to prove the hypothesis is to look at the data from epidemiological studies. Oct. 10 TR at 373. For example, Dr. Bennett agreed that the only method available to determine how much Celebrex is needed (that is, what dose) to create an imbalance sufficient to cause a heart attack is patient studies. Oct. 9 TR at 209, 210. As is explained above, the patient studies do not demonstrate an association between Celebrex 200 mg/d and heart attack or stroke; therefore, the imbalance hypothesis-even if true-(and it is only one of many possible explanations for the apparent increased risk of heart attacks from COX-2 inhibitors at certain doses) does not support Dr. Doherty's opinion that Celebrex is capable of causing heart attacks at 200 mg/d.

***1179 2. Dr. Maryilyn Rymer**

[8] Dr. Maryilyn Rymer's testimony does not provide the missing link. Dr. Rymer is a neurologist and plaintiffs offered her as a stroke expert, essentially to opine that Celebrex causes strokes as well as heart attacks. In her written direct testimony she opines that "the totality of the scientifically reliable evidence supports that [Celebrex] can cause strokes and other cardiovascular events at all therapeutic doses, especially in those individuals who are high risk for cardiovascular events." Rymer Written Direct at ¶ 7. She admits that there is no data from randomized controlled trials to support her conclusion at 200 mg/d; instead, she primarily relies on (1) the imbalance hypothesis, (2) the same Andersohn study upon

which Dr. Doherty relies, and (3) the Wellpoint data, an unpublished observational study of unknown design. In other words, Dr. Rymer, as does Dr. Doherty, ignores the vast majority of the evidence in favor of the few studies that support her conclusion.

The Court has already addressed the imbalance hypothesis and the Andersohn study, neither of which provide scientifically valid support for her opinion in light of the great weight of the epidemiologic evidence. It is worth adding, however, that Dr. Rymer's reliance on the Andersohn heart attack study is inconsistent with her criticism of the Andersohn stroke study. The latter study, performed by the same Andersohn as the heart attack study, indeed, it is the same study but focused on stroke rather than heart attack outcomes, found no statistically significant increased risk of stroke associated with Celebrex use at 200 mg/d. Dr. Rymer criticized the stroke study for not controlling for aspirin use and having a 10 percent error rate; yet the Andersohn heart attack study suffers from the same limitations.

Dr. Rymer relies heavily on an unpublished, non-peer reviewed study from a managed care organization ("the Wellpoint Report"). Dr. Rymer attaches to her written direct testimony a letter from Wellpoint to the FDA summarizing the results of the study. The letter discloses a relative risk from Celebrex use of 1.19 when the data is analyzed to control for "age and other cardiovascular risk factors;" however, this very low risk includes *all* doses of Celebrex. Moreover, the letter does not identify study design, the analysis used, or even the confidence intervals. Dr. Rymer admitted on cross-examination that the study also fails to account for critical compounding factors such as smoking. This unpublished, unreviewed study, which combines all doses of Celebrex, and fails to adjust for critical compounding factors such as smoking, is not a scientifically valid basis for Dr. Rymer's rejection of all the other observational data-including meta-analyses-that do not show a statistically significant increase in the risk of heart attack or stroke at 200 mg/d.

Finally, Dr. Rymer cited Gislason, discussed above, and Brophy,[6] as support for causation at 200 mg/d. Brophy, as Gislason, evaluated the risk of heart attack in patients who had already had at least one heart attack. Brophy, however, did not find a statistically significant increased risk of heart attack at 200 mg/d, even in these high risk patients. And while it did show a greater risk in the high risk population (although not a statistically significant risk), the higher risk found in Brophy and Gislason is contradicted by the results of at least nine other studies, including Dr. Doherty's "strongest evidence" of causation, ***1180** the Andersohn heart study. Such data cannot reliably form the basis for rejecting the overwhelming pattern of evidence that fails to show any statistically significant risk at 200 mg/d.

**3. Extrapolation**

[9] Dr. Doherty, and to some extent Dr. Rymer, also rely on studies of Celebrex 400 mg/d to support their opinion of causation at 200 mg/d. Although Dr. Doherty acknowledges that dose matters with Celebrex, he simply takes the relative risk point estimate of APC for 400 mg/d and cuts it in half (ignoring the confidence interval) to support his opinion that Celebrex at 200 mg/d can cause a heart attack. Oct. 10 TR at 304. When the Court asked Dr. Doherty if there is anything in the scientific literature to support such primitive extrapolation, he failed to identify any scientific support for his method other than his own judgment. *Id.* at 342-43, 378-79. He also admitted that there is no way of knowing what the confidence interval is for 200 mg/d under his unique methodology. *Id.* at 340-41. Such an unscientific, untested methodology cannot support the proffered opinion of causation at 200 mg/d, especially where, as here, Dr. Doherty agrees with all the other experts that there is dose effect with Celebrex.

Plaintiffs' reliance on *In re PPA Products Liab. Litig.*, 289 F.Supp.2d 1230 (W.D.Wa.2003), to argue that causation at 200 mg/d can be inferred from the 400 mg/d data is misplaced. In the *PPA* multi-district litigation the issue was whether PPA, a drug used in cough and cold and appetite suppressant products, can cause strokes. Plaintiffs' experts' opinion that PPA can cause strokes in persons of all ages and genders was based primarily upon a study of women ages 18 to 49. *Id.* at 1235-36. While men were not excluded from the study, their participation was too low to draw any conclusions. *Id.* at 1236. The defendants argued that the evidence was therefore insufficient to support the plaintiffs' experts' opinions that PPA can cause strokes in persons of all ages and genders. *Id.* at 1244. The district court disagreed.

The court found that "it is scientifically acceptable to extrapolate the conclusions of the [study] to these sub-populations." *Id.* at 1244. As to persons older than 49, the court noted that there are no known studies that suggest that drugs get safer as persons get older; thus, it made common scientific sense to extrapolate the results of the study to persons over 49. *Id.* Plaintiffs' experts also attested to the "commonplace" practice of extrapolating between the genders based on "the historical exclusion of women from scientific studies." *Id.*

The justification for extrapolating drug effects between biologically similar demographic groups, however, does not logically extend to the argument that all doses of a compound are harmful; accordingly, plaintiffs' experts could not cite to a single piece of evidence that suggests that their experts' extrapolation is scientifically valid. To the contrary, with nearly all compounds there is usually a threshold that must be met before there is any harm; for example, even water can be harmful if consumed at certain amounts even though there is no harm at smaller amounts. Dr. Doherty claimed that the threshold for Celebrex must be 50 mg/d because that is the dose that is effective for pain relief. That "theory," however, is nothing more than Dr. Doherty's wholly untested, unpublished, and non-peer reviewed justification for his reliance on the 400 mg/d data. Moreover, the great weight of the evidence does not support the extrapolation, that is, studies show that there is no statistically significant association between Celebrex 200 mg/d and the risk of strokes or heart attacks.

***1181** Instead of citing evidence that supports such extrapolation, plaintiffs complain that the evidence of harm at 200 mg/d does not exist because Pfizer did not initiate long term randomized trials at such dose. Such a trial, known as PRECISION, is now underway, but the results will not be available for some time. Plaintiffs cite no case, however, that suggests that they can satisfy their burden of proof based on a lack of evidence; plaintiffs filed these lawsuits and plaintiffs carry the burden of proving today based on currently available scientifically valid evidence that Celebrex can cause heart attacks or strokes at 200 mg/d.

Plaintiffs have not met their burden. In so finding, the Court is relying on the evidence presented by plaintiffs; it has not considered Pfizer's own meta-analyses. And the Court's ruling is not mandated by the lack of randomized clinical trials that show an association at 200 mg/d; plaintiffs could still meet their burden in the absence of such evidence. *See Kennedy v. Collagen Corp.,* 161 F.3d 1226, 1228 (9th Cir.1998). However, the opinion of Dr. Doherty and Dr. Rymer that Celebrex 200 mg/d increases the risk of heart attacks or strokes is not based on a scientific valid methodology; instead, these experts ignore the great weight of the observational studies that contradict their conclusion and instead rely on the handful that appear to support their litigation-created opinion. As the Court explained above, their reasons for doing so are not supported by scientifically valid reasons or methodology. In the words of the Supreme Court, the "analytical gap" between the data and these experts' conclusion is simply too great to make the opinion admissible. *General Elect. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

**B. 400 mg/d**

[10] Pfizer's motion to exclude expert testimony that Celebrex 400 mg/d is capable of causing heart attacks or strokes is defeated by APC, a large, long-term, randomized, placebo-controlled, double-blind, multi-center clinical trial that was halted after 33 months because it demonstrated a statistically significant risk of heart attack, stroke, and heart failure at 400 mg/d (2.6 percent hazards ratio with a confidence interval of 1.1 to 6.1) and 800 mg/d (3.4 percent hazards ratio with a confidence interval of 1.5 to 7.9).[7] The study, co-sponsored by the National Cancer Institute and Pfizer, was designed to compare Celebrex with placebo for the prevention of colorectal adenomas (polyps). The study included a "cardiovascular safety committee" that developed guidelines to evaluate cardiovascular safety. On December 16, 2004, on the basis of the results then available as well as studies of Vioxx and Bextra, and on the recommendation of the safety committee, the APC steering committee stopped the trial. This randomized, placebo-controlled, double-blinded study with an independent committee evaluating cardiovascular endpoints is the "gold standard" of epidemiologic evidence and supports plaintiffs' experts' testimony that Celebrex at 400 mg/d is capable of causing heart attacks or strokes.

Pfizer nonetheless contends that plaintiffs' experts' opinion must be excluded because (1) APC was stopped early, and (2) its results have not been replicated by two other randomized controlled trials that evaluated Celebrex 400 mg/d: ADAPT and PreSAP.

The Court is unconvinced that plaintiffs' experts cannot base their opinions on APC because it was stopped early (after 33 ***1182** months). The APC steering committee halted the trial because the evidence of harm was so significant. To exclude reliance on such studies under these circumstances would mean the more harmful the drug the more difficult it is to prove harm. While such studies must be closely scrutinized due to their early termination, Pfizer's argument goes to the study's weight; Pfizer has not shown that it is not scientifically valid for plaintiffs' experts to rely on the results. Moreover, ADAPT and PreSAP, two studies upon which Pfizer relies, were also halted early because of the APC results.

The Court is also not persuaded that the failure of

ADAPT and PreSAP to replicate APC's results means plaintiffs' expert opinion on 400 mg/d is inadmissible. ADAPT was a randomized, placebo-controlled clinical trial designed to evaluate naproxen and Celebrex 400 mg/d (200 mg twice daily) and the prevention of Alzheimer's dementia.[8] ADAPT found a hazards ratio for Celebrex of 1.10 percent with a confidence interval of .67 to 1.79, that is, no statistically significant association. The study authors, however, cautioned that there are several limitations to their data. First, ADAPT was not designed to detect differences in cardiovascular and cerebrovascular risks and, unlike APC, it did not include a separate cardiovascular safety committee tasked solely with evaluating cardiovascular outcomes. Second, and, according to the authors, the largest limitation of the data is the small number of cardiovascular events. Third, an editorial comment accompanying the study suggests that because study participants eligible to join the trial were required to have a family history of Alzheimer's disease, it is possible the study participants' risk factors differed from the general population. The results of ADAPT need to weighed with the APC results, but ADAPT's conclusions do not make reliance on APC scientifically invalid.

The results of PreSAP, a randomized controlled study with fewer participants than ADAPT or APC, also did not replicate the APC results. PreSAP, as APC, was designed to evaluate Celebrex's effect on the occurrence of colorectal adenomas. Preliminary results from that study did not show a statistically significant increase in cv risk for patients taking Celebrex 400 mg/d, but did not exclude the possibility of a hazards ratio similar to that demonstrated by APC. In addition, PreSAP used the same independent cardiovascular safety committee as APC to assess the risk of Celebrex on adverse cv events. Accordingly, the data from both trials were synthesized to produce a combined estimate of risk of cardiovascular death, heart attack, stroke or heart failure of 1.9 with a confidence interval of 1.1 to 3.1; in other words, combining the raw data showed a statistically significant increase in risk.[9] The study authors combined APC 400 mg/d and 800 mg/d with PreSAP 400 mg/d because the confidence intervals for 400 mg/d and 800 mg/d substantially overlapped. While the weight to be given to this evidence can be argued, in light of this evidence, and the Kearney meta-analysis which found a relative risk greater than one with a confidence interval that barely crossed one, the Court cannot conclude that expert opinion that Celebrex 400 mg/d is capable of causing heart attacks and strokes is scientifically invalid.

***1183 C. Whether Celebrex Causes Heart Attacks or Strokes More Than Three Days After A Patient Stops Taking It**

Plaintiffs do not dispute that Celebrex is not capable of causing hearts attacks or strokes more than three days after a patient stops taking it and they have offered no expert opinion to the contrary. Accordingly, there is no proposed expert testimony on this issue for the Court to exclude.

## D. Remaining Issues

### 1. Strokes

[11] The issue as to whether Celebrex is capable of causing strokes is close. Plaintiffs rely on the testimony of Dr. Rymer, a neurologist and the Medical Director of the Saint Luke's Brain and Stroke Institute at Saint Luke's Hospital in Kansas City, Missouri. She testified that the mechanism of and risk factors for throembolic strokes (excluding cardiogenic embolism) and heart attacks are the same; thus, if Celebrex causes an increased risk in heart attacks it also increases the risk of strokes. Rymer Written Direct ¶ 11-13. Dr. Rymer's testimony is supported by the published literature as nearly all studies of COX-2 inhibitors and cv risk lump strokes together with heart attacks. For example, the Kearney meta-analysis of clinical trials identified the relative risk for "serious vascular events," defined as heart attack, stroke, or vascular death. Indeed, even Pfizer's expert, Dr. Packer, considers the risk of heart attacks and strokes together, and Pfizer does not dispute Dr. Rymer's testimony as to the similar mechanism of heart attacks and strokes.

Pfizer nonetheless asserts that Dr. Rymer's testimony is inadmissible because the randomized controlled trials and observational studies that do separately report strokes and heart attacks do not suggest an association between Celebrex at any dose and strokes. Dr. Rymer explains, however, that none of the randomized controlled studies was designed to look for stroke outcomes, and strokes occur far less often than heart attacks; the studies simply were not designed to find an association or not.

While there is some epidemiologic evidence to dispute her mechanism testimony, that is, evidence that suggests that even though heart attacks and certain strokes are caused by the same mechanism Celebrex does not cause both, there is also some evidence to support her

testimony. On the current record the Court does not find that Dr. Rymer's testimony is scientifically invalid and inadmissible. *See Daubert,* 509 U.S. at 596, 113 S.Ct. 2786 ("Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence.").

**2. Duration**

[12] The Court also denies Pfizer's motion to exclude testimony that Celebrex is capable of causing heart attacks or strokes only after 33 months of continuous use. Because a statistically significant association did not appear in APC until after 33 months does not mean as a matter of scientific fact that none of the adverse cv events that occurred after a shorter duration were not caused by the patient's ingestion of Celebrex.

**3. Specific Causation**

Finally, Pfizer asks the Court to "exclude any opinion that Celebrex caused an individual plaintiff's heart attack or stroke absent a relative risk that exceeds 2.0." This is a question of specific causation as to particular plaintiffs; as the Court does not have before it evidence as to any specific plaintiff the Court declines to grant Pfizer's motion.

***1184 II. Plaintiffs' Motion to Exclude**

[13] Plaintiffs move to exclude the meta-analyses performed by Pfizer's experts. Plaintiffs' experts did not perform any of their own meta-analyses; instead, plaintiffs attack Pfizer's experts' methodologies. Plaintiffs' motion is denied. All of plaintiffs' arguments go to the weight a trier of fact gives to the meta-analyses. Plaintiffs have not shown that the methods employed by Pfizer's experts are not based on good science.

Plaintiffs also move to exclude Dr. Packer from testifying as to an alternative theory to the imbalance hypothesis. Dr. Packer's explanation, which accounts for the difference in outcomes between Vioxx and Celebrex, is based on increased blood pressure, a theory actually supported by plaintiffs' expert Dr. Rymer. In any event, Dr. Packer's testimony satisfies *Daubert.*

**CONCLUSION**

In *Daubert,* the Supreme Court held that federal judges perform a gatekeeping role, 509 U.S. at 597, 113 S.Ct. 2786, and "to do so they must satisfy themselves that scientific evidence meets a certain standard of reliability before it is admitted." *Daubert II,* 43 F.3d at 1316. Plaintiffs' expert testimony that Celebrex 200 mg/d can cause heart attacks or strokes does not meet that standard. Dr. Doherty, a clinical physician with no relevant research experience and who developed his opinion for the purpose of testifying, bases his opinion on a study that he fundamentally misunderstood, is counter to the great weight of the evidence, and, by his own admission, does not make biological sense. The Court cannot find that his opinion is good science. Dr. Rymer's 200 mg/d opinion is also not good science. She ignores all the evidence that contradicts her litigation-created conclusion and instead bases her opinion on the same cherry-picked study as Dr. Doherty, even though that study suffers from the exact same limitations that caused her to reject other studies that do not support her conclusion. She also relies on an unpublished, non-peer reviewed study that does not disclose its design or confidence intervals. If the Court's gatekeeping function means anything, it must mean that these unreliable opinions are not admissible to prove general causation at 200 mg/d.

In all other respects, and for the reasons explained above, the parties' motions are denied.

**IT IS SO ORDERED.**

**All Citations**

524 F.Supp.2d 1166, 75 Fed. R. Evid. Serv. 144

Footnotes

1 Patricia Kearney, et al., *Do selective cycol-oxygenase-2 inhibitors and traditional non-steroidal ant-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials,* British Medical Journal 2006, June 3;

332(7553): 1302-8.

2 Patricia McGettigan, et al., *Cardiovascular Risk and Inhibition of Cyclooxygenase: A Systematic Review of the Observational Studies of Selective and Nonselective inhibitors of Cyclooxygenase 2,* JAMA 2006 Oct 4; 296(13): 633-44.

3 S. Hernandez-Diaz et al., *Non-steroidal anti-inflammatory drugs and the risk of acute myocardial infarction,* Basic Clin. Pharmacol. Toxicol. 2006 Mar; 98(3):266-274, at 270, 273.

4 Frank Andersohn, et al., *Use of First-and Second-Generation Cyclooxygenase-2-Selective Nonsteroidal Anti-inflammatory Drugs and Risk of Acute Amuyocardial Infarction,* Circulation, 2006 Apr 25; 113(16): 1950-7.

5 Gunnar H. Gislason, et al., *Risk of Death or Reincarnation Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Anti-inflammatory Drugs After Acute Myocardial Infarction,* Circulation, 2006 June 27; 113(25): 2906-13.

6 James M. Brophy, *The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction.* Plaintiffs cited this study as being available at heart.bmj.com or at www.heartjnl. com.

7 Scott D. Solomon, et al., *Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention,* N. Engl. J. Med.2005 Mar 17; 352(11): 1071-1080.

8 ADAPT Research Group, *Cardiovascular and Cerebrovascular Events in the Randomized, Controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT),* PLoS Clin Trials 2006; 1(7): e33.

9 Scott D. Solomon, et al., *Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas,* Circulation, 2006 Sep 5; 114(10): 1028-35.

End of Document 

# *In re Bextra & Celebrex*

Supreme Court of New York, New York County

January 7, 2008, Decided

762000/2006

**Reporter**
2008 N.Y. Misc. LEXIS 720 *; 239 N.Y.L.J. 27

In re Bextra and Celebrex

**Subsequent History:** Motion granted by, Dismissed by *Archibald v. Pfizer, Inc., 2009 N.Y. Misc. LEXIS 3863 (2009)*

## Core Terms

Celebrex, stroke, studies, dose, cardiovascular, causation, scientific, patients, plaintiffs', inhibitors, heart attack, epidemiological, relative risk, defendants', reliability, disease, hypothesis, clinical trial, statistical, observational, parties, conclusions, clinical, exposure, causes, increased risk, drugs, confidence, randomized, imbalance

## Case Summary

**Procedural Posture**
In joined products liability actions, defendant pharmaceutical companies made a motion to exclude certain expert testimony and opinions proposed by plaintiff patients relating to the ingestion of an arthritis medication. The patients made a motion to exclude the opinions of and meta-analyses performed by the companies' experts and to exclude the companies' first expert from testifying as to an alternative theory for the "imbalance hypothesis."

**Overview**
The patients took the position that the dosage of the medication, whether 200, 400, or 800 milligrams (mg), created an increased risk of heart attacks and strokes and that they had suffered cardiovascular injury from taking the medication. The court initially determined that the claim of failure to warn of dangers of which the companies knew, or with adequate testing, should have known was indistinguishable from a negligence claim. Causation in a case involving pharmaceutical personal injury was analyzed in terms of general causation as a threshold issue; as it was impossible to offer direct evidence of causation, the patients could rely on expert analyses based on statistical data. The companies had conceded the risk of taking more than 800 mg. Evidence of an increased risk at 400 mg was presented based on reliable scientific studies. However, the scientific evidence did not support the position of general causation at 200 mg as the analyses of the patients' experts of various trials and studies were inconsistent with generally accepted standards and alternative theories were insufficient to bridge the gap between a possible and a significant risk of association at 200 mg.

**Outcome**
The court granted the companies' motion to preclude expert testimony that the medication at 200 mg daily could cause heart attacks and strokes; however, the motion was denied as to expert testimony regarding the medication at 400 and 800 mg daily. The balance of the companies' motion to preclude was denied. The patients' motion to exclude the meta-analyses was denied. Both parties' motions regarding the imbalance hypothesis were denied.

## LexisNexis® Headnotes

Evidence > Admissibility > Expert Witnesses > Daubert Standard

Evidence > Admissibility > Scientific Evidence > Standards for Admissibility

*HN1*[] **Expert Witnesses, Daubert Standard**

Daubert, which is based upon the Federal Rules of Evidence, has as its linchpin evidentiary reliability based upon scientific validity. A Daubert hearing, thus, determines whether the reasoning or methodology underlying the testimony is scientifically valid and whether that reasoning or methodology properly can be applied to the facts in issue. Important to this determination is the following: 1) whether the theory or technique can be tested; 2) whether it has been subjected to peer review and publication, a criterion which the court noted did not necessarily correlate with reliability; 3) submission to the scrutiny of the scientific community; 4) the known or potential rate of error; 5) the existence and maintenance of standards controlling the technique's operation; and 6) general acceptance in the relevant scientific community.

Torts > ... > Elements > Causation > General Overview

Torts > Products Liability > Types of Defects > Marketing & Warning Defects

**HN2[] Elements, Causation**

Failure to warn of dangers of which the manufacturers knew or with adequate testing should have known, though it may be couched in terms of strict liability, is indistinguishable from a negligence claim. Liability will not be found unless (1) the product is "defective" because it is not reasonably safe as marketed; (2) the product was used for a normal purpose; (3) the defect was a substantial factor in causing the plaintiff's injuries; (4) the plaintiff by the exercise of reasonable care would not have both discovered the defect and apprehended its danger; and (5) the plaintiff would not have otherwise avoided the injury by the exercise of ordinary care. Causation in toxic tort or pharmaceutical personal injury cases is analyzed in terms of general (or generic) causation as a threshold issue; then if plaintiff clears that hurdle, the court (and jury) will grapple with the issue of specific causation--whether the drug or the toxin was the cause "in fact" of the particular plaintiff's disease.

Evidence > Admissibility > Expert Witnesses > Daubert Standard

Evidence > Admissibility > Expert Witnesses

**HN3[] Expert Witnesses, Daubert Standard**

Where it is impossible to offer direct evidence of causation, New York law allows plaintiffs to rely on expert analyses based on statistical data to meet their burden. The admissibility and scope of expert testimony is addressed to the trial court's sound discretion. To be admissible, an expert must be qualified, and his/her opinion must be generally accepted in the relevant scientific community. General acceptance does not necessarily mean that a majority of the scientists involved subscribe to the conclusion. Rather it means that those espousing the theory or opinion have followed generally accepted scientific principles and methodology in evaluating clinical data to reach their conclusions.

Evidence > Admissibility > Scientific Evidence > Standards for Admissibility

**HN4[] Scientific Evidence, Standards for Admissibility**

A scientifically-reliable methodology to establish the relationship between an individual's disease and a specific factor suspected of causing that disease entails a three-step process: (1) a determination of the plaintiff's level of exposure to the toxin in question; (2) proof gleaned from the scientific literature that the toxin is capable of producing the illness (general causation) and at what level of exposure the toxin produces illness (i.e., the dose-response relationship); and (3) establishment of specific causation by demonstrating the probability that the toxin caused the particular plaintiff's illness, which involves weighing the possibility of other causes of the illness.

Evidence > Admissibility > Expert Witnesses > Daubert Standard

Evidence > Admissibility > Expert Witnesses > Kelly Frye Standard

**HN5[] Expert Witnesses, Daubert Standard**

When there is no particular novel methodology at issue for which the court needs to determine whether there is general acceptance, the inquiry is more akin to whether there is an appropriate foundation for the experts' opinions rather than whether the opinions are

admissible under Frye. The foundational inquiry shirts away from the general reliability concerns of Frye to the specific reliability of the procedures followed to generate the evidence proffered and whether they establish a foundation for the reception of the evidence at trial. The burden is on the proponent of the evidence to demonstrate the generally accepted reliability of the proffered testimony.

Evidence > Admissibility > Expert Witnesses > Daubert Standard

Evidence > Admissibility > Scientific Evidence > Standards for Admissibility

***HN6*** **Expert Witnesses, Daubert Standard**

Once a scientific method has been deemed accepted, an inquiry must be made as to whether the accepted method was appropriately employed in a particular case.

Torts > ... > Elements > Causation > General Overview

Torts > ... > Proof > Violations of Law > Rules & Regulations

***HN7*** **Elements, Causation**

Standards promulgated by regulatory agencies as protective measures are inadequate to demonstrate legal causation.

Torts > ... > Elements > Causation > General Overview

***HN8*** **Elements, Causation**

A determination of whether an association exists between exposure to the agent and the disease must be based on assessment of the totality of the evidence.

**Counsel:** **[*1]** For the Plaintiffs: Mitchell M. Breit, Whatley, Drake, Kalkis.

For the Defendants: Chris Strongosky, DLA Piper.

**Judges:** Justice Kornreich

**Opinion by:** Kornreich

## Opinion

Defendants in these joined products liability personal injury actions, Pfizer, Inc., Pharmacia Corporation, Pharmacia & Upjohn Company, G.D., Searle & Co. (formerly known as G.D. Searle LLC), and Monsanto Company (collectively "Pfizer defendants" or "defendants"), move to exclude expert testimony and opinions proposed by plaintiffs asserting claims arising from ingestion of Celebrex. Specifically, defendants ask the court to exclude the following opinions by plaintiffs' proposed experts that: (1) 200 mg of Celebrex daily causes heart attacks and strokes; (2) 400 mg of Celebrex daily causes heart attacks and strokes; (3) Celebrex causes strokes; (4) Celebrex caused any individual plaintiff's heart attack or stroke absent reliable proof of a relative risk that exceeds 2.0; (5) Celebrex causes heart attacks or strokes more than three days after a patient stops taking it; and (6) Celebrex causes heart attacks or strokes at durations of less than 33 months of continuous daily use.

Correspondingly, plaintiffs seek to exclude the opinions of and meta-analyses **[*2]** performed by Pfizer's experts Dr. Muhammad Mamdani, Dr. Milton Packer and Dr. Lee-Jen Wei. Plaintiffs also seek to exclude Dr. Packer from testifying as to an alternative theory for the "imbalance hypothesis" that plaintiffs have proposed as mechanistic evidence of general causation. For the reasons stated below, the court grants defendants' motion to preclude expert testimony that Celebrex at 200 mg daily causes heart attacks and strokes. The remaining motions are denied.

I. Background

Celebrex (known generically as Celecoxib) belongs to a general class of pain relievers known as non-steroidal, anti-inflammatory drugs ("NSAIDs"). This class of drugs contains traditional medications sold either over the counter--such as Motrin/Advil (ibuprofen), Aspirin and Aleve (naproxen)--or by prescription--such as Daypro (oxaprozin) and Voltaren (diclofenac). NSAIDs work by inhibiting cyclooxygenase (COX), an enzyme that stimulates synthesis of prostaglandins, which are chemicals produced in the body affecting, inter alia, blood clotting.

Traditional NSAIDs have been a longstanding treatment option for relief of chronic or acute inflammation and

pain associated with osteoarthritis, rheumatoid arthritis **[*3]** and other musculo-skeletal conditions. Traditional NSAIDs, however, have significant adverse side effects. Specifically, they greatly add to the risk of gastrointestinal perforations, ulcers and bleeds ("PUBs"). This risk is increased when high doses are ingested, which is often necessary to remedy chronic or acute inflammation and pain.

In the early 1990s, scientists discovered that the COX enzyme had two forms--COX-1 and COX-2--each of which appeared to have several distinct functions. Scientists believed that COX-1 affected the synthesis or production of prostaglandins responsible for protection of the stomach lining. Consequently, scientists hypothesized that "selective" NSAIDs designed to inhibit COX-2, but not COX-1, could offer the same pain relief as traditional NSAIDs with the reduced risk of fatal or debilitating PUBs. In addition, scientists believed that Cox-2 inhibitors might prove beneficial for the prevention or treatment of other conditions where evidence suggested that inflammation may play a causative role, such as Alzheimer's disease and certain cancers.

In light of these scientific advances, Pfizer and several other pharmaceutical companies began the development of **[*4]** "COX-2 inhibitors" or "coxibs." Thereafter, Pfizer produced Celebrex and Bextra, and Merck produced Vioxx, all COX 2 inhibitors. The Food and Drug Administration("FDA") approved Celebrex for adult arthritis in 1998, Vioxx in 1999 and Bextra in 2001. The recommended dose of Celebrex was and remains 200 milligrams a day ("mg/d") for arthritis and was 400 mg/d for rheumatoid arthritis.

Before and after its initial approval, Celebrex was subjected to a number of clinical trials and observational studies, the main sources of data analyzed by statisticians to determine the risks associated with the use of a particular compound. In clinical trials, the investigator controls organization of the comparison groups (by random selection) and administration of the exposure (here Celebrex). In an observational study, the investigator studies subjects in the community who have received an exposure through their own choice (over-the-counter medication), the actions of a healthcare provider (by prescription) or other circumstances. This method of scientific research is known as "epidemiology." Meta-analyses were conducted. A meta-analysis is a systematic technique used to quantitatively summarize and **[*5]** assess data from clinical trials and observational studies.[1] In addition to the epidemiology, a large amount of scientific literature was written on the effects of Celebrex and other COX-2 inhibitors.

The results of a long-term randomized study of Celebrex known as CLASS ("Celecoxib Long-Term Arthritis Safety Study") were published in 2000. The study was designed to evaluate the gastrointestinal side effects of taking Celebrex at 800 mg/d. Based upon investigator reported cardiovascular ("cv") events, the study showed no increased risk of, heart attack or stroke when Celebrex was compared to Diclofenac or Ibuprofen. Pfizer distributed this study widely to physicians and the medical community. After the CLASS trial was published, however, unpublished data from the trial were released. A number **[*6]** of medical articles analyzing CLASS in light of the unpublished data, found that the cv rate for Celebrex at 800 mg/d was in fact increased when compared with a placebo. See Mukherjee, et al., Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors, JAMA, 2001, 286:954-959 (MDL 1699 Exh. N); Hrachovec, et al., JAMA, 2001, 286:2398-9 (MDL 1699 Exh. O); Juni, Are Selective COX-2 Inhibitors Superior to Traditional Non-Steroidal Anti-Inflammatory Drugs?, BMJ, 2002, 324:1287-8 (MDL 1699 Exh. P); Fitzgerald, Coxibs and Cardiovascular Disease, NEJM, 2004, 351:1709-1711 (MDL 1699 Exh. Q).

Around the same time, a similar study of Vioxx, known as VIGOR, showed a four-fold increase in cv risk for patients, taking Vioxx versus Aleve (naproxen), the most benign of the NSAIDs. The FDA subsequently revised the labels of Celebrex and Vioxx to reflect the cv risk results of these studies. Another Vioxx randomized clinical study, known as APPROVe, was published in 2004. This study demonstrated a two-fold increased risk of cv adverse events for patients taking Vioxx versus a placebo. The APPROVe study contributed to Merck's voluntary removal of Vioxx from the market on September 30, 2004. **[*7]** Meantime, the Adenoma Prevention With Celecoxib Trial ("APC"), a randomized, placebo-controlled study of Celebrex at 200 mg twice daily (400 mg/d) and 400 mg twice daily (800 mg/d) to

---

[1] Celebrex clinical trials referred to by the parties are: TARGET, APC, PreSAP, ADAPT, and CLASS. Celebrex observational studies referred to by the parties are: Huang, Schneeweiss, Jick, Helin-Salmivaara, Brophy, Gislason, Johnsen, Andersohn, N.S. Abraham, et al., Motsko, et al., and WellPoint, Inc. Celebrex meta-analyses referred to by the parties are: Caldwell, Chen, Kearney, McGettigan and Wei.

evaluate whether Celebrex prevents the development of colon polyps, showed dose-related increased cv risk for patients taking Celebrex compared to placebo. The cv risk for 200 mg twice daily was doubled, and the risk for 400 mg twice daily was tripled. The APC steering committee discontinued the trial in December 2004 because of these preliminary results.

In February 2005, the FDA convened two Advisory Committees and a 12-member ad hoc panel to review the data on cv risk and NSAIDs, including COX-2 inhibitors. The 32-person panel, relying on much of the same scientific and medical methodologies and data considered by the parties' experts in this litigation, was unanimous in its conclusion that Celecoxib significantly increases the risk of cardiovascular events in a dose-dependent manner. The panel concluded that COX-2 inhibitors, as a class, increase cv risk versus placebo, but that the data was insufficient to determine if traditional NSAIDs also increase cv risk. The panel gave greater weight to clinical **[*8]** trials than observational studies, commenting that the latter are considered supplemental to randomized, controlled clinical trials due to selection bias and residual confounding. The panel considered observational studies "hypothesis generating" in that they provide clues as to whether a manufacturer should conduct randomized, controlled trials. Minutes and transcript of 2/05 FDA advisory committee meeting, plaintiffs' opposition brief, Exhs 30 and 31. With respect to Celebrex, the panel noted that an excessive cv risk was likely with the 800 mg dose and probable at the 400 mg dose. Id. The panel made no finding with respect to the 200 mg dose and found that APC was the "strongest data" in support of an increased risk of serious, adverse cv events. FDA Decision Memorandum, April 6, 2005, at 4, Declaration of Loren Brown ("Brown Decl."), Exh. 16.

The committee recommended that Celecoxib be allowed to remain on the U.S. market under several conditions, such as the addition of a "black box" warning to the labeling, restrictions on direct-to-consumer advertising and the development of a patient medication guide. Assumptions included that if Celecoxib was to be used, it should be: in patients **[*9]** who have not achieved pain control with nonselective NSAIDs; used in the lowest possible dose for the shortest time necessary and with information to high-risk cardiac patients about the excess cardiovascular risks. The FDA asked Pfizer to remove Bextra from the market, but determined that the benefits of Celebrex outweigh its risks. Celebrex is the only COX-2 inhibitor currently being sold.

The FDA also directed all NSAIDs, including Celebrex, to include a black box warnings on, their labels (not dose related): "CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have similar risk. This risk may increase with duration of use. Patients with cardiovascular disease may be at greater risk." Bennett, et al., Use of Nonsteroidal Antiinflammatory Drugs, An Update for Clinicians: A Scientific Statement From the American Heart Association; circulation 1-9, 2007: 115 (MDL 1699 Exh. EE). The black box warning does not comment on the magnitude of the increase in risk, relative or absolute, and there is no mention of the recommendation for low doses or short duration of treatment. It contains the **[*10]** general statement that "[a]ll NSAIDs may have a similar risk," but includes no recognition of known differences among the nonselective NSAIDs. Id.[2]

Thereafter, thousands of patients and patient representatives filed lawsuits against Merck and Pfizer alleging that the patient had suffered a serious cardiovascular injury due to ingestion of Vioxx and/or Celebrex and/or Bextra. All of the Federal court claims against Merck were consolidated by the Multi-District Litigation Panel ("MDL") and transferred to the Federal District Court in New Orleans. All of the Federal court claims involving Celebrex and Bextra were consolidated in an MDL action and transferred to Judge Charles R. Breyer of the Federal District Court in San Francisco and all of the New York State Celebrex and Bextra claims were joined **[*11]** and transferred to this court. A joint Federal/ New York State hearing on general causation in the Celebrex cases was held in the District Court on October 9-11, 2007, regarding the issues raised in the instant motions. This court and Judge Breyer presided at that hearing with Judge Fern Smith, special master. On November 19, 2007, Judge Breyer issued his memorandum and order determining that plaintiffs failed to demonstrate scientifically reliable evidence that Celebrex causes heart attacks or strokes when ingested at the 200 mg/d dose. Judge Breyer denied defendants' motion to exclude opinion testimony that Celebrex causes heart attacks or strokes when

---

[2] The European Medicine Agency also has issued recommendations on coxibs' use. It recommends that selective COX-2 inhibitors be considered contraindicated in patients with ischemic heart disease and/or stroke, that they be avoided in patients with risk factors for coronary heart disease and that all patients take the lowest effective dose for the shortest time necessary to control symptoms. Id

ingested at the 400 or 800 mg/d doses. In all other respects, the parties' motions were denied.[3]

II. The Parties' Positions

Plaintiffs assert that the scientific tests and literature show that Celebrex significantly increases the risk of cardiovascular thrombotic events at all doses and for all durations. Plaintiffs further contend that the underlying biological mechanism of action (the "imbalance hypothesis" or "Fitzgerald theory") not only explains why certain of the clinical trials and observational studies show a significantly increased risk of cardiovascular events, but also constitutes independent proof of general causation at any dose. Plaintiffs rely on the conclusions of six proposed **[*13]** experts, reports and opinions issued by the Food and Drug Administration ("FDA") and the American Heart Association ("AHA"), the FDA's requirement that Celebrex's label include a "black box warning" and certain clinical and observational studies which establish a significant risk of cardiovascular thrombotic events, myocardial infarction and stroke from the ingestion of Celebrex.

Four of plaintiffs' experts testified at the joint hearing. Dr. Joel S. Bennett, a hematologist and professor of pharmacology, was presented to support the opinion that Celebrex increases the risk of cardiovascular events at all doses and that causation can be shown through the underlying biological mechanism of action, the imbalance theory. Dr. Neil E. Doherty III, a clinical cardiologist, testified to his opinion that Celebrex increases the risk of cardiovascular events at all doses and at all durations. Dr. Nicholas P. Jewell, a statistician, was presented to opine that Celebrex at 200 mg/d is capable of causing a myocardial infarction ("MI"). And, plaintiffs' fourth expert to testify, Dr. Marilyn M. Rymer, a neurologist with a sub-specialty in stroke, opined that because the mechanism for ischemic stroke **[*14]** is the same as for heart attacks, data showing that Celebrex increases the risk of heart attacks also applies to strokes.

Defendants challenge the qualifications of plaintiffs' experts and the reliability of their methodologies and conclusions. Defendants' expert Dr. Milton Packer, a cardiologist and professor of clinical research, testified at the joint hearing. Additionally, defendants presented the written testimony and analyses of Muhammad Mamdani, an epidemiologist/and Professor Lee Jen-Wei, a bio-statistician, opining on the results of the many clinical trials and observational studies, which they argue show the lack of causation for stroke at any dose, the lack of causation for MIs at 200 mg or 400 mg and the lack of causation for stroke or MI at any dose absent a relative risk that exceeds 2.0. Plaintiffs characterize defendants' arguments as going to the weight and not the admissibility of plaintiffs' experts' conclusions.

III. Legal Principles

Liability here is predicated on *HN2*[↑] failure to warn of dangers of which the manufacturers knew or with adequate testing should have known. See *Wolfgruber v. Upjohn Co., 72 AD2d 59, 423 N.Y.S.2d 95*, aff'd on opn below *52 NY2d 768, 417 N.E.2d 1002, 436 N.Y.S.2d 614 (1979)*. Such a claim, though **[*15]** it may be couched in terms of strict liability, is indistinguishable from a negligence claim. Id. Accord *Enright v. Eli Lilly & Co., 77 N.Y.2d 377, 387, 570 N.E.2d 198, 568 N.Y.S.2d 550 (1991)*. Liability will not be found unless: (1) the product is "defective" because it is not reasonably safe as marketed; (2) the product was used for a normal purpose; (3) the defect was a substantial factor in causing the plaintiff's injuries; (4) the plaintiff by the exercise of reasonable care would not have both discovered the defect and apprehended its danger; and (5) the plaintiff would not have otherwise avoided the injury by the exercise of ordinary care. *Wolfgruber, supra at 62*. Causation in toxic tort or pharmaceutical personal injury cases is analyzed in terms of general (or generic) causation as a threshold issue; then if plaintiff clears that hurdle, the court (and jury) will grapple with the issue of specific causation--whether the drug or the toxin was the cause "in fact" of the particular plaintiff's disease. See, e.g., Mary Sue Henifin, Howard M. Kipen & Susan R. Poulter, Reference Guide on Medical Testimony, in REFERENCE MANUAL ON SCIENTIFIC

---

[3] Judge Breyer made his determination using the Daubert, not the Frye, standard. See *Daubert v. Merrill Dow Pharmaceuticals, Inc., 509 U.S. 579, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993)*. *HN1*[↑] Daubert, which is based upon the Federal Rules of Evidence, has as its linchpin evidentiary reliability based upon scientific validity. *Daubert, id. at 588-90*. A Daubert hearing, thus, determines "whether the reasoning or methodology underlying the testimony is scientifically valid and whether **[*12]** that reasoning or methodology properly can be applied to the Facts in issue." *Id. at 592-3*. Important to this determination's the following: 1) whether the theory or technique can be tested; 2) whether it has been subjected to peer review and publication, a criterion which the Court noted did not necessarily correlate with reliability; 3) submission to the scrutiny of the scientific community; 4) the known or potential rate of error; 5) the existence and maintenance of standards controlling the technique's operation; and 6) general acceptance in the relevant scientific community. *Id. at 593-4*.

EVIDENCE 439, 444 (Fed. Jud. Ctr., 2d ed. 2000). The pending motions concern **[*16]** the issue of general causation--whether plaintiffs have met their burden of proving that Celebrex is capable of causing the types of cardiovascular injuries allegedly suffered by plaintiffs in these consolidated actions.

*HN3*[↑] Where, as here, it is impossible to offer direct evidence of causation, New York law allows plaintiffs to rely on expert analyses based on statistical data to meet their burden. See *Nonnon v. City of New York, 32 A.D.3d 91, 105, 819 N.Y.S.2d 705 (1st Dept. 2006)*. "The admissibility and scope of...[expert] testimony is addressed to the trial court's sound discretion." *Hudson v. Lansingburgh Cent. School Dist., 27 AD3d 1027, 1028-1029, 812 N.Y.S.2d 678 (3d Dept. 2006)*. To be admissible, an expert must be qualified and his/her opinion must be generally accepted in the relevant scientific community. *Frye v. United States, 54 App. D.C. 46, 293 F. 1013 (D.C. Cir. 1923)*. See *People v. Wesley, 83 N.Y.2d 417, 422, 423 n.2, 633 N.E.2d 451, 611 N.Y.S.2d 97 (1994)* (Court utilized Frye standard and specifically stated *Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993)*, was not applicable in New York); *Heckstall v. Pincus et al., 19 A.D.3d 203, 797 N.Y.S.2d 445 (1st Dept. 2005)*. "[G]eneral acceptance does not necessarily mean that a majority of the scientists involved **[*17]** subscribe to the conclusion. Rather it means that those espousing the theory or opinion have followed generally accepted scientific principles and methodology in evaluating clinical data to reach their conclusions."[4] *Beck v. Warner-Lambert Co. (NYLJ, Sept. 13, 2002, at 18, col 2), 2002 N.Y. Misc. LEXIS 1217, 2002 NY Slip Op 40431(U)*. See *Lewin v. County of Suffolk, 18 A.D.3d 621, 622, 795 N.Y.S.2d 659 (2d Dept. 2005)* (where no scientific organization or national board had expressly recognized plaintiff's theory and peer-reviewed scientific articles and textbooks relied upon by plaintiff's experts did not establish causal relationship, expert's testimony was "fundamentally speculative" and inadmissible); *Pauling v. Orentreich Med'l. Group, 14 A.D.3d 357, 787 N.Y.S.2d 311 (1st Dept.)*, lv. denied *4 N.Y.3d 710, 830 N.E.2d 1146, 797 N.Y.S.2d 817 (2005)* (plaintiff failed to meet burden of proof at Frye hearing where no medical literature submitted to support theory and no scientific or medical board recognized causal relationship); *Marsh v. Smyth, 12 A.D.3d 307, 785 N.Y.S.2d 440(1st Dept. 2004)* (Frye test met where expert's deductions were supported by medical literature); *Saulpaugh v. Krafte, 5 A.D.3d 934, 774 N.Y.S.2d 194 (3d Dept.)*, lv. denied *3 N.Y.3d 610, 820 N.E.2d 292, 786 N.Y.S.2d 813 (2004)* (broad statement of scientific acceptance without accompanying support, insufficient **[*18]** to establish scientific acceptance of theory); *Lara v. N.Y.C. Health and Hosp. Corp., 305 A.D.2d 106, 757 N.Y.S.2d 740 (1st Dept. 2003)* (Frye test not met where no reported medical cases or formal studies supported theory); *Selig v. Pfizer, Inc., 290 A.D.2d 319, 735 N.Y.S.2d 549 (1st Dept.)*, lv. denied *98 N.Y.2d 603, 772 N.E.2d 605, 745 N.Y.S.2d 502 (2002)* (where clinical data did not support expert's theory of causal link and expert failed to set forth other scientific evidence based on accepted principles to support causal link, expert precluded).

*HN5*[↑] When there is "no particular novel methodology at issue for which the Court needs to determine whether there is general acceptance..., the inquiry...is more akin to whether there is an appropriate foundation for the experts' opinions, rather than whether the opinions are admissible under Frye." *Parker v. Mobil Oil Corp., 7 NY3d 434, 447, 857 N.E.2d 1114, 824 N.Y.S.2d 584 (2007)*. The foundational inquiry shirts away from the "general reliability concerns of Frye to the specific reliability of the procedures followed to generate the evidence proffered and whether they establish a foundation for the reception of the evidence at trial." *People v. Wesley, supra at 429*. Accord *People v. LeGrand, 8 N.Y.3d 449, 457, 867 N.E.2d 374, 835 N.Y.S.2d 523 (2007)*. The burden is on the proponent of the evidence to demonstrate the generally accepted reliability of the proffered testimony. *Parker, supra at 437*. Thus, plaintiffs here must show that their experts not only rely on generally **[*20]** accepted scientific principles and methodologies, but also that in arriving at their conclusions, they look at the totality of the

---

[4] *HN4*[↑] A scientifically-reliable methodology to establish the relationship between an individual's disease and a specific factor suspected of causing that disease entails a three-step process: (1) a determination of the plaintiff's level of exposure to the toxin in question; (2) proof gleaned from the scientific literature that the toxin is capable of producing the illness (general causation) and at what level of exposure the toxin produces illness (i.e., the dose-response relationship); and (3) establishment of specific causation by demonstrating the probability that the toxin caused the particular plaintiff's illness, which involves weighing the possibility of other causes of the illness. *Manusco v. Consolidated Edison Co. of New York, Inc., 56 F. Supp. 2d 391, 399 (1999)*; **[*19]** *In re Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124, 1131 (1995)*; *Wills v. Amerada Hess Corp., 2002 U.S. Dist. LEXIS 1546, 2002 WL 140542 (SD NY, Jan. 31, 2002)*; *Amorgianos v. National R.R. Passenger Corp., 303 F.3d 256, 268 (2002)*; *Castellow v. Chevron, 97 F. Supp. 2d 780, 795-798 (2000)*.

evidence and do not ignore contrary data. See *Selig v. Pfizer, Inc., 185 Misc.2d 600, 607, 713 N.Y.S.2d 898 (Sup. Ct. N.Y.County 2000)* (finding that expert failed to follow accepted scientific methodology by ignoring contrary clinical studies), aff'd, *290 AD.2d 319, 735 N.Y.S.2d 549 (1st Dept. 2002)*.

IV. Principles of Epidemiology

Nearly all of the scientific evidence regarding the efficacy and risk of Celebrex is derived from epidemiological sources, that is, statistical analysis of data from clinical trials and observational studies. Epidemiology is hardly novel. It is a reliable scientific methodology that focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause disease in a particular individual?). Reference Guide on Epidemiology (p 336), found in the Reference Manual on Scientific Evidence (2d ed) (2000) ("the Guide"). The Guide emphasizes that "an association is not equivalent to causation" [id. (emphasis in original)], and that the question of "specific causation... [is] beyond the domain of **[*21]** the science of epidemiology." Id. at 381. The parties' experts, by and large, agree with these fundamental principles of epidemiological evaluation as related to causation.

The parties further acknowledge the method for applying these principles as explained in the Guide. Hence, an expert must first determine "whether an association exists between exposure to the agent and the disease." Id. at 348. An association must be based on an assessment of the totality of the evidence and must be statistically significant, that is, beyond the play of chance. Id. "Once an association has been found between exposure to an agent and development of a disease, researchers consider whether the association reflects a true cause-effect relationship." Id.

Epidemiologists speak in the statistical language of risks and probabilities. The risk of injury from a suspected cause is expressed as relative risk. To calculate relative risk, the number of occurrences of an illness or injury in an exposed group is divided by the number of occurrences in the control, or unaffected group. If the given illness or injury occurs with equal frequency between the exposed and control groups, the relative risk would be 1.0. **[*22]** A relative risk of 1.0 is considered inconclusive, in that a researcher cannot state that a suspected agent does or does not cause the illness or injury (i.e., the "null hypothesis" or "no association"). Id. A relative risk of less than 1.0 suggests that a suspected agent does not cause the disease. A relative risk greater than 1.0 suggests that the substance may cause a given disease.

To gauge the reliability and credibility of their reports, statisticians use a proposition known as the confidence interval. The confidence interval is not a "burden of proof" in the legal sense. Rather, it is a common sense mechanism upon which statisticians rely to confirm their findings. The confidence interval has two components--a percentage and an interval or range. The percentage portion is established by the statistician in advance of performing the studies. Frequently, this percentage is set at 95 percent, although that value is somewhat arbitrary. The interval, on the other hand, represents a range of possible values at high and low ends of a scale of relative risk. Id. See, e.g., Kenneth Rothman, Modern Epidemiology 119 (1986). At a 95 percent interval the true relative risk value will be between **[*23]** the high and low ends of the confidence interval 95 percent of the time. See Neil Cohen, Confidence in Probability: Burdens of Persuasion in a World of Imperfect Knowledge, *60 N.Y.U.L. Rev. 385, 398-400 (1985)* ("Confidence in Probability").

As Judge Breyer so aptly explained in his recent opinion in the Celebrex MDL litigation, "[I]f a given study showed a relative risk of 1.40 (a 40 percent increased risk of adverse events), but the 95 percent confidence interval is .8 to 1.9, we would say that we are 95 percent confident that the true value, that is, the actual relative risk, is between .8 and 1.9. Because the confidence interval includes results which do not show any increased risk, and indeed, show a decreased risk, that is, it includes values less than 1.0, we would say the study does not demonstrate a 'statistically significant' increased risk of an adverse outcome." When a study does show a relative risk where both the top and the bottom values are greater than 1.0, the study supports finding a "statistically significant" increased risk. See *In Re Silicone Gel Breast Implant Prod. Liab. Lit., 318 F.Supp.2d 879, 892 (C.D. Ca. 2004)*. Proof that a relative risk is greater than 2.0 **[*24]** is arguably relevant to the issue of specific, as opposed to general, causation and is not required for plaintiffs to meet their burden in opposing defendants' motion.

Even when an appropriately designed study yields evidence of a statistical association between a given substance and a given health outcome, epidemiologists generally do not accept such an association by itself as proof of a causal relationship between the exposure and the outcome. Epidemiologists generally look to several additional criteria to determine whether a statistical

association is indeed causal. These criteria are sometimes referred to as the Bradford Hill criteria, after the author of a leading statement of the relevant principles, which are: (1) strength of association; (2) consistency of association; (3) specificity of association; (4) temporality of the association; (5) biological plausibility; (6) coherence; (7) experimental verification; (8) biological analogy; and (9) dose-response relationship. A. Bradford Hill, The Environment and Disease: Association or Causation, 58 PROC. ROYAL SOC'Y MED. 295, 295-300 (1965).

V. Conclusions of Law

The lion's share of evidence offered by plaintiffs to carry their burden **[*25]** is comprised of epidemiological data, an established and reliable scientific field based on the gathering of data and the statistical analysis of the information. The issue before the court, therefore, is not the general acceptance of epidemiology by the relevant scientific community, but rather the challenged experts' application of the accepted scientific principles--the foundation for the experts' opinions. See *Parker, supra at 447* (***HN6***[↑] once method deemed accepted, inquiry made as to whether accepted method appropriately employed in particular case).

A. Dose

The court is in complete accord with the MDL court's conclusions that "dose matters" and that plaintiffs' experts have essentially conceded this point. MDL court's decision at p.10. As stated in the Reference Manual on Scientific Evidence, "a dose-response relationship means that the more intense the exposure, the greater the risk of disease." Ann. Ref. Man. Sci. Evid. 2d ed., 2005-06, p.531. Plaintiffs rely heavily on the Parker decision to argue that dose should not be material to this court's decision. The Court of Appeals in Parker determined that specific quantification of the dose or exposure level is not always necessary to **[*26]** find an expert opinion on causation reliable. *Parker, supra, 7 N.Y.3d at 448*. The Parker decision did not, however, distinguish between proof of general versus specific causation, but rather concluded that the proffered evidence fell short of proving either level of causation. *Id. at 449* (finding insufficient reliable proof supporting experts' conclusion that exposure to benzene as component of gasoline caused plaintiff's illness). Key to the Parker decision was the difficulty in an environmental toxin exposure case of establishing with specificity the level of toxicity in general, as well as any individual's actual exposure. Environmental toxin cases are distinguishable from pharmaceutical cases; pharmaceuticals are dose-specific. Moreover, the plaintiffs in Parker presented no epidemiological studies showing an increased risk of the plaintiff's illness as a result of exposure to the specific toxin in question. Nor was there a plethora of scientific evidence showing a lack of significant association. The exception to the general rule that dose is an important factor in assessing causation, noted in *Parker*, simply does not apply here.

B. Celebrex at 400 and 800 mg/d

Defendants rightfully **[*27]** have conceded that taking more than 800 mg/d of Celebrex for more than a brief period increases the risk of cardiovascular injury. Direct Examination of Muhammad Mamdani at p. 24 [CONCLUSION]; Direct Examination of Milton Packer at p. 8; Defendants' Motion at p. 7; Packer Hrg. Tr. at 628. The court's analysis, therefore, will focus on the more commonly prescribed doses, 200 (discussed below) and 400 mg/d. Evidence of increased risk at 400 mg/d exists. As discussed above, APC was a large, long-term, randomized, placebo-controlled, double-blind, multi-center clinical trial. It was designed by defendant Pfizer with the National Cancer Institute, to compare Celebrex with a placebo for the prevention of polyps, and it included a committee to develop guidelines and monitor cardiovascular safety. That committee stopped the trial after 33 months because it demonstrated a statistically significant risk of heart attack, stroke and heart failure at 400 mg/d (confidence interval of 1.1 to 6.1), and 800 mg/d (confidence interval of 1.5 to 7.9). People were getting hurt, and the committee made the ethical decision to stop administering the drug.

Plaintiffs' reliance on the APC results is not, as **[*28]** defendants argue, "cherry-picking." The APC trial was the only long-term trial of its size and duration to date. As defendants themselves concede, double-blind, randomized clinical trials are the "gold standard" for assessing whether an exposure is associated with an outcome. Mamdani Direct at p. 6. Although defendants note certain imperfections in APC--it was stopped early and its results have not been replicated by other randomized controlled clinical studies--these imperfections do not render APC so unreliable as to exclude it from the scientific evidence underlying the experts' opinions. Further, PreSAP, a colon polyp prevention clinical trial of Celebrex at 400 mg/d, also sponsored by the National Cancer Institute and Pfizer, was stopped early by the same safety committee that stopped APC and for the same reasons (a demonstrable risk of harm to the participants). The PreSAP trial results, when not viewed in a vacuum, did

not exclude the possibility of a risk ratio like the one found by APC. In 2006, however, a published analysis of the combined data from APC and PreSAP concluded, "Celecoxib at 200 or 400 mg twice daily showed a nearly 2-fold-increased cardiovascular risk." Solomon, **[*29]** et al., Effect of Celecoxib on Carsdiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas, Circulation, 2006; 114:1028-1035 (MDL 1699 Exh. L). The weight of this evidence can be debated by the parties' experts at trial, but the court will not exclude it and the opinions based on it at this preliminary stage.

Moreover, there was ADAPT, an Alzheimer's trial of Celebrex at 200 mg twice daily (400 mg/d). Although it showed no increased cv risk for Celebrex versus placebo, certain factors individual to this study suggest that the results are questionable. For example, as the American Heart Association found, the ADAPT trial had "major limitations." The trial included a very high rate of patients lost to follow-up (almost 10 percent), a large number of enrollees who did not receive their study medication, a lack of specified criteria for the cardiovascular events, no central adjudication of the reported non-fatal events and a small number of reported cardiovascular deaths, myocardial infarctions and strokes. See Use of Non-steroidal Antiinflammatory Drugs, An Update for Clinicians: A Scientific Statement From the American Heart Association; circulation **[*30]** 1-9, 2007 (MDL 1699 Exh. EE). Further, as the MDL court recognized, it is possible that the study participants' risk factors differed from the general population because their eligibility to participate hinged on a family history of Alzheimer's disease. This court agrees that "the results of ADAPT need to be weighed with the APC results, but ADAPT's conclusions do not make reliance on APC scientifically invalid." MDL opinion at p. 23. Indeed, the Kearney meta-analysis of all randomized clinical trials comparing Celebrex 400 mg/d to a placebo or naproxen, found a relative risk greater than 1.0 with a confidence interval that barely crossed 1.0. This result could be fatal to plaintiffs' case if the underlying trials were shown to be identical, as well as perfectly constructed and implemented. Alas, that was not the case. Otherwise the parties would have nothing about which to argue.

The parties, too, have presented the court with a wealth of additional materials, including published and unpublished studies, meta-analyses of studies and articles. Some appear to support plaintiffs' position and some appear to support defendants' position, depending on which set of experts is interpreting **[*31]** the results. The reliability of each of these studies was hotly debated by the parties, and the court has reviewed each study and the parties' various interpretations and conclusions. It appears that when a particular study reaches a result unsupportive of one party's position, the latter has an argument as to why that study is unreliable. Although close analysis does reveal a certain element of unreliability in some of the studies (e.g., Andersohn, discussed infra), and the relevance of certain studies is questionable for various reasons (e.g., the study was not stratified by dose, it combined Celebrex with other coxibs or it was the wrong type of study [cohort vs. case control, etc.], there is still enough evidence to admit plaintiffs' expert conclusions as to the higher doses of Celebrex, particularly as to patients with a history of cardiovascular problems or who use aspirin. E.g., APC, APC combined with PreSAP, Brophy Study, Gislason Study, Singh Study, Abraham Study, Johnsen Study. As discussed below, however, the same cannot be said for Celebrex at 200mg/d.

C. Celebrex at 200 mg/d

1. Regulatory and Industry Warnings and Opinions

To the extent that plaintiffs and their experts rely **[*32]** on conclusions reached by the FDA advisory panel, as expressed in its April 6, 2005 Decision Memorandum and related materials, their reliance is misplaced. Although the panel's conclusions were reached after a review of scientifically reliable data, the conclusions themselves do not address the issue of whether 200 mg/d of celebrex is capable of causing heart attacks and strokes. The FDA's advisory panel reviewed a large body of data: an internal survey by the FDA's Center for Drug Evaluation and Research of available data regarding the cardiovascular safety issues for COX-2 inhibitors and NSAIDs; the regulatory histories, New Drug Applications, and post-marketing databases of the various NSAIDs; FDA and sponsor background documents prepared for the advisory committee meeting; all the materials, data and presentations of interested parties; and the results of the numerous clinical trials and epidemiological studies concerning NSAIDs. Yet, neither the panel nor the FDA concluded from the plethora of materials, that 200 mg/d of Celebrex poses a significant cv risk. Nor is the Black Box Warning required by the FDA on all marketed Celebrex (200 mg/d being the commonly prescribed dose) **[*33]** dose specific. It speaks only of a possible increase in risk for people with heart disease.

Plaintiffs and their experts also rely on the warnings of the American Heart Association, as expressed in the

Guidelines on coxib use they issued in 2005 and the Update they issued in 2007, co-authored by plaintiffs' expert Dr. Joel S. Bennet.[5] Although the court finds the recommendations and analyses of both the FDA advisory panel (comprised of prestigious scientists and scientific organizations) and the AHA persuasive, they do not establish the necessary causative link. As the court in Parker recognized, "[S]tandards*HN7*[↑] promulgated by regulatory agencies as protective measures are inadequate to demonstrate legal causation." *7 N.Y.3d at 450*.

2. Epidemiological Evidence

The scientific evidence does not support plaintiffs' position of general causation at 200 mg/d. Plaintiffs' experts' analyses of the various trials and studies, in key respects, are inconsistent with generally accepted standards, **[*34]** and their alternative theories are insufficient to bridge the considerable gap between a possible and a significant risk of association at 200 mg/d. The court wants to emphasize that its decision is based on the statistical evidence presented by plaintiffs, which represents the evidence known to date on the toxic effects of Celebrex. As repeatedly noted by plaintiffs, that evidence does not include long-term, randomized clinical trials at the 200 mg/d dose. [6] Future studies, such as the PRECISION trial, might yield different results. However, the instant motions must be decided on the science and data available today.

To begin, the meta analyses do not support causation at 200 mg/d. A meta-analysis cited by all of the experts ("Kearney meta-analysis") included published and unpublished tabular data from 138 randomized trials (145,373 patients) comparing COX-2 inhibitors either to placebo or to a traditional NSAIDs. Patricia Kearney, et al., Do selective cycol-oxygenase-2 inhibitors and traditional nonsteroidal **[*35]** antinflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials, British Medical Journal 2006. See Direct Examination of Dr. Milton Packer, Exh. 7. The Kearney meta-analysis included information on myocardial infarction, stroke and vascular death rates in patients treated with Celebrex, and it combined the particular doses. At 200 mg/d the mean was below 1.0, which indicates lack of a significant risk at that dose. The study concluded, "Overall, we found no significant difference in the incidence of a serious vascular events between selective COX-2 inhibitors and traditional NSAIDs." Id.

Similarly, a meta-analysis of 11 observational studies of patients taking Celebrex at doses commonly used in the community that was conducted by Patricia McGettigan, the most comprehensive analysis of Celebrex observational studies published to date, showed that while Vioxx increased the risk of adverse cv events, Celebrex as compared to Naproxen, did not. McGettigan, et al., JAMA 2006; 296:1633-44 [Brown Aff., Exh. 38]. See Bennett Deposition at 249-50, 515-16, 572-73; Moye Bibliography, Ref. 100 [Brown Aff., Exh. 39]; Rymer Deposition at 337; Bennett Hrg. Tr. at 165. **[*36]** Dr. Wei's meta-analysis is consistent with these meta-analyses.

Moreover, out of 32 studies (29 published) cited by defendants, plaintiffs chose only 8 to plead their case. This smacks of "cherry-picking", skewing their analysis by only looking at the helpful studies. Such practice contradicts the accepted method for an expert's analysis of epidemiological data. As explained in the Guide (cited supra at 348), *HN8*[↑] determination of "whether an association exists between exposure to the agent and the disease" must be based on assessment of the totality of the evidence. Adding insult to injury, of the 8 studies plaintiffs cite, 2 do not provide any analysis stratified by dose (Johnsen and Helin-Salmivaara). Consequently, plaintiffs' experts cannot rely on them as a sufficient foundation for their opinions regarding 200 mg/d.

Three of the studies did evaluate the relation of Celecoxib dose to cardiovascular event, and in that regard, they have greater relevance. Nonetheless, on closer scrutiny, these studies do not hold up. The Brophy, et al. study, published on line in 2006 and in hard copy in 2007 (MDL 1699 Exh. W), found a significant risk for patients with a history of myocardial infarction **[*37]** (95 percent CI: 1.06 to 1.84) and no significant risk for patients with no such history (95 percent CI: 0.88 to 1.20). The finding with respect to patients with a prior MI history, however, was limited to those using higher doses of Celebrex, AE200 mg/d (95 percent CI: 1.00 to 2.54). Two studies by Andersohn, et al. (MDL 1699 Exh. S) showed a significant risk of MI for patients taking low and high doses of Celebrex, but the findings are questionable. They suggested an increased

---

[5] Interestingly, Dr. Bennett conceded at the hearing that he could not say that at 200mg/d, the preponderance of clinical evidence suggests celebrex is associated with cv events (Bennett Hrg. Tr. at 166-167).

[6] The court cannot help but recognize at this juncture, that plaintiffs claim that ingestion of Celebrex at any duration increases cv events. Thus, short term studies are relevent.

risk only where patients took the drug for less than 3 months, not for longer durations, a finding contrary to the standard warning accompanying the marketed product. Additionally, the second Anderson study, which focused on patients who had experienced a schemetic stroke, found no increased risk associated with Celebrex as a function of dose or duration. Then too, Anderson involved only 15 events. All of the experts emphasized that the fewer the events, the less reliable the study results.

Another study completed in 2006 by Gislason (MDL 1699 Exh. X) and cited by plaintiffs, used two study designs which yielded contradictory results. Data analyzed using the first design did find a significant risk in patients **[*38]** with a history of cv problems, but data analyzed using the case-crossover design, an analysis employed to compensate for confounders, showed no significant risk associated with use of Celebrex at low doses. Furthermore, the study did not control for smoking or aspirin use, both acknowledged confounding factors, and involved only 6 events.

Finally, plaintiffs rely on an unpublished, non-peer reviewed study from a managed care organization ("the Wellpoint Report"). However, the Wellpoint Report combined all doses of Celebrex and failed to account for critical confounding factors such as smoking. Rymer, Hrg. Tr. 512-519, 544-546. As the MDL court observed in its opinion, "[I]t is thus unsurprising that most of plaintiffs' experts agree that the available evidence at 200 mg/d is inadequate to prove causation." MDL opinion at p. 12; Hrg Tr. at 159:1-11, 166:8-167:19 [Bennett]; Bennett Depo. at 92-93; 537 [Brown Reply Aff., Exh. 108]; Wright Depo. at 82-83, 92 [Brown Reply Aff., Exh. 106]; Moye Depo. at 268 [Brown Reply Aff., Exh. 109]; Jewell Depo. at 130-31 [Brown Reply Aff., Exh. 110]. See Jewell Hrg. Tr. At 412, 417, 418, 422.

3. Other Arguments

Plaintiffs seek to fill the statistical gap **[*39]** by making the following arguments: (1) You can extrapolate from statistical results for higher doses of Celebrex (400 ansd 800 mg/d) or for other COX-2 drugs (Vioxx and Bextra); (2) Dose is not dispositive because COX-2 drugs "as a class" significantly increase the risk of thrombotic events; and (3) The underlying biological mechanism of action, the imbalance theory, independently establishes a significant risk of thrombotic events. The court will address these arguments in the context of discussing the qualifications and opinions of particular experts.

Dr. Neil Doherty

Plaintiffs' cardiology expert Dr. Neil Doherty is simply not qualified to draw expert conclusions based on the use of epidemiological evidence. He is a clinical cardiologist who sees patients 98 percent of his physician time. He does not have any specialized epidemiology training. He has not published any research since 1992, and his 13 publications are unrelated to the subject matter of these lawsuits. He has never participated in an observational study of any kind, had not designed a clinical trial since 1977 while a student, and his testimony displayed his lack of experience regarding epidemiological principles and **[*40]** terminology. Doherty, Hrg Tr at 32S-357. [7]

Doherty's testimony also conflicted with that of plaintiffs' other experts in key respects. At his deposition, Doherty identified the heart attack portion of the Andersohn study as the "strongest" evidence of risk at 200 mg/d, even though that portion of the study failed to adjust for confounding factors such as aspirin use and the severity of heart disease. Doherty later contradicted himself and testified at the hearing that studies should adjust for heart disease, which was consistent with the testimony of plaintiffs' stroke expert Dr. Rymer, who criticized the stroke portion of the Andersohn study for its failure to adjust for aspirin use. Andersohn, et al. STROKE 2006; 37:1725-1730, at 1727; Doherty Rep. at 8; Doherty, Hrg Tr at 322:6-9; Rymer Written Direct Examination P34. Although Doherty had based his expert opinion primarily

---

[7] For example, during Doherty's deposition he was unable to explain the difference between a cohort study and a case control study, the two main types of observational studies. He, then, managed to deliver a scholarly response at the joint hearing, showing that his education on this subject had occurred between the time of his deposition and the hearing. Doherty, Hrg Tr at 348-355. A cohort study identifies patients who are taking the drug and those who are not, them follows both groups for a certain amount of time to determine if they have the alleged bad outcome, which in this case could be a cardiovascular problem of some kind. The study then compares the rate of bad outcomes in both groups to compute the "relative risk." See Federal Judicial Center, Reference Manual on Scientific Evidence 338-340 (2d ed. 2000), cited supra. A control study identifies people who had a cardiovascular problem, then reviews their medical records to determine how many of them were taking the drug around the time their problem manifested. The study then identifies an equal number of people who did not have a cardiovascular problem and determines how many of them **[*41]** were taking the drug. An "odds ratio" is then computed from the data, and if it is 1.0, then it means that the percentage of people taking Celebrex in both groups is the same, or that taking Celebrex did not increase their risk of a cardiovascular problem. Id.

on the Andersohn study, he incorrectly identified it as a "cohort" study and insisted that the **[*42]** analysis used by that study was a "cox proportional analysis," the one.most commonly used for cohort studies. As the MDL court noted, the Andersohn study was instead a "case control study nested within a cohort study," and it used a "logistic regression" analysis. MDL decision at pp. 15-16. Doherty's lapses are more than minor faux pas; they reveal a fundamental flaw in his ability to reliably analyze epidemiological information. What is more, Doherty apparently became interested in Celebrex and its possible association with cv risk after he was retained by plaintiffs in this litigation, well after the connection between COX-2 inhibitors and adverse cv events became an issue of public concern.

Doherty (and Dr. Rymer to some degree) sought to overcome the lack of direct statistical evidence by arguing that you can extrapolate general causation at 200 mg by looking at the results of trials and studies involving 400 and 800 mg/d. Doherty's rationale for this theory is just another example of his lack of scientific experience and expertise. He testified that you can take the relative risk point for 400 mg/d and just cut it in half, ignoring the confidence interval; he failed to identify **[*43]** any scientific support for this theory. Doherty, Hrg. Tr. at pp. 304, 340-343, 378-79. Nor did plaintiffs provide any scientific or other support for Doherty's theory, which is contradicted by the evidence developed to date showing no significant risk of association between 200 mg/d of Celebrex and cv problems.

For all of these reasons, Doherty is excluded as an expert witness for plaintiffs on the issue of general causation. If, however, the plaintiffs wish to call him as a clinical cardiologist to establish specific causation of a particular plaintiff's cv problems and his testimony is relevant to the underlying biological mechanism of disease (not the imbalance hypothesis), then the court will consider whether to allow such testimony at the appropriate time.

Dr. Joel S. Bennett

Dr. Joel S. Bennett, a Hematologist and Professor of Pharmacology, testified to his opinion to a reasonable degree of medical certainty that Celebrex increases the risk of cardiovascular events. Dr. Bennett is eminently qualified to testify as an expert regarding the thrombotic risks associated with taking Celebrex, both from a mechanistic and epidemiological standpoint. Although he is neither a cardiologist **[*44]** nor a statistician, he has abundant experience working with the relevant scientific concept and COX-2 inhibitors, including Celebrex. He has authored a plethora of published journal articles, texts, chapters, editorials and abstracts, has received numerous awards, including in the area of cardiology, has lectured extensively, and is jointly board certified in both Internal Medicine and Hematology. He is a member of numerous national societies, including the American Heart Association (AHA). His accomplishments are impressive, and include his co-authoring an article for the AHA entitled, Use of Nonsteroidal Antiinflammatory Drugs, An Update for Clinicians: A Scientific Statement From the American Heart Association; circulation 1-9, 2007: 115 (MDL 1699 Exh. EE). Prior to publication of that Update, which was issued by the AHA to guide physicians in their recommendations about the use of NSAIDS, including Celecoxib, he was also a co-author of a 2005 Advisory from the AHA on the use of NSAIDS. The Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDS):A Science Advisory from the American Heart Association; Circulation; 111:1713-1716, 2005 (MDL Exh. 41).

As a result, Dr. Bennett's testimony **[*45]** that the clinical evidence does not demonstrate a significant risk of Celebrex at 200 mg/d increasing cardiovascular risk on a population basis, is compelling. Bennett Hrg. Tr. at 159, 166-7. [8] He explicitly stated that he was not testifying to causation (id. at 160) and refused to testify that Celebrex at 200mg/d could be a causative factor. Id. at 161. Nevertheless, Dr. Bennett testified that regardless of the statistical results, the underlying biological mechanism of action (the "imbalance hypothesis" or the "Fitzgerald theory"), could be a risk factor contributing to the causation of cardiovascular problems in a given patient. Id. at 159-161. Dr. Bennett explained the hypothesis, which was originally developed by Dr. Garrett Fitzgerald. In essence, the hypothesis asserts that COX-2 inhibitors as a class, inhibit the COX-2 enzyme, thereby, preventing the cells in arteries from making prostacyclin (an anti-clotting agent) and making them more reactive to "aggregates" like thrombaxane, which promote clotting. Hence, the hypothesis posits, the resulting imbalance could increase the risk of a thrombus (clot) occurring when plaque ruptures, causing blood flow to the heart or brain to **[*46]** cease. Id. at 100-160, 203. See Gunnar H. Gislason, et al., Risk of Death or Reincarnation Associated With the Use of Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal

[8] Dr. Jewell also testified that the statistical evidence does not show an increased risk at 200 mg/d (Jewell Hrg. Tr. at 412, 417, 418, 422).

Antiinflammatory Drugs After Acute Myocardial Infarction, Circulation, 2006 June 27; 113(25): 2906-13.

The court is troubled by Dr. Bennett's testimony that the theory is premised on a biological effect of COX-2 inhibitors as a class, instead of identifying the effect of specific COX-2s, since he also testified that Vioxx, Celebrex and Bextra "are different drugs, and they are different biochemically" (id. at 123:2-3), and he explained that biochemical differences in drugs relate to different potencies. Id. at 123:23-25. Accordingly, any use of this theory to establish causation would have to be tailored to Celebrex, as opposed to a different COX-2 or Cox-2s in general. More important, Dr. Bennett testified, "An hypothesis is an idea that leads to experimentation so you can derive Facts." Id. at 217. The Facts derived from experimentation, here, do not support the **[*47]** hypothesis that Celebrex at 200mg/d causes cv events. As explained supra, there is insufficient statistical evidence to support any conclusion that Celebrex is capable of causing cv problems at 200 mg/d. So, at least with respect to that category of cases, the Fitzgerald Hypothesis is irrelevant. Without proof of an association, the hypothesis is inadmissible.

Dr. Marilyn M. Rymer

Dr. Rymer, plaintiffs' stroke expert, is a Professor of Medicine at UMKC School of Medicine and Medical Director for the Brain Stroke Institute in Kansas City, one of the prominent stroke programs in the country. She is a Fellow of the American Heart Association, author of the stroke center handbook and of the Stroke Atlas and served as an expert consultant to Pfizer on stroke. She opined, to a reasonable degree of medical certainty, that: (1) because the mechanism for ischemic stroke (not the "imbalance" theory) is the same as for heart attacks, data showing that Celebrex increases the risk of heart attacks also applies to ischemic strokes (Rymer Hrg. Tr. at 482:16-25, 485:13-22.); (2) the mechanism of COX-2 inhibitors, including Celebrex, causes strokes and other cardiovascular events by increasing thrombogenesis **[*48]** due to an increase in prostacyclin synthesis (the imbalance effect) (id. at 485:23-486:5.); and 3) the increase in blood pressure caused by all NSAIDs, but particularly Cox 2 inhibitors, increases the risk of small vessel disease strokes. Id. at 488-9, 491.

The court rejects defendants' argument that Dr. Rymer is unqualified to testify about observational studies. Although a large part of her work has involved clinical trials, she has devised and worked with observational studies involving patients in her institute's stroke database (id. at 467:25-472:4.) and is intimately familiar with the review and analysis of epidemiological evidence. Her specific opinions regarding the toxic effect of Celebrex on stroke pose greater difficulty.

None of the studies or trials that were done were adequately designed or powered to specifically detect stroke. Id. at 521-522. However, as the MDL court concluded, "[N]early all studies of COX-2 inhibitors and cv risk lump strokes together with heart attacks." MDL Opinion at p. 24. Moreover, Dr. Rymer testified that the underlying mechanism for ischemic stroke (blockage of blood flow) is the same as for heart attacks and that people at risk for heart attacks **[*49]** are equally at risk for ischemic stroke. Id. at pp. 481-485, 534-535, 547-551. Further, she testified that hypertension and a rise in blood pressure, a side effect of NSAIDs, is a cause of stroke, particularly small vessel disease stroke. Defendants have not presented the court with any evidence to conclude "there is a generally or widely held view in the scientific community rejecting . . . [Dr. Rymer's] conclusions outright." *Marso v. Novak, 42 A.D.3d 377, 378, 840 N.Y.S.2d 53 (1st Dept. 2007)*. Without definitive scientific proof to the contrary, the court is not prepared to exclude expert testimony finding that Celebrex at doses of 400 mg/d or greater is capable of causing ischemic stroke. On the other hand, with regard to Celebrex at 200mg/d, the scientific evidence, whether for heart attack or stroke, is just not there. Dr. Rymer's reliance on Wellpoint, an unpublished study which did not adjust for major confounders such as smoking and did not distinguish between dose, is to no avail.

4. Remaining Issues

Defendants' seek to exclude any opinion that Celebrex is capable of causing cv events more than three days after a patient stops taking it. This point is not in dispute, and there was no related expert **[*50]** testimony proffered. Consequently, such opinion testimony is precluded. The court, however, denies defendants' motion to exclude any opinion that Celebrex is capable of causing cv events when taken continuously for less than 33 months. The APC trial was ended at 33 months because patients were getting hurt. There is simply no scientific correlation between the 33 month period and the onset of cv problems.

Moreover, the court denies plaintiffs' motion to preclude the testimony of defendants' expert Dr. Milton Packer. Dr. Packer is a cardiologist who has spent his career to date researching the mechanisms of action, and

evaluating the efficacy and safety, of cardiovascular drugs. He has held many leadership positions in the cardiovascular field and received prestigious academic appointments. Dr. Packer is currently the Chair of the Department of Clinical Sciences at the University of Texas Southwestern Medical school, where he also holds the Gayle and Paul Stoffel Distinguished Chair in cardiology and leads a Master's program educating and training physicians on designing, analyzing and interpreting clinical research studies. He has authored nearly 300 papers, articles, reviews, book **[*51]** chapters and other reference materials that have been published in peer-reviewed journals and other scientific venues and has presented to the FDA on the principles and methods of interpreting clinica research studies.

Dr. Packer disputes the validity and relevance of the Fitzgerald "imbalance hypothesis." In brief, Dr. Packer contends that the hypothesis has not been accepted in the scientific community since it has not been clinically proven. Packer, Written Direct at 23. Further, he raises serious concerns about the validity and reliability of the "imbalance" hypothesis grounded in the lack of scientific evidence and medical testimony regarding prostacycline, thromboxane and hypertension. Given his credentials and the scientific bases for his opinions, Dr. Packer's testimony may come in to refute plaintiffs' imbalance hypothesis.

Plaintiffs' motion to exclude the meta-analyses of defendants' experts, also, is denied. Plaintiffs' objections go to the weight of these experts' analyses and testimony, and not their admissibility. Finally, at this juncture, the court denies defendants' motion to preclude evidence of specific causation absent a relative risk that exceeds 2.0. The hearing **[*52]** was concerned with general causation alone. Accordingly, it is

ORDERED that the Pfizer defendants' motion to exclude the opinion by plaintiffs' experts that 200 mg of Celebrex daily is capable of causing cardiovascular injury is granted; and it is further

ORDERED the Pfizer defendants' motion to exclude the opinion by plaintiffs' experts that 400 mg of Celebrex daily is capable of causing cardiovascular injury is denied; and it is further

ORDERED that the Pfizer defendants' motion to exclude the opinion by plaintiffs' experts that 800 mg of Celebrex daily is capable of causing cardiovascular injury is denied; and it is further

ORDERED that the Pfizer defendants' motion to exclude the opinion by plaintiffs' experts that absent reliable proof of a relative risk that exceeds 2.0, Celebrex is capable of causing any individual plaintiff's cardiovascular injury, is denied without prejudice; and it is further

ORDERED that the Pfizer defendants' motion to exclude the opinion by plaintiffs' experts that Celebrex causes heart attacks or strokes at durations of less than 33 months of continuous daily use is denied; and it is further

ORDERED that plaintiffs' motion to exclude the meta-analyses of defendants' **[*53]** experts is denied; and it is further

ORDERED that the parties' motions to exclude testimony both supporting and refuting the imbalance hypothesis is denied.

---

End of Document

2010 WL 1047618

**This decision was reviewed by West editorial staff and not assigned editorial enhancements.**

United States District Court,
S.D. New York.

IN RE PFIZER INC. SECURITIES LITIGATION.

Nos. 04 Civ. 9866(LTS)(JLC), 05 md 1688(LTS).
|
March 22, 2010.
|
As Amended March 29, 2010.

**Attorneys and Law Firms**

Grant & Eisenhofer P.A., by: Jay W. Eisenhofer, Esq., Francis P. Karam, Esq., New York, NY, by: Geoffrey C. Jarvis, Esq., Richard Schiffrin, Esq., Wilmington, DE, Barroway Topaz Kessler Meltzer & Check LLP, by: Benjamin J. Sweet, Esq., Andrew L. Zivitz, Esq., Radnor, PA, Seeger Weiss LLP, by: David R. Buchanan, Esq., Christopher Adam Seeger, Esq., Philadelphia, PA, for Lead Plaintiff.

Cadwalader, Wickersham & Taft LLP, by: Gregory A. Markel, Esq., New York, NY, DLA Piper U.S. LLP, by: Cara Dyonne Edwards, Esq., Loren H. Brown, Esq., New York, NY, Tucker Ellis & West LLP, by: Charles Q. Socha, Esq., Denver, CO, for Defendants.

## *OPINION AND ORDER*

LAURA TAYLOR SWAIN, District Judge.

***1** The above-captioned putative class action litigation has been consolidated for pretrial purposes in the Southern District of New York pursuant to the June 21, 2005, order of the Judicial Panel on Multidistrict Litigation. The member actions share factual questions arising from allegations that Pfizer, Inc. ("Pfizer"), and other named defendants violated federal and state securities laws and committed fraud by misrepresenting and/or concealing the safety risks of Pfizer's COX–2 inhibitor drugs, Celebrex and Bextra.

Pending before this Court are Plaintiffs'[1] and Defendants'[2] motions to preclude from introduction into evidence in the above-captioned matter pursuant to Federal Rules of Evidence 702 and 104(a) the testimony of certain experts regarding the cardiovascular risk[3] associated with Celebrex and/or Bextra. Plaintiffs move to preclude the testimony of Defendants' expert Lee–Jen Wei, Ph.D. ("Dr.Wei"). Defendants move to preclude the testimony of Plaintiffs' experts David Madigan, Ph.D. ("Dr.Madigan"), Curt D. Furberg, M.D., Ph.D. ("Dr.Furberg"), Richard A. Kronmal, Ph.D. ("Dr.Kronmal"), Lawrence Baruch, M.D. ("Dr.Baruch"), Joel S. Bennett, M.D. ("Dr.Bennett"), and Nicholas P. Jewell, Ph.D. ("Dr.Jewell"). For the reasons stated below, both motions are denied.

## *BACKGROUND*

Plaintiffs allege that Defendants violated federal and state securities laws and committed common-law fraud by concealing the results of various medical studies concerning two Pfizer drugs, Celebrex and Bextra, and by making misstatements and omissions in their public filings and statements. The surviving allegations and issues in this litigation are summarized in the Court's July 1, 2008, Opinion and Order (docket entry no. 90) concerning Defendants' motion to dismiss the Complaint, familiarity with which is presumed.

At Defendants' request and pursuant to this Court's January 12, 2009, order, a hearing was set "to determine whether, on or before December 17, 2004, there was reliable scientific evidence that Celebrex or Bextra was associated with increased cardiovascular risk (the *Daubert* hearing)." Following the submission of expert reports and the deposition of the experts at issue, both parties filed motions (docket entry nos. 139 and 144) to preclude expert testimony, together with voluminous exhibits. These motions were fully briefed on September 25, 2009. In late October 2009, the Court held a five-day *Daubert* hearing which included thorough direct and cross-examination of certain experts, the use of demonstrative exhibits, and the submission of extensive written direct testimony. Following the conclusion of the *Daubert* hearing, the Court ordered both parties

to file supplemental submissions. These post-hearing submissions and all responses thereto were filed on January 8, 2010. The Court has listened carefully to all of the hearing testimony and has reviewed thoroughly the parties' written submissions, documentary evidence, and demonstratives. Readers' familiarity with that record is presumed. For the reasons that follow, both parties' motions to preclude expert testimony are denied.

*DISCUSSION*

***2** Federal Rule of Evidence 702 provides that, "[if] scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." (West 2006). Preliminary questions of admissibility are determined by the court. Fed.R.Civ.P. 104(a). Where, as here, the admissibility of expert scientific or technical testimony is challenged, the proponent of the evidence must demonstrate admissibility to the satisfaction of the Court under Rule 104(a) by establishing scientific or technical reliability by a preponderance of the evidence. *See Bourjaily v. United States,* 483 U.S. 171, 175–76, 107 S.Ct. 2775, 97 L.Ed.2d 144 (1987); *Falise v. Am. Tobacco Co.,* 258 F.Supp.2d 63, 66 (E.D.N.Y.2000). The determination as to whether proffered scientific or technical evidence will "assist the trier of fact to understand the evidence or to determine a fact in issue" is in essence a question of the relevance, or "fit," of the proffered evidence. *See Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 590, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). Evidence is relevant when it has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Fed.R.Evid. 401 (West 2006). The Court must determine whether the proffered testimony has a sufficiently "reliable foundation" to permit its consideration. *Daubert,* 509 U.S. at 597.

Rule 702 specifically requires examination of the qualifications of the proffered expert to testify to pertinent scientific knowledge, whether the facts or data upon which the expert relies are sufficient, whether the methodology employed is valid and whether its application by the expert in formulating the testimony is proper. *Id.* at 592–93.

In *Daubert,* the Supreme Court held that the trial judge's "gatekeeping responsibility" requires the court to "ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Id.* at 589. The *Daubert* Court identified a number of factors that, while not constituting a "definitive checklist or test," could be considered by a district court in evaluating the reliability of a proffered expert: "whether a theory or technique had been and could be tested, whether it had been subjected to peer review, what its error rate was, and whether scientific standards existed to govern the theory or technique's application or operation." *Nimely v. City of New York,* 414 F.3d 381, 396 (2d Cir.2005) (citing *Daubert,* 509 U.S. at 593–94). The trial judge should "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 152, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999). "[T]he law grants a district court the same broad latitude when it decides *how* to determine reliability as it enjoys in respect to its ultimate reliability determination." *Id.* at 142; *see also id.* at 141 ("[A]s the Court stated in *Daubert,* the test of reliability is 'flexible,' and *Daubert's* list of specific factors neither necessarily nor exclusively applies to all experts or in every case."). Questions of credibility generally do not render an expert's testimony inadmissible. *See Daubert,* 509 U.S. at 596; *Hemmings v. Tidyman's, Inc.,* 285 F.3d 1174, 1188 (9th Cir.2002). Nor should district courts prejudge the weight of conflicting evidence or substitute the judgment of the court for that of the jury. *See In re Joint E. & S. Dist. Asbestos Litig.,* 52 F.3d 1124, 1133 (2d Cir.1995).

***3** Here, Defendants challenge the admissibility of testimony by six individuals trained in medicine and/or statistics proffered by Plaintiffs as evidence of increased cardiovascular risk associated with Celebrex and Bextra prior to December 17, 2004. The Court, having reviewed

carefully the record, is persuaded that Plaintiffs have carried their burden of demonstrating that each of their challenged witnesses is possessed of the requisite qualifications to testify as to his respective opinion regarding the interpretation of clinical trials and/or analysis and interpretation of data.

Defendants contend, among other things, that Plaintiffs' proffered evidence that there was reliable scientific evidence prior to December 17, 2004, that Celebrex and Bextra were associated with increased cardiovascular risk is inadmissible because Plaintiffs' experts have defined cardiovascular risk too broadly and/or inconsistently, and have not presented evidence of statistically significant indicia of thromboembolic risk. As noted above (*see* footnote 3), this argument is inconsistent with Defendants' own articulation of the subject matter of the hearing. It bears noting that this *Daubert* process was initiated at an early juncture in the case, prior to significant discovery and prior to the preparation of the opinions proffered here, at Defendants' request. Defendants cannot now be heard to complain that Plaintiffs failed to tailor their opinions to a view of the issues that Defendants chose not to share until after the opinions had been formulated. Nor is the use of the term "cardiovascular" or attention to non-thromboembolic cardiovascular issues inconsistent with claims in the complaint or, indeed, with a number of statements by Defendants that are quoted in the complaint and challenged as misleading. (*See, e.g.*, Compl. ¶¶ 41, 74–75, 84–87, 90–94, 111, 118–19, 127–29, 144, 169.) The ultimate issues for the fact finder in this litigation do not involve medical causation of injuries but, rather, include whether Pfizer should have disclosed certain information it had earlier than it did, and whether the undisclosed information rendered misleading Defendants' public representations as to the existence of cause for concern about the safety of the two drugs.

Furthermore, Plaintiffs have demonstrated, by competent, credible testimony, that the non-thromboembolic "endpoints" utilized in their analyses of pre-December 2004 Pfizer study data are derived from scientific principles of sufficient validity and/or from Pfizer's own analytical methods. The record is sufficient to demonstrate the relevance of evidence of the associations identified in Plaintiffs' evidentiary proffers and thus to render Defendants' thromboembolic association arguments ones that go to the weight, rather than to the admissibility, of Plaintiffs' evidence.

The Court has considered carefully the record and all of Defendants' other arguments concerning the admissibility of the challenged testimony and finds that Plaintiffs have met their Rule 702 burden with respect to each of the challenged proffers. The Court's principal conclusions with respect to each of Plaintiffs' witnesses are summarized below.

***4** The Court concludes further that Defendants have carried their Rule 702 burden with respect to the proffered rebuttal testimony of Dr. Lee–Jen Wei, principally for the reasons summarized below.

*Dr. Madigan*

Dr. David Madigan holds a doctorate in statistics, and is currently Professor in and Chair of the Department of Statistics at Columbia University. Dr. Madigan has taught and published extensively in the field of statistics. He has served as Director of Rutgers University's Rutgers Institute of Biostatistics and currently serves as an editor of a peer-reviewed academic statistics journal, *Statistical Science.* Dr. Madigan has consulted for various pharmaceutical companies and otherwise applied his scientific training to questions of drug safety and public health. Dr. Madigan opines as to the import of a meta-analysis he performed on data that was in existence during the relevant period to determine its significance with respect to the cardiovascular safety of Celebrex. Dr. Madigan's credentials as a statistician amply qualify him to testify as an expert with respect to his interpretation of the data he analyzed. Plaintiffs have met their burden with respect to the qualifications of Dr. Madigan.

Dr. Madigan's written submissions and testimony described clearly and justified cogently his statistical methods, selection of endpoints, decisions regarding event classification, sources of data, as well as the conclusions he drew from his analysis. Indeed, Dr. Madigan's meta-analysis was based largely on data and endpoints developed by Pfizer. All four of the endpoints that Dr. Madigan used in his analysis—Hard CHD, Myocardial Thromboembolic Events, Cardiovascular Thromboembolic Events, and CV Mortality—have been

employed by Pfizer in its own research and analysis. The use of Hard CHD in the relevant literature combined with the use of the other three endpoints by Pfizer in its own 2005 meta-analysis will assist the trier of fact in determining Pfizer's knowledge and understanding of the pre-December 17, 2004, cardiovascular safety profile of Celebrex. The assistance Dr. Madigan received from Dr. Lawrence Baruch, a practicing cardiologist whose qualifications are discussed *infra,* and Dr. Curt Furberg, a prominent cardiovascular epidemiology researcher whose qualifications are discussed *infra,* in the classification of deaths that occurred in the studies he reviewed was appropriate given that Dr. Madigan's own training is not in medicine. Any weaknesses in the classification of fatal adverse events made by Dr. Baruch and Dr. Furberg were attributable to the limitations of the data created by and, later in the context of litigation, produced by Pfizer. Given that the goal of Dr. Madigan's analysis was to determine what knowledge Pfizer had or could have had based on the data available to it at the time, any lack of precision in the adverse event classification consultations performed in conjunction with Dr. Madigan's meta-analysis fail to so seriously indict Dr. Madigan's opinion as to render it inadmissible under *Daubert.* Nor are the differences between the fatal event classifications performed by Dr. Baruch and Dr. Furberg, and later relied upon by Dr. Madigan, so significant as to render Dr. Madigan's meta-analysis "junk science." Plaintiffs have met their burden regarding the relevancy of the content of Dr. Madigan's expert opinion to the ultimate questions of drug safety at issue in this securities litigation, as well as its satisfaction of the other Rule 702 criteria.

*Dr. Furberg*

***5** Dr. Curt D. Furberg is currently Professor of Public Health Sciences and Senior Advisor to the Dean for Health Services Research and Health Policy at Wake Forest University. Dr. Furberg holds both M.D. and Ph.D. degrees and has a broad range of experience and expertise in the field of public health. He has published extensively on topics including clinical trials and non-steroidal anti-inflammatory drugs ("NSAIDs"). Dr. Furberg has been lead investigator in numerous clinical trials and worked in both the public and private sectors, having been asked by both the pharmaceutical industry and the FDA to evaluate safety of COX–2 inhibitors. Plaintiffs offer Dr. Furberg's opinions regarding the review he conducted of the medical literature and clinical studies for Celebrex and Bextra. Based on his reading of the relevant literature and review of the available study data, Dr. Furberg submits that information was available to Pfizer prior to December 17, 2004, that demonstrated a scientifically significant risk of adverse cardiovascular events associated with the use of Celebrex and Bextra.

The breadth of knowledge, experience, and expertise Dr. Furberg brings to proceedings in this case is considerable. Dr. Furberg has wide-ranging training and practice in both clinical and research settings. His opinions are based on individual study data available to Pfizer and, to arrive at them, he employed the methods and analysis he has applied in his lengthy and distinguished career as an expert in the fields of drug safety and clinical trial design. Dr. Furberg's background in and publishing about drug safety and clinical trials well suits him to assist the jury in its determination of what, if any, association between Celebrex and/or Bextra and cardiovascular risk existed on or before December 17, 2004. Defendants' motion to preclude the testimony of Dr. Furberg is therefore denied.

*Dr. Kronmal*

Dr. Richard A. Kronmal is a Professor of Biostatistics and Statistics at the University of Washington and holds a doctorate in the field of biostatistics. Dr. Kronmal's academic experience involves extensive peer-reviewed publication on the topic of cardiovascular disease. He currently directs a research center at the University of Washington that designs, conducts, and analyzes clinical studies with an emphasis on cardiovascular disease. Dr. Kronmal has served on numerous data safety monitoring boards, which are responsible for ensuring the safety of patients participating in clinical trials and for monitoring such trials for possible early termination due to excessive risks. Plaintiffs offer Dr. Kronmal's opinions concerning his interpretation of Pfizer's clinical trial data, which he finds demonstrate a statistically significant cardiovascular risk associated with Celebrex and Bextra prior to December 17, 2004.

Dr. Kronmal applied his substantial specialized knowledge and experience to assess the design and results of clinical trials of Celebrex and Bextra using established

statistical methods. In his analysis, he relied on SAS data provided by Pfizer, as well as on several other studies. Dr. Kronmal persuasively explained and defended, *inter alia,* his use of non-APTC endpoints and the particular strengths and weaknesses of certain clinical circumstances. Dr. Kronmal's qualifications and methods satisfy the *Daubert* standard and his testimony derived therefrom is relevant to the determination of cardiovascular risk. Therefore, Dr. Kronmal's testimony is admissible.

*Dr. Jewell*

***6** Dr. Nicholas P. Jewell is a professor of Professor of Biostatistics and Statistics at the University of California, Berkeley. Dr. Jewell's teaching and research has dealt with the design and interpretation of clinical trials. Dr. Jewell has published peer-reviewed articles in the area of the application of statistical analysis to clinical trial data, and has authored a widely used statistics-for-epidemiology textbook. Dr. Jewell is offered by Plaintiffs as a rebuttal expert, and his testimony centers on the methodologies employed in the meta-analysis performed by defense expert Dr. Lee–Jen Wei.

While he does not provide his own analysis or conclusions regarding the safety of Celebrex or Bextra prior to December 17, 2004, Dr. Jewell offers opinions relevant to the ultimate issues in this case. Dr. Jewell's report speaks directly to the weight the jury should assign to Dr. Wei's meta-analysis and his testimony will assist the jury in its interpretation and assessment of Defendants' evidence. Plaintiffs have amply sustained their burden to demonstrate the relevancy and reliability of Dr. Jewell's opinions, and thus his testimony is admissible.

*Dr. Baruch*

Dr. Lawrence Baruch holds an M.D. and practices cardiology as the Director of the Heart Failure and Echocardiography Programs at the Bronx Veteran Affairs Medical Center. He has also currently serves as an attending cardiologist at Mt. Sinai Hospital in New York City. Dr. Baruch is offered as a rebuttal expert by Plaintiffs. His opinions that the events witnessed in the Bextra CABG clinical trials can be generalized, that Celebrex and Bextra are associated with, contribute to, and can cause cardiovascular events, and that the available clinical data suggest that COX–2 inhibitors increase the risk of cardiovascular events are offered to dispute the testimony offered by Defendant. Dr. Baruch's experience, including his experience training cardiology fellows and medical students, meets Plaintiffs' burden to qualify him as an expert.

Dr. Baruch's training and practice in the field of cardiology as detailed in his expert report qualify him, under *Daubert,* to testify regarding the cardiovascular effects of Celebrex and Bextra, especially on patients undergoing certain surgical procedures. The relationship between the two forms of Bextra, parecoxib and valdecoxib, is also properly within the scope of Dr. Baruch's expertise such that his opinions on the matter are admissible. Dr. Baruch's testimony will assist the jury in its evaluation of the weight to assign to certain clinical studies, such as the CABG trials, in determining whether Pfizer breached disclosure obligations. Defendant's motion to preclude Dr. Baruch's testimony is denied.

*Dr. Bennett*

Dr. Joel Bennett holds an M.D. and is a Professor of Medicine and Pharmacology at the University of Pennsylvania School of Medicine. His publications include peer-reviewed articles and textbook chapters on platelet function, and he has written specifically about NSAIDs and COX–2 inhibitors. Plaintiffs have satisfied their burden to qualify Dr. Bennett as an expert. The testimony of Dr. Bennett deals with the origin and operation of the FitzGerald (or "Imbalance") Hypothesis, Plaintiffs' posited mechanism for the harm caused by COX–2 inhibitors. This hypothesis has been deemed plausible and credible in the relevant medical literature, and is well within Dr. Bennett's field of expertise based on his training, experience, and history of publication. Dr. Bennett's testimony, while about a mechanism not proven conclusively or uniformly accepted, is far from baseless speculation and concerns a theory that has been subject to, and approved for publication by, peer review. The testimony of Dr. Bennett satisfies the *Daubert* standard and Defendants' motion to preclude his testimony is denied.

*Dr. Wei*

*7 Dr. Lee–Jen Wei holds a Ph.D. and is currently a Professor of Biostatistics at the Harvard University School of Public Health. He has served on the editorial boards of a number of scientific journals as well as an FDA Advisory Committee. Dr. Wei's publications in peer-reviewed journals are extensive, and he has performed numerous meta-analyses of clinical trial data in the course of his academic career. In the instant litigation, Defendants seek to offer Dr. Wei's meta-analysis of data relating to the safety of Celebrex and his interpretation thereof.[4] Defendants satisfy the standard to qualify Dr. Wei as an expert, and his opinion is clearly relevant to the ultimate issue of alleged misrepresentation or concealment of safety risk.

Dr. Wei's methodology, the validity of which Plaintiffs contest and the novelty of which Plaintiffs seek to highlight, appears to have survived the rigors of peer review at least once, and is subject to critique by virtue of its transparency. Dr. Wei's report, supplemented by his declaration, is sufficient to meet Defendants' burden of demonstrating that his testimony is the product of reliable principles and methods. He has explained his methods, which can be tested. Plaintiffs' critiques of Dr. Wei's choices regarding which trials to include in his own meta-analysis, the origins of the data he used, the date at which he undertook his meta-analysis, and at whose behest he performed his analysis all go to the weight of Dr. Wei's testimony. Given the variety of clinical trials available to aggregate and disagreement regarding which studies were of the highest medical and scientific quality, most "powerful,"[5] and appropriate to extrapolate from, Plaintiffs' main objection to Dr. Wei's methodology—his use of potentially novel "sensitivity analyses"[6] instead of patient years to account for duration when performing his meta-analysis—speaks to the appropriate weight to assign Dr. Wei's testimony, rather than its inadmissibility. Vigorous cross-examination of an expert as to a study's purported inadequacies allows the jury appropriately to weigh the alleged defects and reduces the possibility of prejudice. *Fireman's Fund Fund Ins. Companies v. Alaskan Pride Partnership,* 106 F.3d 1465, 1468 (9th Cir.1997); *United States v. L.E. Cooke Co.,* 991 F.2d 336, 342 (6th Cir.1993). The ultimate conclusions of Dr. Wei's meta-analysis speak directly to the cardiovascular safety of Celebrex and therefore would assist a jury in its determination of Defendants' knowledge of the same. Accordingly, Plaintiffs' motion to preclude Dr. Wei's testimony is denied.

*Conclusion*

The extensive submissions that are the subject of the instant motions satisfy the standards of qualification and reliability established by Federal Rule of Evidence 702 and elucidated in *Daubert.* While the cross-motions raise significant issues with respect to potential flaws, limitations and credibility of the experts' opinions, these concerns go ultimately to the weight of the opinions. Because the *Daubert* standard is satisfied with respect to all experts whose preclusion was sought, both parties' motions are denied in their entirety.

**8 This order resolves docket entry nos. 139 and 144.

SO ORDERED.

**All Citations**

Not Reported in F.Supp.2d, 2010 WL 1047618, 82 Fed. R. Evid. Serv. 134

Footnotes

1 "Plaintiffs" refers to the putative class of investors who purchased or acquired Pfizer stock between October 31, 2000 and October 19, 2005 (the "Class Period") on whose behalf Lead Plaintiff Teachers' Retirement System of Louisiana is prosecuting this action.

2 "Defendants" refers to Pfizer and corporate officers Henry McKinnell, John LaMattina, Karen Katen, Joseph Feczko, and Gail Cawkwell.

3 Although the complaint (docket entry no. 51–*see, e.g.,* at 18–25) speaks in terms of cardiovascular risk, as did the order (drafted jointly by the parties) setting the Daubert hearing (docket entry no. 120), Defendants sought in this motion practice

to advance the argument that only evidence relating to the narrower subset of thromboembolic (*i.e.,* clot-related) risk should be deemed relevant to the question of Defendants' potential liability in this case. While Defendants are free to argue this point as the case goes on, it is facially inconsistent with the Plaintiffs' articulation of their claims and nothing in the pleadings or in the record thus far persuades this Court that the broader question of cardiovascular risk is so irrelevant to the issues presented in this litigation as to render inadmissible evidence relating to such risk.

4 The Court notes that, moments before Dr. Wei was to be cross-examined at the *Daubert* hearing, Defendants withdrew substantial portions of Dr. Wei's supplemental rebuttal report based on a purportedly "slight error in calculation." (*Daubert* Hr'g Tr. 814–15, Oct. 29, 2009.) Defendants withdrew from Dr. Wei's supplemental rebuttal report Exhibit A; Demonstrative Exhibits DE3, DE4, DE5, DE6; Exhibits 17, 18, 19, 20, 21, and 22 from Appendix D; and Tables 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 38. Nothing in this order should be construed to permit the admission into evidence of the withdrawn materials or the analysis on which they rely.

5 The term "powerful" is used here in its statistical sense, referring to "the probability of finding a statistically significant association of a given magnitude (if it exists) in light of the sample sizes used in the study." Michael D. Green et al., Reference Guide on Epidemiology, *in* Reference Manual on Scientific Evidence at 362 (Federal Judicial Center 2d ed.2000).

6 The Court notes that Dr. Wei's "new" method was never given a precise name in the parties' filings or in the *Daubert* hearing testimony. The method referred to was apparently developed in 2007 and subjected to peer review soon thereafter. It was described in contrast to the method of imputation by Plaintiffs' expert Dr. Jewell, and as a "random effects model" by Defendants' rebuttal expert, Dr. William Weintraub. (*Daubert* Hr'g Tr. 753, Oct. 22, 2009.)

End of Document