UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

In re: AVANDIA MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	:	**AVANDIA MDL 1871** **2007-MD-1871**
THIS DOCUMENT APPLIES TO:	:	
DEBORAH A. BURFORD, et al. Plaintiffs, v. *GLAXOSMITHKLINE, PLC, et al.*, Defendants.	:	CASE NO. 07-5360

MEMORANDUM OPINION AND ORDER

Rufe, J. **January 11, 2011**

Presently before the Court are GlaxoSmithKline LLC's (GSK's) Motions to Exclude the Testimony of Plaintiffs' proposed Specific Causation Expert Witnesses Nicholas DePace, M.D.[1] and Judy Melinek, M.D,[2] Plaintiffs' responses thereto, and GSK's replies. The Court has reviewed each expert's report and heard oral argument regarding the admissibility of the expert testimony on January 4, 2011. For the reasons set forth below, the Court denies the motion to exclude the case-specific causation testimony of Dr. DePace and grants the motion to exclude the case-specific causation testimony of Dr. Melinek.

[1] Doc. No. 17.

[2] Doc. No. 26.

Background

James Burford ("Burford") was diagnosed with obesity, high triglycerides, high LDL, low HDL, and high blood pressure in the years prior to his diagnosis with diabetes. In June 2004 he was diagnosed with Type II diabetes and was initially treated with Metformin. This course of treatment failed to control his blood sugar. As a consequence, in April 2005 his dose of Metformin was doubled, and on August 23, 2005 Avandia was first prescribed to be taken along with the previously increased dose of Metformin. On December 23, 2005, Burford's Avandia dose was doubled to 8 mg, the maximum recommended dose. About three weeks later, he reported a single incident of sweating and heart racing, which was treated with Xanax for anxiety. His Metformin dose was doubled again in June 2006. A third Type II diabetes medication, Amaryl, a sulfonylurea, was added later.[3] On November 21, 2006, Burford died of myocardial infarction.[4] He was 49 years old, 72 inches tall, and 236 lbs. Prior to his death, he reportedly golfed weekly, exercised at home several times per week, and was a non-smoker.

Plaintiffs wish to offer Drs. DePace and Melinek as expert witnesses who would testify that Burford's use of the medication Avandia, which is manufactured by GSK, caused the fatal myocardial infarction he suffered. GSK challenges the admissibility of this evidence, asserting that both experts used unreliable methods to reach their independent conclusions that Avandia

[3] Although Dr. DePace reports that Burford began treatment with Amaryl on November 21, 2006, the same day Burford died, he does not mention the significance, if any, of this timing. Plaintiffs' Reponse to GSK's Motion to Exclude the Testimony of Dr. Melinek indicates that Amaryl was added in October 2006.

[4] This was the conclusion of the pathologist who conducted his autopsy. GSK argues that he died of cardiac arrest due to atherosclerotic progression, which is not attributable to Avandia.

was a "but-for" cause of Mr. Burford's myocardial infarction.[5]

Standard of Review

Federal Rule of Evidence 702 reads:

> [I]f 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 fact 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.

The Third Circuit has distilled this rule to two essential inquiries: 1) is the proffered expert qualified to express an expert opinion; and 2) was the expert opinion formulated using a reliable process or technique?[6]

Under the Third Circuit framework, the focus of the Court's inquiry must be on the experts' methods, not their conclusions. Therefore, the fact that Plaintiffs' experts and defendants' experts reach different conclusions does not factor into the Court's assessment of the reliability of their methods. The experts must use good grounds to reach their conclusions, but not necessarily the best grounds or unflawed methods.[7]

Here, the scientific question the experts address is whether there is a reasonable degree of medical certainty that Avandia caused Burford's fatal myocardial infarction. Under the

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[5] The parties agree that North Carolina law governs the substantive legal issues in this case. Under North Carolina law, a plaintiff must prove that "but for" Defendant's negligence, the injury would not have occurred. Gibson v. Ussery, 675 S.E.2d 666, 668 (N.C. Ct. App. 2009).

[6] In re TMI Litig., 193 F.3d 613, 664 (3d Cir. 1999).

[7] In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744-5 (3d Cir. 1994); Holbrook v. Lykes Bros. S.S. Co., 80 F.3d 777, 784 (3d Cir. 1996).

applicable North Carolina law, a Plaintiff must prove that without Defendant's negligence, the injury would not have occurred.[8] Therefore, in this case Burford's specific causation witnesses must be able to testify that Burford's injury would not have occurred "but for" his ingestion of Avandia. To meet the Daubert standard, the experts must demonstrate that they have good grounds for their causation opinion (i.e. the opinion is not based on subjective belief, unsupported inferences, or speculation).[9]

Discussion

Dr. DePace

Dr. DePace is a clinical cardiologist who has reviewed James Burford's medical history and opines that Avandia was a substantial contributing factor to Burford's fatal myocardial infarction[10] and that without Avandia he would not have suffered that injury. He was not Burford's treating physician. GSK argues that Dr. DePace has no factual basis for attributing Burford's myocardial infarction to Avandia and rejects his proposed general causation testimony as unreliable.[11]

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[8] See supra note 5.

[9] See, Daubert v. Merrell Dow Pharms. Inc., 509 U.S. 579, 590 (1993).

[10] Burford's autopsy report indicates that he died from myocardial infarction, specifically a ruptured atherosclerotic plaque. GSK may dispute this conclusion at trial.

[11] It is not the Court's understanding that Plaintiffs intend to use Dr. DePace as a general causation expert, and therefore will not subject his opinion regarding Avandia's causal association with myocardial infarction to the same level of scrutiny as it would for an expert who is put forth for that purpose. The Court notes that it is appropriate for Dr. DePace to rely in part on the opinions of the general causation experts in this case. In Re TMI Litig., 193 F.3d 613, 697 (3d Cir. 1999). Moreover, the Court finds that Dr. DePace used reliable methods to arrive at his opinion that Avandia is a significant risk factor for myocardial infarction generally, and can cause or contribute significantly to the occurrence of myocardial infarction in an individual. Specifically, he reviewed the published literature on the topic, applied multiple Bradford-Hill criteria to the association (temporal relationship, biologically plausible mechanisms, replication of findings, strength of association, etc.). In this opinion, the Court will focus its attention on Dr. DePace's methods for reaching his conclusion that Avandia was a "but-for" cause of *Burford's* myocardial infarction.

Dr. DePace includes in his report a review of the scientific literature on Avandia and myocardial infarction, including the NISSEN meta-analysis, GSK's own meta-analysis, the FDA's meta-analysis, and various other observational studies. He particularly notes the increased risk when Avandia is used in combination with Metformin or ACE inhibitors, as Burford was on combination therapy using Avandia, Metformin and ACE inhibitors.

Dr. DePace looks at the primary risk factors for myocardial infarction and finds that Burford: 1) was a 49 year old male; 2) had been a non-smoker for thirty years, and had minimal increased risk from his remote smoking history; 3) was being treated with medication for dyslipidemia; 4) was being treated with medication for hypertension; 5) had no family history of coronary artery disease or premature cardiac death (his father drowned and other close family members were living and had good cardiac health); 6) was being treated with multiple medications for Type II diabetes (blood sugar control); and 7) was overweight but not sedentary. Dr. DePace discusses the role of each of these factors in the progression of Burford's atherosclerosis.

Dr. DePace's report then outlines three biologically plausible mechanisms by which Avandia can cause myocardial ischemic events, but goes on to note that there is no record evidence that any of the three were factors in Burford's death. First, Avandia can have an adverse impact on cholesterol and lipid metabolism, but there is no evidence that it changed Burford's lipid profile. Dr. DePace testified that the effect of Avandia on Burford's lipid profile was neutral, and further testified that "I can't say with a reasonable degree of medical certainty that in this particular case, James Burford's high particle count and LDL high particle count

contributed to the plaque destabilization," thus ruling out one plausible causal mechanism.[12] Second, Avandia can increase Lp-PLA2, and increases in Lp-PLA2 are correlated with increases in stroke, myocardial infarctions, and other ischemic events. It does not appear that Burford's Lp-PLA2 levels were ever tested, but more importantly, Dr. DePace does not opine that there is a *causal* relationship between Lp-PLA2 and myocardial infarction. Finally, Dr. DePace suggests that triple therapy with Avandia + Metformin + sulfonylurea increases the risk of hypoglycemia, and hypoglycemia is correlated with an increase in myocardial infarctions. It appears that Burford had just begun taking his sulfonylurea (Amaryl) on the day he died, but Dr. DePace does not discuss how this very recent addition of Amaryl supports or detracts from his proposed mechanism. Dr. DePace also has no evidence, other than Burford's wife's report that he had a headache in the days prior to his death, to support a finding that Burford experienced any episodes of hypoglycemia, and he acknowledged in his deposition that he could not say, with a reasonable degree of medical certainty, that hypoglycemia was the biological mechanism for this plaque rupture.[13]

GSK moves to exclude Dr. DePace's testimony, arguing that his opinion is simply based on a temporal relationship between Burford's use of Avandia and his death. They note that Burford was at high risk for myocardial infarction even before taking Avandia, as he was diabetic, obese, had high LDL and low HDL, and high blood pressure. Furthermore, Dr. DePace testified that "it would be difficult for me not to implicate Avandia as a significant and contributing and causative factor in the plaque rupture unless there were other extraneous factors

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[12] April 17, 2010 Deposition of Dr. DePace at 152.

[13] April 17, 2010 Deposition of Dr. DePace at 208.

that triggered the heart attack in the clinical history such as playing racquetball [or other unaccustomed exertion]."[14] GSK argues that Dr. DePace failed to rule out the other risk factors as causes of Burford's myocardial infarction, failed to adequately explain the mechanism by which Avandia caused his heart attack, and, in fact, failed to point to any evidence, other than the mere ingestion of Avandia for fifteen months, indicating that Avandia played a causal role in Burford's death.

The Court agrees that Dr. DePace makes an improper inferential leap in his expert report. Specific causation cannot be proved by merely pointing to evidence of general causation and an adverse outcome in a specific case. In Dr. DePace's report, he does not rule out the other risk-factors which could have caused or contributed to Burford's death, or tie plausible mechanisms to the evidence regarding Burford's condition.

Dr. DePace did a better job of ruling out risk-factors other than Avandia in his deposition testimony, noting that Burford's blood pressure was fairly well controlled by medication, although "not optimized at the secure or safety level,"[15] and his dyslipidemia was fairly well controlled, but also not optimal.[16] Dr. DePace notes that his blood sugar, while not optimal overall, was in a good range with regard to his cardiac risk (i.e. neither too high nor too low, both of which increase a diabetic's risk for heart attack).[17]

GSK makes much of Dr. DePace's admission that Avandia has *not* been found to cause or

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[14] April 17, 2010 Deposition of Dr. DePace at 98.

[15] April 17, 2010 Deposition of Dr. DePace at 69-70, 216.

[16] April 17, 2010 Deposition of Dr. DePace at 72.

[17] April 17, 2010 Deposition of Dr. DePace at 217.

increase the risk for the atherosclerosis found in Burford's heart, which was a prerequisite condition for Burford's injury. Dr. DePace also acknowledges that there is no evidence that Avandia impacted Burford's LDL or HDL concentrations,[18] and agrees that Burford's obesity (which dated back to 1991 or earlier), dyslipidemia (first measured and detected in 2000), hypertension (dating back to 2000), and diabetes (diagnosed in 2004) would all contribute to atherosclerosis.[19] GSK further argues that Dr. DePace connects Burford's death to Avandia based only on the epidemiological research.

Dr. DePace attributes Burford's death to the destabilization or rupture of Burford's atherosclerotic plaque, not to the presence of atherosclerosis per se. Having reviewed Dr. DePace's deposition testimony, the Court finds that Dr. DePace did rely in part on general epidemiological research, but also based his opinion upon the record evidence regarding Burford's medical condition. Dr. DePace notes that although Burford was at high risk from diabetes and atherosclerosis, it is very unusual for a forty-nine year old man in the high risk group to die of myocardial infarction, especially when medical risk factors (lipids, blood pressure, and blood sugar levels) are reasonably well controlled and in the absence of other triggering events (smoking, stimulant drugs such as cocaine, unusual physical exertion). Therefore, he opines that in the absence of Avandia, Burford would not have suffered a atherosclerotic rupture, leading to his fatal myocardial infarction.

Reading together his report and his deposition testimony, the Court finds that Dr. DePace's opinion is based on an application of his expertise and experience to the facts of the

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[18] April 17, 2010 Deposition of Dr. DePace at 88-89.

[19] April 17, 2010 Deposition of Dr. DePace at 58-69.

case using a sound methodology (an understanding of the medical literature, a careful review of the patient's medical records, and an application of the differential diagnosis process). The Court finds support in Dr. DePace's deposition testimony which evidences that he does not rely solely upon the literature suggesting that Avandia increases the risk of heart attack in users. Although this is a very close case, the Court finds that Dr. DePace did adequately and reliably, although perhaps not optimally, rule out alternative causes in reaching his opinion.[20] His opinion is therefore admissible and it will be left to the fact finder to assess the weight of that evidence.

Dr. Melinek

Dr. Melinek is a forensic pathologist who is an Assistant Medical Examiner in San Francisco, CA. In a very brief report, the substance of which covers less than two pages, Dr. Melinek opines that Burford suffered a fatal myocardial infarction due to a ruptured atherosclerotic plaque in the coronary artery,[21] and further opines that Avandia was a significant contributing cause of his death. To form her opinion, she relied upon general research on Avandia, package inserts and warnings for Avandia published by GSK, the reports and testimony of other experts, Burford's death certificate and the medical examiner's reports, a hospital autopsy report, and her own analysis of Burford's tissue samples from prepared slides. She also had access to Burford's medical records dated January 3, 1991 through his death on November 21, 2006.

GSK argues that without general causation there can be no specific causation, and notes

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[20] In re Paoli II, 35 F.3d at 744-5; Holbrook, 80 F.3d at 784.

[21] If GSK presents evidence to dispute the official cause of death at trial, the Court finds that Dr. Melinek is well qualified to provide an expert opinion as to whether Burford died from myocardial infarction or from cardiac arrhythmia arising from atherosclerotic coronary artery disease.

that Dr. Melinek is not qualified to opine as to general causation, nor does she attempt to do so in her report.[22]

GSK also argues that Dr. Melinek cannot opine that Avandia was a contributing factor in Burford's death without ruling out other risk factors and possible causes. Dr. Melinek does not argue that Burford's cholesterol, blood pressure, and blood sugar were well controlled by medication at the time of his death, but rather opines that these were ongoing risk factors which, in combination with Avandia, increased his risk of having a myocardial infarction and dying.

The problem for this Court is *not* that Dr. Melinek fails to identify that Avandia as the sole cause of Burford's myocardial infarction. Rather this Court is troubled by the fact that Dr. Melinek points to nothing more than the epidemiological research to support her opinion that Avandia played a role in *Burford's* fatal myocardial infarction. Turning to Dr. Melinek's deposition testimony, the Court finds no testimony from which it can conclude that Dr. Melinek used reliable methods to conclude that Avandia was a contributing cause of death in this specific case.

Dr. Melinek did find some evidence of congestive heart failure (CHF) in Burford's lungs and opined that CHF was a component of his death, although not the immediate cause of death. However, GSK highlights the fact that CHF can be the result of a MI, rather than a contributing cause, and Dr. Melinek admits that this is true.

For the reasons set forth above, the Court finds that Dr. Melinek's opinion is largely based upon studies showing an increased risk of cardiovascular mortality and myocardial

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[22] The Court need not reach this issue, as it rejects Dr. Melinek's opinion regarding causation on other grounds.

infarctions for patients taking Avandia.[23] The Court concludes that Dr. Melinek made an improper inferential leap from general causation to specific causation in her report, without any evidence to show that Avandia caused or even contributed to Burford's myocardial infarction. Accordingly, the Court will not permit Dr. Melinek to testify as to her opinion regarding the role of Avandia in Burford's death.

[23] Melinek Report (M.R.) at 2.