"JAWS"
Attacks On The *Daubert* Trilogy
A Case Study: The Parlodel® Litigation

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I. INTRODUCTION

A. In March 1999, the Supreme Court issued its third opinion in six years regarding the admissibility of expert evidence. *See Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993); *General Electric Co. v. Joiner*, 522 U.S. 136 (1997); *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999) (hereinafter "the *Daubert* Trilogy"). The opinion in *Kumho Tire* concluded one battle of the experts by making it clear that a trial court's gatekeeping obligation applies to "non-scientific" experts as well as scientific experts. *See Kumho Tire Co.*, 526 U.S. at 149. *Kumho Tire* did not, however, bring an end to the expert wars. To the contrary, it has had the practical effect of extending the front lines of the expert wars to *all* kinds of expert testimony. *See, e.g.*, Carr, Dabney J. *et al.* "After *Kumho Tire*: Challenging Non-Scientific Experts," 41 *For the Defense* 12, 13 (Defense Research Institute 1999).

B. This article examines the litigation over the pharmaceutical Parlodel® in general, and an appeal argued this week in the Eleventh Circuit in particular, as a representative battle in the continuing expert wars. The purpose of the case study is to learn:

1. How courts are applying the *Daubert* Trilogy in pharmaceutical cases; and

2. The latest tactics employed to wage the expert wars in pharmaceutical cases.

C. At a minimum, the Parlodel® litigation should be of interest to pharmaceutical defense counsel because:

1. Recent proceedings reflect that it is a determined and organized attempt by the plaintiffs' bar to eliminate, or at least minimize the importance of, epidemiological evidence in toxic exposure cases.

a. Plaintiffs are pursuing appeals of two district court opinions excluding contested scientific evidence in both the Tenth Circuit (*Hollander v. Sandoz Pharmaceuticals Corp.*, 95 F. Supp.2d 1230 (W.D. Okla. 2000)) and the Eleventh Circuit (*Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F. Supp.2d 1347 (N.D. Ga. 2001)), notwithstanding an unsuccessful appeal of the exclusion of the same evidence in the Eighth Circuit (*Glastetter v. Novartis Pharmaceuticals Corp.*, 107 F. Supp.2d 1015 (E.D. Mo. 2000), *aff'd* 252 F.3d 986 (8th Cir.) (*per curiam*), *pet. for reh'g and reh'g en banc denied* (8th Cir. 2001)).

b. The *Siharath* appeal currently pending before the Eleventh Circuit has captured the attention of distinguished legal and medical scholars, as evidenced by the three *Amicus Curiae* briefs filed in support of the Plaintiffs-Appellants. The *Amicus* briefs were filed by two law professors and a professor of medicine who have authored parts of the Federal Judicial Center's *Reference Manual on Scientific Evidence*, and three other distinguished professors of medicine, one of whom served as Editor-in-Chief of the *New England Journal of Medicine* from 1991 through 1999. *See infra* § IV.

2. In the Eleventh Circuit appeal of *Siharath*, the Plaintiffs-Appellants argue that the standard of review is *de novo* because the district court misinterpreted the *Daubert* Trilogy. *See infra* § IV.A. This argument appears to be an invitation to retreat from *Joiner*'s holding that "abuse of discretion is the proper standard by which to review a district court's decision to admit or exclude scientific evidence." *See Joiner*, 522 U.S. at 146.

D. This article begins with some background on Parlodel® and an overview of the scientific evidence at issue in the litigation. It then recounts lower court opinions determining the admissibility of the contested scientific evidence and summarizes the briefs of the parties and the *Amici Curiae* in the *Siharath* appeal argued in the Eleventh Circuit this week. Lastly, the article offers some explanations of the significance of the battle over the experts in the Parlodel® litigation.

II. BACKGROUND

A. Parlodel®:

1. Parlodel® is manufactured by Sandoz Pharmaceuticals Corporation ("SPC"), which is now Novartis Pharmaceuticals Corporation. *See Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F. Supp.2d 1347, 1349 (N.D. Ga. 2001).

2. Parlodel® blocks secretion of the hormone prolactin, which induces the breasts to secrete milk. *See Rider v. Sandoz Pharmaceuticals, Corp.* and *Siharath v. Sandoz Pharmaceuticals Corp.,* Corrected Brief of Defendants-Appellees, Case Nos. 01-11965-BB, 01-11966-BB (consolidated) (Appeal to the 11th Circuit, filed Aug. 30, 2001) (hereafter "Brief of Defendants-Appellees"), at 7. Significantly, Parlodel®'s active ingredient, bromocriptine mesylate, has been associated with vasodilatory properties and *hypo*tensive effects. *See* Brief of Defendants-Appellees at 7-8.

3. SPC began selling Parlodel® in 1980 as a treatment for amenorrhea (the absence of menstruation) and galactorrhea (milk flow not related to childbirth or nursing). *See Rider v. Sandoz Pharmaceuticals, Corp.* and *Siharath v. Sandoz Pharmaceuticals Corp.,* Joint Brief and Appendix of Plaintiffs-Appellants, Case Nos. 01-11965-BB, 01-11966-BB (consolidated) (Appeal to the 11th Circuit, filed July 18, 2001, 2001) (hereafter "Brief of Plaintiffs-Appellants"), at 5 and n.3. SPC continued to market Parlodel® for the prevention of physiologic lactation ("PPL") from 1980 through 1994. *See* Brief of Defendants-Appellees at 8; *see also* Brief of Plaintiffs-Appellants at 6.

4. In 1983, the FDA issued an "ADR Highlights" about Parlodel® and reports of hypertension, seizure or stroke. *See* Brief of Plaintiffs-Appellants at 6. In 1983 and 1985, the FDA asked SPC to include a warning about hypertension, seizure and stroke in the drug's labeling. *See id.* at 7.

5. In 1987, at the FDA's request, SPC revised the Parlodel® package insert to include a statement regarding adverse effects such as seizure, stroke and myocardial infarction

and issued a "Dear Doctor" letter to advise of the labeling changes. *See Eve v. Sandoz Pharmaceutical Corp.*, 2001 U.S. Dist. LEXIS 4531 at *18 (S.D. Ind. 2001).

6. "[I]n June 1989, the FDA reported to its Maternal Health Drugs Advisory Committee 'that it had received a total of 85 serious ADEs, including 10 deaths, since approval of [Parlodel® use for PPL] in 1980.'" Brief of Plaintiffs-Appellants at 7. Although it recognized that the ADE's did not prove that Parlodel® caused hypertensive crises, seizures or cerebral vascular accidents, the FDA concluded that "'in the aggregate [they] suggested that bromocriptine may be the cause of these serious adverse experiences.'" *Id.*

7. In 1989, the FDA twice requested that SPC withdraw Parlodel®'s indication for PPL, and in 1994, it initiated withdrawal proceedings. In January 1995, SPC voluntarily withdrew the drug as indicated for PPL. *See id.* at 9.

8. Parlodel® remains FDA-approved for the treatment of other conditions, including Parkinson's disease, amenorrhea, and galactorrhea. *Eve*, 2001 U.S. Dist. LEXIS 4531 at *11; Brief of Defendants-Appellees at 7-8.

B. Overview of scientific evidence regarding a possible association between Parlodel® and strokes or seizures

1. Epidemiological studies

a. Kenneth Rothman, *An Epidemiological Evaluation of the Possible Relation Between Bromocriptine, Puerperal Seizures and* Strokes, (Epidemiologic Resources, Inc. Sept. 30, 1998) (referred to as "ERI" or the "ERI Study"):

i. This study concluded that there is no statistically reliable association between Parlodel® and stroke. "The ERI study, commissioned by [SPC], is the only epidemiologic study using case controls and cohorts that has sought to determine whether a causal relationship exists between Parlodel® and stroke. This study reviewed hospital records of 280,096 postpartum women. Out of a total of ten postpartum strokes in this population, only one occurred in a woman who had taken Parlodel®." *Siharath*, 131 F. Supp.2d at 1356.

ii. This study also concluded that "although there is a positive association between bromocriptine and seizures among those [patients in the study] who also received [another drug not at issue in the *Siharath* or *Rider* cases], there is a weak *negative* association among those who did not receive [the other drug]." *Id.* at 1357 (emphasis in original).

b. Andrea D. Witlin, et al., *Postpartum Stroke: A Twenty-Year Experience*: This study concluded that postpartum women who take bromocriptine are eight times less likely to experience stroke than other patients who are exposed to the drug. *Id.* at 1358; *see also* Brief of Defendants-Appellees at 9 n. 6 (noting that Witlin studied approximately 130,000 women).

c. HCIA, Inc., *Postpartum Complications and Parlodel®* (October 1995): This study was commissioned by SPC and "analyzed 533,816 delivery records from 128 hospitals" to track postpartum complications to correlate them with Parlodel® use. *Siharath*, 131 F. Supp.2d at 1357. "For both preexisting and non-preexisting hypertensive women, the study concluded that there existed a *negative* association between bromocriptine … and hypertension." *Id.* (emphasis in original).

d. R.M.C. Herings, et al, *Bromocriptine and Suppression of Postpartum Lactation*, Pharmacy World and Science 17:133-37 (1995): "In this study, investigators compared hospital admission and drug use of 2,130 women to identify the existence of ischemic heart disease, hypertension, and cerebrovascular events such as stroke before, during and after use of Parlodel® for postpartum lactation. The study found that no women whatsoever were admitted to hospitals for any of these conditions during the presumed exposure period or in the following two months." *Siharath*, 131 F. Supp.2d at 1357. "The authors noted that significant adverse events may 'wrongly be associated with bromocriptine use' because of the confounding fact that pregnancy itself causes such events." Brief of Defendants-Appellees at 9 n.8.

2. **Case reports and dechallenge / rechallenge tests**

a. SPC's Drug Monitoring Center concluded that bromocriptine "probably" caused an ischemic stroke (i.e., strokes caused by the lack of blood flow to the brain) in one case report. The patient in this case, however, was 62 years old, was not postpartum, had longstanding hypertension, and suffered from a life-threatening pituitary disease that admittedly can lead to stroke. *Siharath*, 131 F. Supp.2d at 1360.

b. In another case, a 23 year-old German woman who took Parlodel® for three months suffered from hypertension and cerebellar incoordination. The patient in this case, however, was not postpartum and was taking Parlodel® to treat a pituitary condition that can itself lead to hypertension and incoordination. Moreover, the patient had multiple sclerosis, the classic symptom of which is cerebellar incoordination. *Id.*

c. A 22 year old French woman who took Parlodel® to suppress PPL later developed hypertension and convulsions. The case report reveals, however, that she was hypertensive before delivery, that her hypertension decreased after taking Parlodel®, and that she suffered from postpartum eclampsia, which can lead to seizures and stroke. *Id.*

d. In another case, a 20 year old Arkansas woman took Parlodel® to suppress PPL and later developed hypertension. Some plaintiffs' experts have emphasized the dechallenge aspect of this case (i.e., the discontinuation of the drug treatment), because the patient's hypertension improved after she was taken off Parlodel®. *Id.* at 1361. Defense experts have minimized this aspect of the case, however, since the patient's hypertension continued for four or five days after she was taken off the drug. *Id.*

3. **Animal Studies**

a. Bertholet and Sutter study of the "hind limb" of a dog: "This study attempted to determine, by injecting bromocriptine into the hind leg of a dog, whether bromocriptine acts as a vasoconstrictor and, if so, at what point vasoconstriction takes place." *Id.* at 1367-68. Plaintiffs maintain that this study demonstrates that Parlodel® is a vasoconstrictor, but admit that it does not show that Parlodel® causes stroke. *Id.* at 1368. Defendants question the relevance and reliability of this study because vasoconstriction occurred at 1,250 times the human dosage and because the interspecies variation between dog arteries and human arteries is unknown. *Id.*

b. Carotid artery study: This study "attempted to determine the effects of bromocriptine on the carotid artery of a dog." *Siharath*, 131 F. Supp.2d at 1368. Plaintiffs contend that this study demonstrated that bromocriptine is a vasoconstrictor, but admit that it does not demonstrate that the drug causes stroke. *Id.* Defendants contend that the study only demonstrated an increase in vascular resistance, which could have any number of causes other than vasoconstriction. *Id.* Defendants also contend that the study used a flawed method to record blood flow. *Id.*

c. Pithed animal studies: Plaintiffs contend that a number of studies conducted on pithed rats, mice, dogs, cats and rabbits show vasoconstriction caused by bromocriptine so severe that the tails of rats and mice and the ear margins of dogs became deprived of blood and fell off. *Id.* at 1369. Defendants criticize the method of these studies on the grounds that pithed animals are particularly susceptible to changes in blood pressure because the area of the brain controlling the cardiovascular system has been obliterated. *Id.*

4. **FDA Action**

a. By 1983, SPC and the FDA began receiving reports relating Parlodel® to "hypertension and related effects." *Kuhn v. Sandoz Pharmaceuticals Corp.*, 14 P.3d 1170, 1174 (Kan. 2000). In 1989, the FDA asked SPC to voluntarily withdraw Parlodel® from the market. *Id.* at 1175. SPC declined to do so, and on August 17, 1994, the FDA issued a paper stating that it had initiated procedures for withdrawing approval of Parlodel® to prevent PPL. *Id.* The next day, SPC withdrew the Parlodel® indication for the prevention of lactation in the United States. *Id.*

b. On August 24, 1994, the FDA issued the following statement:

> Since approval of bromocriptine for use in preventing physiological lactation, FDA has received a number of reports of serious and life-threatening adverse experiences (hypertension, seizures, and CVA's [cardiovascular accidents]) associated with the use of bromocriptine for this indication. FDA believes that the number of women experiencing such adverse experiences may well be greater than those reported to the FDA. The above evidence, in aggregate, calls into question bromocriptine's safety for use in postpartum women given that bromocriptine may be responsible for hypertension, seizures and CVA's in a small but

> significant number of patients. … Accordingly, the Director concludes that the potential risks associated with the use of bromocriptine for the prevention of physiological lactation outweigh its limited benefits and bromocriptine is no longer shown to be safe for use in preventing physiological lactation.

Siharath, 131 F. Supp.2d at 1365-66 (quoting 59 Fed.Reg. 43347, 43351 (Aug. 24, 1994)).

5. **Effects of Other Ergot Alkaloids**

a. "Plaintiffs' argument in this regard is as follows: Parlodel®'s active ingredient is bromocriptine. Bromocriptine is a semi-synthetic ergot alkaloid. Ergot alkaloids are a class of drugs that can cause vasoconstriction. Vasoconstriction can lead to hypertension, seizures and ischemic strokes. Hemorrhages are another type of stroke, so it is possible that they also are caused by Parlodel®." *Siharath*, 131 F. Supp.2d at 1364.

b. Defendants argue that there is no evidence that ergot alkaloids cause hemorrhagic (i.e., bleeding) strokes, only ischemic (i.e., lack of blood to brain) strokes, and that no epidemiological studies or learned treatises link ergot alkaloids to hemorrhagic strokes. *Id.* at 1365. Defendants also argue that bromocriptine differs significantly from other ergot alkaloids in its chemical structure and in that it can act as either a vasoconstrictor or a vasoldilator, depending upon vascular tone. *Id.* at 1364.

6. **Learned Treatises**

a. Treatises supporting Plaintiffs:

i. "In the *Physician's Desk Reference* … there is well-documented evidence of strokes in women receiving bromocriptine for postpartum breast milk suppression…" *Id.* at 1369 (*quoting* M.D.B. Stephens, ed., *Detection of New Adverse Drug Reactions* 383).

ii. "Drug interactions and use after pregnancy can induce life-threatening responses," and "[s]evere HT [hypertension] with stroke has been reported after use for suppression of lactation." *Siharath*, 131 F. Supp.2d at 1369 (*quoting* Williams & Wilkins, *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning* 26 tbl. 1-34, 867 & 868).

iii. "Adverse effects [for bromocriptine] which occur more rarely, but which are serious … include unusual and continuing headache, vision changes, seizures or strokes." *Siharath*, 131 F. Supp.2d at 1369 (*quoting* USP, *Material Safety Data Sheet* (1995)).

iv. "Many postpartum patients who developed stroke and/or seizures in association with bromocriptine therapy complained of constant and often

progressively severe headaches hours prior to the acute event." *Siharath*, 131 F. Supp.2d at 1370 (*quoting American Hospital Formulary Service Drug Information* 2560 (1995)).

b. Treatises supporting Defendants:

i. Dukes, *Meyler's Side Effects of Drugs* (13th ed. 1996): Discusses bromocriptine but fails to state that Parlodel® causes stroke. *Siharath*, 131 F. Supp.2d at 1370 (noting that this treatise is edited by one of plaintiffs' experts, Dr. Dukes); *see also* Brief of Defendants-Appellees at 9-10.

ii. Kittner, et al., "Pregnancy and the Risk of Stroke," 33 *New Eng. J. Med.* 768-74 (1996): Pregnancy is a risk factor for stroke. Specifically, Kittner found an increased relative risk of 28.3 for intracerebral hemorrhagic stroke in postpartum women. *See* Brief of Defendants-Appellees at 7, 37.

iii. Ellenhorn, *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning* (2d ed. 1997): This text includes a table summarizing the disparate properties of different ergots. Brief of Defendants-Appellees at 40. It also reports the vasoconstrictive property of bromocriptine as zero. *Id.*

III. HISTORY OF PARLODEL® LITIGATION

A. Federal district courts excluding plaintiff's expert causation testimony

1. ***Brumbaugh v. Sandoz Pharmaceuticals Corp.*, 77 F. Supp.2d 1153, 1157 (D. Mont. 1999).** After being brutally attacked by her boyfriend, plaintiff delivered a baby by cesarean section. 77 F. Supp.2d at 1155. Plaintiff's treating physician prescribed Parlodel® for plaintiff to reduce her breast engorgement. *Id.* Plaintiff suffered a seizure shortly thereafter. *Id.* In support of plaintiff's case against SPC, plaintiff's expert relied on anecdotal case reports and his theory that drugs similar to Parlodel® are vasoconstrictors, but he did not rely on any epidemiological studies. *Id.* SPC, on the other hand, relied on five studies, two of which were epidemiological, that showed no statistically significant relationship between Parlodel® and strokes. *Id.* at 1155. The court was persuaded that Parlodel® caused vasodilation rather than vasoconstriction. *Id.* The court held that plaintiff's expert's opinions were too unreliable and speculative to be admissible. *Id.* at 1157. Accordingly, the court granted defendant's *Daubert* motion and defendant's motion for summary judgment. *Id.*

2. ***Caraker v. Sandoz Pharmaceuticals Corp.*, 172 F. Supp.2d 1046 (S.D. Ill. 2001); final order entered 2001 U.S. Dist. LEXIS 22397 (Nov. 21, 2001).** Plaintiff suffered an intracerebral hemorrhage after taking Parlodel® to suppress lactation after child birth. 172 F. Supp.2d at 1047. Plaintiff's experts attempted to link the two events. *Id.* Noting that the court "is not required to simply 'take the expert's word for it,'" the court excluded the testimony of plaintiffs' experts as scientifically unreliable. *Id.* (citation omitted) (stating that the court must "rigorously scrutinize" the sufficiency of the data relied upon by the expert, the

reliability of the principles and methods employed by the expert and the reliability of the expert's application of the principles and methods to the facts of the case).

a. The court noted that plaintiff admitted that most of her data, including case reports, animal studies, chemical inferences, FDA actions and flawed epidemiological studies, individually would not show that Parlodel® causes intracerebral hemorrhage, but argued that cumulatively, the data shows such a causal link. *Id.* at 1048. After analyzing the evidence relied upon by plaintiff's experts piece by piece and in the aggregate, the court concluded that plaintiff's experts' methodology was questionable and based on insufficient data. *Id.* at 1053.

b. The court was suspect of plaintiff's experts' use of the differential diagnosis method. For such a method to be effective in the realm of science "as opposed to its use by treating physicians in the practice of medicine out of necessity," the experts must rely on sufficient and reliable data to rule in and rule out potential causes. *Id.*

c. The court determined that the epidemiological studies relied upon by both parties were flawed. 2001 U.S. Dist. LEXIS 22397 at *15-17. The court, however, "imposes no absolute epidemiology requirement or any other requirement, except reliability and relevance." *Id.* at *18.

3. ***Glastetter v. Novartis Pharmaceuticals Corp.*, 107 F. Supp.2d 1015, 1044-45 (E.D. Mo. 2000), *aff'd* 252 F.3d 986, 989 (8th Cir. (per curiam), *petition for reh'g and reh'g en banc denied* (8th Cir. 2001).**

a. Plaintiff and her husband sued Novartis Pharmaceuticals Corp. after plaintiff suffered an intracerebral hemorrhage following 13 days of Parlodel® drug therapy after the birth of her second child. 107 F. Supp.2d at 1017. Plaintiffs' experts, Drs. Kulig and Petro, employed the differential diagnosis method, which involved ruling out other possible causative factors, and concluded that Parlodel® caused plaintiff's intracerebral hemorrhage. *Id.* at 1019-28.

b. Defendant moved *in limine* to exclude plaintiffs' causation experts and for summary judgment. *Id.* at 1016. After a *Daubert* hearing, the court concluded that plaintiffs' causation evidence failed the test set forth in *Daubert* for scientific reliability and awarded summary judgment to defendant. *Id.*

c. Plaintiffs' experts conceded that their differential diagnosis method "is not helpful in assessing general causation." *Id.* at 1027. Plaintiffs then came forward with the following evidence to support their claim that Parlodel® can cause intracerebral hemorrhages: "(1) peer reviewed articles, texts, and treatises; (2) multiple human dechallenge and rechallenge studies and reports; (3) an epidemiology study on stroke and Parlodel, which plaintiffs admit is 'underpowered and thus partially flawed' …; (4) determinations by the FDA that Parlodel is unsafe because of stroke and other vasospastic risks; and (5) allegedly hidden internal company admissions by Sandoz concluding that Parlodel can cause such conditions...." *Id.* at 1028.

d. The court found this evidence insufficient to establish general causation. *Id.*

i. First, as SPC and plaintiff's own expert noted, case reports do not establish causation. *Id.* at 1029-30. The court did not believe that the case reports, including dechallenge / rechallenge information, were sufficient "to establish the requisite causation, as they fail to take into account the postpartum incidence of stroke and other factors." *Id.* at 1031 (citation omitted).

ii. Second, the court rejected findings in several published texts and articles relied upon by plaintiffs' experts because they were "simply case reports." *Id.* at 1033-34. The court also was not persuaded by other texts and articles regarding the tendencies of other ergot alkaloids in the same family as bromocriptine to cause hypertension, vasospasm and stroke. *Id.* at 1034. The court found that plaintiffs' evidence does not establish that "bromocriptine and the other ergots have sufficiently similar physiological effects to warrant comparison." *Id.* (citation omitted). Moreover, the court noted that vasospasm is a different injury than intracerebral hemorrhage. *Id.*

iii. Third, the court found plaintiffs' reliance on the FDA's withdrawal of approval for bromocriptine for use in preventing lactation "is misplaced." *Id.* at 1036. The FDA did not affirmatively state that there is a connection between bromocriptine and intracerebral hemorrhage, only that bromocriptine "'*may* be an additional risk factor in patients who are already at risk for seizures and strokes.'" *Id.* (emphasis in original). Thus, the FDA's statement does not establish the reliability of plaintiffs' experts' causation testimony. *Id.*

iv. Fourth, the court determined that none of the SPC documents relied upon by plaintiffs established that Parlodel causes intracerebral hemorrhages. *Id.* at 1036-37 (noting that some of the documents merely reflected case reports).

v. Fifth, the court found a lack of similarity between the animal studies relied upon by plaintiffs' experts and the facts of this case. *Id.* at 1044.

vi. Finally, the court emphasized that although plaintiffs' experts admitted that epidemiological evidence is the "best evidence supporting a connection between a drug and an adverse effect," they did not rely on epidemiological evidence to support their position that Parlodel® causes stroke. *Id.* at 1042. Plaintiffs' experts admitted that they did not know of a statistically significant epidemiological study demonstrating an association between bromocriptine or Parlodel® and stroke or intracerebral hemorrhage. *Id.* at 1042-43. "In the absence of their own epidemiological evidence supporting the conclusions of their experts that Parlodel can cause [intracerebral hemorrhage], the best plaintiffs can do is attack defendant's studies. However, … such attacks do not 'meet the law's requirements,' because plaintiffs 'must come forward with reliable scientific evidence of [their] own to defeat a summary judgment motion when [the] case is based on the expert's proof.'" *Id.* at 1044 (citation omitted).

e. Thus, the court held that "in the absence of reliable scientific evidence supporting their causation testimony, plaintiffs' experts must be excluded" and defendant is entitled to summary judgment *Id.* at 1045.

4. ***Hollander v. Sandoz Pharmaceuticals Corp.*, 95 F. Supp.2d 1230, 1238-39 (W.D. Okla. 2000) (appeal pending).** Plaintiff suffered a hemorrhagic stroke after ingesting Parlodel®. 95 F. Supp.2d at 1232. In support of their theory that Parlodel® can cause strokes, plaintiff's experts relied on determinations by the FDA that the safety of Parlodel® had not been demonstrated, a finding of causation by a Kentucky jury, incidents of challenge/de-challenge/re-challenge data, case reports, the effects of other ergots, animal studies and epidemiological studies. *Id.* at 1234-35. After a *Daubert* hearing, the court excluded testimony of Dr. Kulig and three other experts as unreliable and granted defendant's motion for summary judgment. *Id.* at 1234.

a. Defendant challenged plaintiff's experts causation evidence on the grounds that plaintiff's experts: "(1) cannot explain how Parlodel causes vasoconstriction, which then causes hypertension and strokes; (2) improperly rely on anecdotal case reports and temporal proximity, which do not constitute scientifically reliable bases for their opinions; (3) improperly reason that because some ergot alkaloids, which are in the same class as bromocriptine may also cause hypertension; and (4) improperly rely on animal studies that are too different from the facts presented by this case to be reliable." *Id. at 1235.* The court agreed with defendant. *Id.*

b. The court rejected case reports as a scientific basis for establishing causation. *Id.* at 1237. Likewise, the court rejected plaintiff's expert's reliance on FDA determinations because the FDA's standard of proof is lower than that required by courts. *Id.* at 1234, n.9, 1237. As for the epidemiological studies relied upon by plaintiff's experts, the court found that none showed a statistically significant link between Parlodel® and strokes. *Id.* at 1236.

c. The court did not conclude that expert testimony must be based on epidemiology to be admissible. *Id.* at 1237, n.22. Instead, the court concluded that "due to the absence of supportive epidemiological evidence, the differences between bromocriptine and the other ergot alkaloids, the dissimilarity of the animal studies, and the unreliability of case reports, the data and methods relied on by the plaintiffs' experts do not furnish a scientifically valid basis for their conclusion that Parlodel causes strokes." *Id.* at 1238-39.

5. ***Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F. Supp.2d 1347 (N.D. Ga. 2001).** With this decision, the United States District Court for the Northern District of Georgia, Atlanta Division, addressed defendants' motions to exclude and for summary judgment in two cases: *Siharath v. Sandoz Pharmaceuticals Corp.* and *Rider v. Sandoz Pharmaceuticals Corp.*

a. Facts of *Siharath:* In 1989, Ms. Siharath, age 17, delivered her second child, decided not to breast feed and started taking Parlodel® for the prevention of lactation. *Siharath,* 131 F. Supp.2d at 1349. Shortly thereafter, Ms. Siharath suffered three seizures and a subarachnoid hemorrhagic stroke. *Id.* Plaintiff's treating physicians were unable

to diagnose the cause of her stroke and did not find evidence of cerebral vasoconstriction. *Id.* None of Ms. Siharath's treating physicians concluded that Parlodel® was a cause of her stroke, and none of them testified as experts on her behalf in the litigation. *See* Brief of Defendants-Appellees at 4-5. Ms. Siharath filed suit in 1995 claiming that her 1989 ingestion of Parlodel® caused her stroke. *Siharath*, 131 F. Supp.2d at 1349.

b. Facts of *Rider:* In 1993, Mrs. Rider, age 39, had a child, decided not to breast-feed, and began taking Parlodel® to suppress lactation. *Id.* at 1350. Shortly thereafter, she suffered an intracranial hemorrhagic stroke. *Id.* After testing, Mrs. Rider's doctors determined that vasospasm caused her stroke and that her significant history of smoking, her hemorrhagic AVM, abnormal vascularity or left-sided structural lesion were all possible etiologies of her stroke. *Id.*; Brief of Defendants-Appellees at 5. None of Mrs. Rider's treating physicians concluded that Parlodel® was a cause of her stroke, and none of them testified as experts on her behalf in the litigation. Brief of Defendants-Appellees at 5.

c. Plaintiffs' experts opined that Parlodel®'s active ingredient bromocriptine, as an ergot alkaloid, causes hemorrhagic stroke by vasoconstriction in some postpartum women. *Siharath*, 131 F. Supp.2d at 1355. Defendant moved *in limine* to exclude plaintiffs' expert witnesses and for summary judgment on the ground that plaintiffs could not prove causation. *Id.* at 1350. Defendant argued that plaintiffs' experts' testimony fails to meet *Daubert*'s requirements because plaintiffs' experts: "(1) have failed to provide any evidence, either published or unpublished, that Parlodel® increases one's risk of stroke; (2) rely on uncontrolled and unreliable spontaneous reports and anecdotal case reports as the basis for their opinions; and (3) cannot show that their opinions have an acceptable error rate or are otherwise generally accepted." *Id.* at 1352.

d. After a three day evidentiary hearing, the district court excluded plaintiffs' experts' opinions as neither scientifically reliable nor relevant and granted summary judgment to defendants. *Id.* at 1350, 1355-56.

i. The court pointed out that epidemiological studies are the primary method to prove causation in toxic tort cases. *Id.* at 1356. The epidemiological studies investigating a possible link between Parlodel® and strokes, however, did not show a statistically significant relationship between the two and therefore did not support plaintiffs' causation theory in this case. *Id.* at 1356-58. The court concluded that "the lack of epidemiological studies supporting Plaintiffs' claims creates a high bar for Plaintiffs to surmount with respect to the reliability requirement, but it is not automatically fatal to Plaintiffs' case." *Id.* at 1358 (stating that if other reliable scientific knowledge exists, plaintiffs can overcome this hurdle).

ii. The court held that the anecdotal case reports relied upon by plaintiffs' experts did not involve cases where Parlodel® caused hemorrhagic stroke in postpartum women, nor do they satisfy scientific method requirements sufficient to establish causation. *Id.* at 1359. In addition, the court concluded that the medical treatises relied upon by plaintiffs' experts were nothing more than case reports and similarly were unreliable. *Id.* at 1370.

iii. The court rejected plaintiffs' experts' comparisons of bromocriptine to similar drugs because they raised "serious questions of 'fit.'" *Id.* at 1363.

iv. The court also would not permit plaintiffs to rely on the FDA's determinations that the risks of Parlodel® outweighed its benefits in suppressing lactation. *Id.* at 1366. The FDA's risk-utility standard is lower than the standard of proof required in tort actions. *Id.*

v. The court determined that none of the animal studies relied upon by plaintiffs' experts establish that Parlodel® causes stroke in animals or humans. *Id.* at 1367. The animal studies also had flaws that "prevent any conclusion that they 'fit' with Plaintiffs' causation theory." *Id.*

vi. The court concluded that none of plaintiffs' evidence, individually or collectively, establishes a prima facie case that Parlodel® causes stroke. *Id.* at 1370. The court held that as one of plaintiffs' experts previously wrote, "one cannot lump together lots of hollow evidence in an attempt to determine what caused a medical harm." *Id.* at 1371.

vii. The court rejected plaintiffs' arguments that they "have employed the same methodology as is applied by doctors throughout the world in their clinical practices" and that plaintiffs' experts used "the best methodology available." *Id.* at 1372. The court found that their opinions were not supported by reliable scientific evidence and instead seemed based more on their personal opinions. *Id.*

viii. The court noted that defendant "continually researched" whether there was an association between Parlodel® and strokes and had not established causation. *Id.* at 1373. The court did not want to create "an unintended disincentive for pharmaceutical companies to engage in ongoing research as to their products' safety" by lowering the *Daubert* standard based on anecdotal evidence. *Id.*

B. Federal courts of appeals excluding plaintiff's expert causation testimony

1. ***Glastetter v. Novartis Pharmaceuticals Corp.*, 107 F. Supp.2d 1015, 1044-45 (E.D. Mo. 2000), *aff'd* 252 F.3d 986, 989 (8th Cir. (per curiam), *petition for reh'g and reh'g en banc denied* (8th Cir. 2001).** Plaintiff and her husband filed suit after Mrs. Glastetter suffered an intracerebral hemorrhage while taking Parlodel® to suppress lactation after child birth. 252 F.3d at 987-88. The district court excluded plaintiff's experts' proposed causation testimony as not scientifically valid and granted defendant summary judgment. *Id.* at 988. On appeal, the Eighth Circuit affirmed the decision of the district court.

a. The Eighth Circuit held that plaintiffs' experts "failed to produce scientifically convincing evidence that Parlodel causes vasoconstriction." *Id.* at 989. Plaintiffs' experts relied on published case reports, human re-challenge/de-challenge data, medical treatises, animal studies, analysis of the vasoconstrictive properties of other ergot alkaloids, defendant's

internal documents, and the FDA's decision that the possibility of harm from Parlodel®, including the possibility of stroke and seizure in certain women, outweighed its benefits as a lactation suppressant. *Id.* at 988-89. The Eighth Circuit agreed with the district court, however, that all of the data the experts relied on in support of their opinions were unreliable. *Id.* at 990-91. Specifically, the Eighth Circuit found that: none of the animal studies concluded that intracerebral hemorrhage was associated with bromocriptine; the leading toxicology treatise concluded that bromocriptine does not have any vasoconstrictive properties; case reports "are not scientifically valid proof of causation"; defendant's documents did not "admit" that Parlodel® causes intracerebral hemorrhage; and the FDA's standard for evaluating pharmaceuticals is different than the court's causation standard. *Id.*

b. The Eighth Circuit concluded that "[v]iewed in isolation, [plaintiffs'] different pieces of scientific evidence do not substantiate her experts' conclusion that Parlodel can cause [intracerebral hemorrhages]. Likewise, we do not believe that the aggregate of this evidence presents a stronger scientific basis for [plaintiffs'] supposition that Parlodel can cause [intracerebral hemorrhages]." *Id.* at 992.

c. The Eighth Circuit stated that contrary to plaintiffs' assertion, the district court did not require that she introduce epidemiological evidence of causation to satisfy *Daubert*'s requirements. *Id.* The parties agreed that the epidemiological evidence was inconclusive regarding links between Parlodel® and intracerebral hemorrhages. *Id.* The Eighth Circuit noted that the "absence of epidemiological evidence did not doom [plaintiffs'] case," but "epidemiological evidence might have assisted [plaintiffs] in establishing causation, and thus its absence limited the available tools with which she could prove causation." *Id.*

2. **Eleventh Circuit:** *Siharath v. Sandoz Pharmaceuticals Corp.* and *Rider v. Sandoz Pharmaceuticals Corp.* (appeal of exclusion of plaintiff's causation evidence pending) (oral argument on May 2, 2002).

3. **Tenth Circuit:** *Hollander v. Sandoz Pharmaceuticals Corp.* (appeal of exclusion of plaintiff's causation evidence pending).

C. State court Parlodel® cases excluding plaintiff's expert causation testimony

1. ***Revels v. Novartis Pharmaceuticals Corp.*, No. 03-98-00231-CV, 1999 WL 644732 (Tex. App. Aug. 26, 1999) (unpublished op.), *reh'g denied* (Tex. App.), *petition for review denied* (Tex. 2000).** In this case, plaintiff suffered heart failure and sudden death after taking Parlodel® to suppress lactation after the birth of her third child. 1999 WL 644732 at *1. Plaintiffs offered seven experts to testify that Parlodel® could cause coronary artery vasospasm in the general population and caused plaintiff's coronary artery vasospasm in this case. *Id.* Plaintiffs' experts relied on case reports, adverse event reports submitted to the FDA, one report of a bromocriptine challenge/re-challenge test, FDA findings, and analysis of structurally similar compounds to support their causation opinion. *Id.* at *2. The trial court excluded plaintiffs' experts' testimony as unreliable under Texas's *Daubert* analog, and the Court of Appeals of Texas affirmed. *Id.* at *6. The court held that "[w]hile the case reports

illustrate an association between adverse drug experiences and Parlodel, the [Texas] supreme court has clearly warned that such an association does not equate to causation." *Id.* at *5.

D. Federal district courts admitting plaintiff's expert causation testimony

1. ***Brasher* v. *Sandoz Pharmaceuticals Corp.*, 160 F. Supp.2d 1291 (N.D. Ala. 2001).** Plaintiffs suffered strokes shortly after delivering children and taking Parlodel® to stop postpartum lactation. The court concluded that the proffered experts opinions that plaintiffs' strokes were caused by their ingestion of Parlodel® were sufficiently reliable and admissible. 160 F. Supp.2d at 1299 (denying defendants' motion for summary judgment).

a. Defendants argued that "absent a scientifically appropriate epidemiological study showing an increased risk of stroke associated with Parlodel use, plaintiffs' experts' opinions are nothing more than unscientific speculation." *Id.*

b. The court held that the proffered opinions that plaintiffs' strokes were caused by "cerebral arterial spasms arising from the vasoconstrictive effects of the Parlodel both women were taking" were "based on 'good grounds' tied to the scientific method" and "possess sufficient evidentiary reliability (that is, trustworthiness) that a jury should be allowed to consider the opinions in the determination of the facts of this case." *Id.* at 1296.

i. The court stated that plaintiffs' experts relied on: (1) animal studies that showed that Parlodel® has vasoconstrictive properties; (2) the fact that other ergot alkaloids are known to cause vasoconstriction; (3) case reports suggesting that women taking Parlodel® have suffered hypertension, stroke and myocardial infarction, including those reported to the FDA; and (4) several treatises and medical textbooks, which identify bromocriptine as a risk factor for stroke. *Id.* at 1296. The court also noted that scientists routinely use such evidence to draw conclusions. *Id.*

ii. "Although it is true that none of these bits of evidence establish conclusively that Parlodel can cause vasoconstriction and vasospasm, taken together they present a compelling picture, one which can support a reasonable scientific inference." *Id.*

iii. The court further held that "[u]nquestionably, epidemiological studies provide the best proof of the general association of a particular substance with particular effects, but it is not the only scientific basis on which those effects can be predicted. In science, as in life, where there is smoke, fire can be inferred, subject to debate and further testing." *Id.* The court found that the fact that the lack of epidemiological studies is due to the difficulty and danger in structuring such a study and the rarity of strokes in women of child-bearing years. *Id.* at 1297.

iv. The court decided to leave for the jury to determine whether defendants' alternative explanations for plaintiffs' strokes, such as history of smoking, obesity, and family history of stroke, have merit. *Id.* at 1299.

v. The court in *Brasher* did not feel obligated to follow the Eighth Circuit Court of Appeals' recent decision affirming the grant of summary judgment in favor of SPC in *Glastetter v. Novartis Pharmaceuticals Corp.*, 252 F.3d 986 (8th Cir. 2001). *Id.* at 1299 n.17. The *Brasher* court noted that the *Glastetter* court relied on an outdated treatise and that the more recent edition of the treatise indicated a relation between bromocriptine and seizure and stroke. *Id.*

2. ***Eve v. Sandoz Pharmaceutical Corp.*, 2001 U.S. Dist. LEXIS 4531 (S.D. Ind. 2001).** The court concluded, based on the written submissions of the parties, that the testimony of plaintiffs' experts Drs. Kulig and Petro are "scientifically reliable and therefore admissible." 2001 U.S. Dist. LEXIS at *55.

a. In this case, Drs. Kulig and Petro relied upon case reports, treatises, texts and journals, human re-challenge studies, inferences based on similarities of other chemical compounds, adverse drug reports submitted to the FDA, FDA regulatory findings, defendants' internal documents and animal studies to support their causation opinions. *Id.* at *60-61, *66-73. The court held that the "cumulation of this evidence satisfies the *Daubert* requirements of scientific reliability." *Id.* at *61.

b. The court stated that although plaintiffs' experts admitted that they do not have any epidemiological evidence to support their opinions, "*Daubert* simply requires reliable evidence." *Id.* at *57.

c. The court noted that the "Seventh Circuit chastises trial court judges who act as overly aggressive gatekeepers." *Id.*

3. ***Globetti v. Sandoz Pharmaceuticals, Corp.*, 111 F. Supp.2d 1174 (N.D. Ala. 2000).** Plaintiff's experts opined that plaintiff's myocardial infarction was caused by her ingestion of Parlodel® after delivery of her sixth child. 111 F. Supp.2d at 1176. Plaintiff's experts relied on animal studies, case reports, adverse drug reaction reports submitted to the FDA, medical textbooks, the results of a 1993 de-challenge/re-challenge experiment, and the "generally accepted notion in the medical community" that Parlodel is a risk factor for myocardial infarction because of its vasoconstrictive effects. *Id.* Defendant argued in support of its *Daubert* challenge that absent an epidemiological study showing an increased risk of myocardial infarction associated with the use of Parlodel®, plaintiff's experts' opinion is sheer speculation. *Id.* The court held that plaintiff's experts' causation opinion "is based on 'good grounds' tied to the scientific method" and "possesses sufficient evidentiary reliability… that a jury should be allowed to consider it." *Id.* at 1177.

a. "Although defendant is correct that there is no epidemiological study showing an increased risk of [myocardial infarction] associated with bromocriptine, there is more than adequate evidence of a scientific nature from which a reliable conclusion can be drawn about the association." *Id.* at 1179. Thus, the court "inferred" that plaintiff's myocardial infarction was caused by her ingestion of Parlodel®. *Id.*

b. The court agreed with plaintiffs that an epidemiological study of the association between Parlodel® and myocardial infarction is not practical because of the rarity of myocardial infarctions among postpartum women. *Id.*

c. Whether there are alternative causes of plaintiff's myocardial infarction is a question that goes to the weight to be given plaintiff's experts, not the admissibility of their opinions. *Id.*

d. The court explained why it disagreed with other courts that had excluded similar evidence:

> The court believes that in those cases the *Daubert* standard was applied incorrectly, creating much too high a standard of admissibility. Both of these cases seem to equate *Daubert*'s reliability standard with scientific certainty, which is far from what the Supreme Court intended in *Daubert*. [The other courts] failed to recognize that *Daubert* does not require, or even allow, the trial court to determine the scientific 'correctness' or certainty of the evidence, but only that the facts from which the opinion is *inferred* are themselves sufficiently reliable.

Id. at 1180 (finding plaintiff's experts' opinions scientifically reliable and denying defendant's motion for summary judgment on medical causation).

4. ***Kittleson v. Sandoz Pharmaceuticals Corp.*, Civil No. 98-2277 (N.D. Minn. March 3, 2000) (unpublished).** The court summarily held that plaintiffs presented sufficient causation evidence to allow the case to withstand defendants' *Daubert* challenge and proceed to the jury.

E. Federal courts of appeals admitting plaintiff's expert causation testimony

None reported to date.

F. State court Parlodel® cases admitting plaintiff's expert causation testimony

1. ***Kuhn v. Sandoz Pharmaceuticals Corp.*, 14 P.3d 1170 (Kan. 2000).** After the birth of her child, plaintiff received one Parlodel® tablet, and shortly thereafter became ill, went into a coma and died. 14 P.3d at 1173-74. Plaintiffs' experts' conclusions were based on the medical methodology of differential diagnosis. *Id.* at 1177. At trial, the court found plaintiffs' experts' causation opinions unreliable, excluded them and granted SPC summary judgment. *Id.* at 1173. The Supreme Court of Kansas reversed the trial court's award of summary judgment in favor of SPC, finding that the trial court erred in applying the *Frye* test to exclude plaintiffs' experts' testimony on causation. *Id.*

a. Applying a *de novo* standard of review, the Supreme Court of Kansas determined that *Frye* was not applicable in this case because it requires a showing that the basis for an expert's opinion is generally accepted as reliable within the expert's field before

it may be admissible. *Id.* at 1178-79. The court found that the experts in this case were offering "pure opinion," which is distinguishable from testimony based on scientific method or technique, and therefore the *Frye* test did not apply. *Id.* at 1179-81. "Pure opinion" is "an expert opinion developed from inductive reasoning based on the expert's own experience, observation or research." *Id.* at 1179. The court held that "pure opinion is tested by cross-examination of the witness." *Id.*

b. The Supreme Court of Kansas further found that the trial court erred when it required plaintiffs to prove both general and specific causation. *Id.* at 1184. The Supreme Court of Kansas held that a finding of general causation is not necessary. *Id.* The court reasoned:

> 'Cases that have not imposed this requirement [general causation] typically involve injuries that may be placed in the 'sporadic accident model of tort law.' In [these] cases, where only a single plaintiff or a few plaintiffs have allegedly suffered an injury due to some exposure, a medical doctor will be permitted to render an opinion as to whether the exposure caused the plaintiff's injury solely on an examination of the plaintiff and a differential diagnosis of the source of the plaintiff's injury, sometimes supplemented with toxicological evidence. …. In many of these cases there is relatively little epidemiological data available and the courts are reluctant to burden 'first plaintiffs' with the task of using epidemiology to prove general causation.

Id. at 1184-85 (citations omitted). Thus, the Supreme Court of Kansas reversed the decision of the trial court excluding the experts and remanded the case with directions. *Id.* at 1185.

2. ***Sandoz Pharmaceuticals Corp. v. Roberts*, No. 89-CI-653 (Ky. Ct. App. Aug. 9, 1996).** Plaintiff was hospitalized for pregnancy-induced hypertension. *Id.* at 2. After she delivered her baby, her blood pressure returned to normal. *Id.* Although Parlodel® was not indicated for plaintiff because of her previous hypertension, it was administered pursuant to her doctor's standing orders at the hospital. *Id.* In addition, plaintiff had suffered adverse effects from the drug ten months earlier when she had taken it for infertility. *Id.* Shortly after taking Parlodel® postpartum, plaintiff suffered a stroke and ended up severely disabled. *Id.* at 3. After the trial of this case, the jury returned verdicts against SPC and awarded plaintiff over $1,000,000 in compensatory and $1,000,000 in punitive damages. *Id.* at 2, 4. On appeal, SPC contends that appellees failed to establish legal causation. *Id.* at 2. The Kentucky Court of Appeals affirmed the judgment of the trial court. *Id.*

a. Plaintiff's experts relied on their review of plaintiff's medical records, the depositions of other witnesses, epidemiological studies, peer-reviewed medical articles and their own professional experiences with Parlodel®. *Id.* at 8-9. The Kentucky Court of Appeals held that "the information which they relied upon is of a type reasonably relied upon by experts in the medical field when forming opinions." *Id.* at 9 (citing *Glaser v. Thompson Medical Co., Inc.*, 32 F.3d 969 (6th Cir. 1994) (where the article and studies relied upon by the experts were "not definitive or conclusive," but they were data upon which medical experts

reasonably rely on a daily basis). Thus, the court held that the trial court did not abuse its discretion by permitting them to form opinions based on this information. *Id.*

b. The Kentucky Court of Appeals held that "legal causation may be established by such circumstantial evidence as would permit a jury to reasonably infer that the drug was a legal cause of the plaintiff's injury." *Id.* at 4.

c. The Kentucky Court of Appeals determined that *Daubert* was not controlling in this case and applied Kentucky Rule of Evidence 702. *Id.* at 6. In applying that rule, the court concluded that the experts' scientific testimony assisted the jury in determining the cause of plaintiff's stroke, the experts were qualified, and their opinions were scientifically reliable. *Id.* at 6-7.

IV. 11th CIRCUIT APPEAL OF *SIHARATH / RIDER*:

A. Brief of Plaintiffs-Appellants

1. Plaintiffs-Appellants contend that the standard of review for the district court's exclusion of evidence is *de novo* because the district court misapplied *Daubert*. *See* Brief of Plaintiffs-Appellants at 15. *Compare General Electric v. Joiner*, 522 U.S. 136, 141 (1997) ("abuse of discretion is the proper standard of review of a district court's evidentiary rulings.").

2. With respect to the merits, Plaintiffs-Appellants first argue that the district court established a "statistics plus a checklist" standard for the admissibility of expert testimony regarding medical causation, which standard is beyond what science requires and contrary to the law. *See* Brief of Plaintiffs-Appellants at 17-18, 28-32.

a. According to Plaintiffs-Appellants, the *Daubert* Trilogy requires only that an expert provide "an empirically supported rational explanation within the bounds of normal scientific discourse." *Id.* at 21.

b. Plaintiffs-Appellants allege that their experts satisfied the *Daubert* standard by relying on empirical evidence in the form of: i) dechallenge / rechallenge tests on ten patients; ii) the ERI epidemiological study showing a relative risk of 8.4; iii) animal studies showing that bromocriptine can cause either vasodilation or vasoconstriction; iv) case reports; and v) the chemical structure of ergot alkaloids. *See id.* at 25-28 and n.26.

c. In addition, Plaintiffs-Appellants maintain that the district court misapplied the *Daubert* Trilogy when it imposed a "statistics plus a checklist" standard which would require all of the following for admissibility: i) peer-reviewed epidemiological literature; ii) a predictable chemical mechanism; iii) general acceptance of a causal relationship in the scientific literature; iv) a plausible animal model; and v) dozens of well-documented case reports. *See id.* at 17-18, 28-32 (citing *Siharath*, 131 F. Supp.2d at 1370). They emphasize that the scientific method is an untidy and loosely defined process of testing and refinement akin to the piecemeal completion of a crossword puzzle by various scientists. They argue that the

adoption of such a stringent definition of scientific knowledge would have resulted in the rejection of the work of Galileo, Newton, Einstein and Benjamin Franklin. *See* Brief of Plaintiffs-Appellants at 29-32. It also would require greater intellectual rigor from scientists in the courtroom than they apply in their daily practices, contrary to the requirements of *Kumho Tire*.

3. Plaintiffs-Appellants next argue that reversal is appropriate even under a less stringent standard of review because the district court abused its discretion by making fundamental mistakes about the facts. *See* Brief of Plaintiffs-Appellants at 33-42.

a. Plaintiffs-Appellants take issue with the district court's conclusion that "Plaintiffs have not pointed to a single case report involving a postpartum woman who suffered a hemorrhagic stroke." *Siharath*, 131 F. Supp.2d at 1361. They cite five published reports of such events, some of which covered more than one case. They also point out that at least one FDA scientist concluded in 1985 that Parlodel® causes stroke. *See* Brief of Plaintiffs-Appellants at 34.

b. According to Plaintiffs-Appellants, the district court also abused its discretion by concluding that the epidemiological evidence either shows no relationship or a negative relationship between Parlodel® and stroke. Although they acknowledge that it is not statistically significant, they emphasize that the relative risk yielded in the ERI Study was 8.4 and that the other studies were not conducted under appropriate controls. Thus, they argue that the epidemiological evidence "does not point away from causation," as the district court found, but rather is either "indeterminate or perhaps a weak indication of causation." *Id.* at 38.

c. Plaintiffs-Appellants also contend that the district court ignored seven reports of rechallenge / dechallenge testing in a total of ten patients, five of whom were postpartum. They maintain that these data demonstrate that bromocriptine causes vasoconstriction. *See id.* at 39-42.

4. Lastly, Plaintiffs-Appellants imply that the district court abused its discretion by "preferentially relying on exclusionary precedent" from other Parlodel® cases excluding expert testimony. *See id.* at 43. They argue that the court's reliance on earlier Parlodel® cases failed to recognize that "lawyers working on a new kind of toxic tort litigation can take several cases and several years to learn about the science and how to present it to a judge or jury." *Id.* They also emphasize that "the reasons for avoiding a rush to judgment are especially compelling in the Parlodel[®] litigation because epidemiology . . . simply cannot provide an answer." *Id.* at 48.

B. Amicus Brief of Margaret A. Berger and Jerome P. Kassirer

1. Margaret A. Berger teaches evidence, civil procedure, science and the law, and toxic torts at Brooklyn Law School. From 1993 to 1996, she was the Reporter for the Advisory Committee on the Rules of Evidence. She has authored chapters in both editions of the Federal Judicial Center's *Reference Manual on Scientific Evidence*. *See* Amicus Brief of Prof. Margaret Berger and Dr. Jerome Kassirer at 1-2.

2. Dr. Jerome P. Kassirer is a Distinguished Professor at Tufts University School of Medicine and a Professor Adjunct of Medicine at the Yale University School of Medicine. He teaches clinical reasoning at both institutions and co-authored a leading textbook on that subject. From 1991 to 1999, he was the Editor-in-Chief of the *New England Journal of Medicine*. *See id.* at 2.

3. In describing their interest in the case, Professor Berger and Dr. Kassirer state that they "venture no opinion on whether Parlodel[®] does cause strokes," but believe that the trial court "misconceived its role" by deciding causation in a *Daubert* hearing, instead of leaving the causation question for the jury. *See id.* at 5-6. They argue that the test the trial court applied for admissibility in a toxic tort case "would have the effect of making it virtually impossible for any plaintiff to overcome the causation hurdle." *Id.* at 6. The brief does not indicate whether Professor Berger and Dr. Kassirer are being compensated.

4. Professor Berger and Dr. Kassirer first argue that the district court applied a formula to decide the question of admissibility, and in so doing, both misinterpreted the *Daubert* Trilogy and failed to grasp "how the medical community would undertake a causality assessment under the circumstances in these cases." *See id.* at 5.

a. The legal premise of this syllogism is the uncontroversial notion that the *Daubert* Trilogy makes clear there is no legal formula for determining the admissibility of expert evidence. The overriding principle is merely that the proffered expert address the particular issue "with the same intellectual rigor that an expert in the relevant field would use . . . ." *Id.* at 11-12.

b. The scientific premise of this syllogism is that there is no scientific formula within the medical community for determining whether a potentially toxic substance causes an observed medical condition. According to Professor Berger and Dr. Kassirer, the determination of medical causation can depend upon a multitude of factors, such as biology, chemistry, temporal connection, the gravity of the medical condition, dechallenge and rechallenge tests, differential diagnoses, animal studies and statistical data. *See id.* at 13-15. Although they recognize the strength of epidemiological studies and the fact that doctors rely heavily on such studies in toxicity cases, they emphasize that the availability and usefulness of human epidemiological studies is limited. Accordingly, they argue that "[p]hysicians try to incorporate *any* reliable data that seem to bear on a possible causal relationship" into their clinical decision-making. *See id.* at 16 (emphasis in original).

c. The conclusion of Professor Berger's and Dr. Kassirer's syllogism is that the trial court erred by deciding the admissibility of the proffered evidence using a formula, instead of determining how the medical community would make such a determination. According to Professor Berger and Dr. Kassirer, the district court erroneously "equate[d] proof of general causation with epidemiology," *id.* at 18, and in so doing, ignored *Kumho Tire's* admonition about matching "'certain kinds of questions to certain kinds of experts.'" *Id.* at 18 (quoting *Kumho Tire*). The testimony of Plaintiffs'-Appellants' experts is admissible, they argue, because the experts considered some kinds of evidence medical experts would use in a

clinical setting to determine causation: epidemiological and toxicological evidence, case reports, and dechallenge / rechallenge tests. *Id.* at 20.

5. Professor Berger and Dr. Kassirer also argue that the district court confused the issues of admissibility and sufficiency of the evidence and imposed a stringent scientific standard of proof that is higher than the preponderance of the evidence.

a. Professor Berger and Dr. Kassirer contend that the district court conflated the sufficiency of the evidence standard with the admissibility standard when it required the Plaintiffs-Appellants to produce evidence that would allow a reasonable jury to find general and specific causation to a reasonable degree of medical certainty. *See id.* at 22-25; *see also Siharath*, 131 F. Supp.2d at 1352. They argue that the court should have first determined whether the proffered evidence was admissible and then determined if it was sufficient to establish general causation, not vice versa. In proceeding otherwise, they argue, the district court evaded the summary judgment standard and acted as fact finder instead of gatekeeper, thereby violating the Seventh Amendment right to a jury trial. *See id.* at 23-24.

b. In addition, Professor Berger and Dr. Kassirer argue that the December 2000 amendments to Rule 702 do not impose a sufficiency standard for admissibility because those amendments were adopted by a rule-making process and therefore must be construed narrowly. *See* Fed. R. Evid. 702 (allowing an expert to testify "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"). To construe the amendments otherwise would work "a shift in the existing balance of power between plaintiffs and defendants, and a curtailment of the right to trial by jury." *See* Amicus Brief of Berger-Kassirer at 27.

c. Lastly, Professor Berger and Dr. Kassirer maintain the district court's requirement that scientific evidence of general causation be more than inconclusive is much higher than the preponderance of the evidence standard. In other words, they argue that by requiring the plaintiffs to satisfy the scientific standard for conclusive proof, the district court imposed a standard that is "far more demanding than the preponderance of the evidence standard generally applicable in civil litigation." *Id.* at 28.

C. Amicus Brief of Michael D. Green and Sander Greenland

1. Michael D. Green is a professor of law at Wake Forest University. He is a co-author of the epidemiology chapter in the Federal Judicial Center's *Reference Manual on Scientific Evidence* (2d ed. 2000), and a co-Reporter for the American Law Institute's *Restatement (Third) of Torts: Liability for Personal Harm (Basic Principles)*. *See* Amicus Brief of Green-Greenland at 1.

2. Sander Greenland is a professor of epidemiology at UCLA School of Public Health, a professor of statistics at UCLA College of Letters and Science, and research professor of preventive medicine at UCLA School of Medicine. He is the co-author of one of the

leading texts on epidemiology and author or co-author of 230 peer-reviewed epidemiologic and statistical articles. *See id.*

3. In describing their interest in the case, Professors Green and Greenland point out that they are not being compensated for preparing their brief. Their interest is in "having courts understand the appropriate role of epidemiology in lawsuits in which the causal role of an agent is at issue." *See id.* at 1-2. They "only seek to urge certain scientific and legal principles be employed by this Court in deciding this appeal." *Id.*

4. Professors Green and Greenland criticize the district court for adopting a standard that either requires epidemiological evidence in toxic tort cases as a threshold matter or, at a minimum, raises the bar for proof of general causation in the absence of epidemiological evidence. They argue that because toxic agents differ, the evidence required to prove causation by various toxic agents must be flexible. *See id.* at 6-15.

a. According to Professors Green and Greenland, an understanding of how the biological mechanisms of an agent operate on the human body is sufficient evidence of medical causation (e.g., a bloody nose may be caused by a punch). In the case of toxic agents, however, the biological mechanisms by which varying diseases occur are rarely well enough understood to play a substantial role in proof of causation. *See id.* at 6-7.

b. Professors Green and Greenland recognize that where a substantial body of epidemiological evidence exists, it is often the best evidence of general causation (e.g., Benedictin, breast implant, asbestos and DES litigation). *See id.* at 7-9. Nevertheless, they also recognize potentially enormous impediments in the development of epidemiological evidence, such as the rarity of certain conditions or diseases, the ethical issues that can arise in exposing subjects to potentially toxic agents, and the time and expense required to conduct a valid epidemiological study. *See id.* at 5, 10-11.

c. Accordingly, they contend that where epidemiological evidence is understandably absent, courts should consider other evidence of causation without skepticism based upon the absence of epidemiological evidence. *See id.* at 14-15.

5. Professors Green and Greenland next argue that because epidemiological evidence is understandably absent in the case of Parlodel®, courts should consider other evidence of causation, including case reports, dechallenge / rechallenge tests, biological mechanism evidence, chemistry and animal toxicology studies. *See id.* at 15-21.

a. Professors Green and Greenland acknowledge the limited probity of animal toxicology studies where a substantial body of epidemiology exists. They argue, however, that because of the absence of epidemiological evidence, the district court should have more carefully assessed the probative value of the bromocriptine animal studies, rather than summarily dismissing them on the basis of case law from the Benedictin and breast implant litigation, where substantial epidemiological evidence existed. *See id.* at 16-18.

b. Similarly, Professors Green and Greenland recognize that as a general matter, case reports are not sufficient to establish general causation. *See id.* at 18. They maintain, however, that in unusual circumstances, case reports can have "considerable saliency in proving causation." *Id.* at 19. The unusual circumstances that might make case reports probative include cases where there is an acute reaction to a toxic agent as opposed to a latent reaction, where there are few competing causes (e.g., because the disease is rare) and where the proportion of case reports to the population exposed is substantial. *See id.* Several of these circumstances are present in the Parlodel® litigation.

D. Amicus Brief of Howard Kipen and Daniel Wartenberg

1. Howard Kipen, M.D., M.P.H., is Professor and Acting Chair of the Department of Environmental & Community Medicine at the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School. He is a co-author of the chapter "Reference Guide on Medical Testimony" in the current edition of the Federal Judicial Center's *Reference Manual on Scientific Evidence*. He has also authored over 100 scientific articles on topics including epidemiological and clinical exposures including asbestos, benzene and the Gulf War syndrome. *See* Amicus Brief of Kipen-Wartenberg at 1.

2. Daniel Wartenberg, Ph.D., is a Professor in the Department of Environmental & Community Medicine at the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School. He has authored over 100 scientific articles on topics including nuclear workers, Gulf War syndrome and various other toxic exposures. *See id.* at 1-2.

3. In describing their interest in this case, Drs. Kipen and Wartenberg state that they "are concerned about this case because they believe it represents a departure from how medicine and science actually determine causation in toxic exposure situations." *Id.* at 2. Neither they nor their counsel are being compensated for their work in this case. *See id.* at 2-3.

4. Drs. Kipen and Wartenberg first argue that the district court's decision is premised upon a mistaken view of the certainty involved in causation decisions in the scientific and medical fields. They emphasize that it is extremely rare to have definitive scientific proof of causation, that there is no formula for determining causation, and that doctors and scientists routinely make critical judgments regarding causation based upon a variety of data sources and fields of expertise. Thus, while the scientific evidence could lead to varying conclusions regarding the alleged causal relationship between Parlodel® and postpartum stroke, the conclusions offered by Plaintiffs'-Appellants' experts are based on exactly the type of information and offered to the level of certainty that is typical in the medical and scientific communities. *See id.* at 6-9.

5. Drs. Kipen and Wartenberg also argue that the district court made several specific errors in its evaluation of the scientific evidence.

a. First, they contend that the district court ignored powerful evidence in the form of dechallenge / rechallenge tests. They maintain that these tests are analogous to

controlled laboratory experiments and are in many ways superior to epidemiological studies because they eliminate many types of bias and confounding. *See id.* at 9-11.

b. Second, they argue that the district court gave the case reports short shrift. Although they acknowledge that individual case reports have limited value in determining causation, they maintain that a significant number of case reports, as in this instance, should be given substantial weight until the causal associations they depict are called into question by epidemiological or other evidence. *See id.* at 11.

c. Lastly, Drs. Kipen and Wartenberg assert that the district court misinterpreted the epidemiologic evidence. Like the Plaintiffs-Appellants, they emphasize that that the only true epidemiological study yielded a relative risk of 8.4. Thus, they argue that the epidemiology points toward rather than away from causation. *See id.* at 12.

E. Brief of Defendants-Appellees

1. As an initial matter, SPC maintains that the trial court's decision may only be reversed for an abuse of discretion. *See* Brief of Defendants-Appellees at 10. It emphasizes that the deferential abuse of discretion standard "'applies as much to the trial court's decisions about how to determine reliability as to its ultimate conclusion.'" *Id.* at 10 (quoting *Joiner*, 522 U.S. at 141-43).

2. SPC argues as a general matter that the district court properly exercised its discretion as gatekeeper in finding that the Plaintiffs-Appellants failed to carry their burden of proving the reliability and relevance of their experts' testimony.

a. First, SPC argues that the district court did not abuse its discretion because it provided ample support for its determination that the contested evidence was not reliable. *See* Brief of Defendants-Appellees at 17-18.

i. The court considered the reliability factors set forth in *Daubert* and concluded that "plaintiffs' theory is largely untested and without peer review, '[t]he rate of error is unknown,' and '[t]he theory has not attained general acceptance within the scientific community.'" *Id.* at 17 (*quoting Siharath*, 131 F. Supp.2d at 1355-56; *see also Glastetter*, 107 F. Supp.2d at 1045 n.28.

ii. The court also found the experts' methodology unreliable due to unjustified reliance on anecdotal case reports, unexplained disregard for chemical dissimilarities and improper extrapolation of animal studies. *See id.* at 17-18.

b. Second, SPC argues that the district court properly found that the data, such as the results of animal studies, cited by plaintiffs' experts was not relevant because it did not "fit" the plaintiffs' causation theory. *See id.* at 18; *Siharath,* 131 F. Supp.2d at 1363-65, 1367. Specifically, the district court determined that

> [t]hree scientifically unwarranted 'leaps of faith' exist in [plaintiffs'] causal chain. First, a serious question exists whether bromocriptine is like other ergot alkaloids since it generally causes hypotension rather than hypertension. Second, even if Parlodel® can occasionally cause hypertension, Plaintiffs have not established that it can cause hypertension so severe as to cause seizures and stroke in humans. Third, even if Parlodel® can cause hypertension severe enough to cause stroke in humans, Plaintiffs have not shown that it causes hemorrhagic stroke. … In this case, 'there is simply too great an analytical gap between the data and the opinion proffered.'

Siharath, 131 F. Supp.2d at 1371 (*quoting Joiner*, 522 U.S. at 146).

3. SPC also argues that the district court did not abuse its discretion given the consistency of its opinion with other Parlodel® cases. Noting the Eighth Circuit's decision and the majority of district court opinions that have excluded similar evidence in Parlodel® cases, SPC argues that "the fact 'that other courts, after thoroughly sifting through the scientific data, have come to the same decision, and indeed have even excluded some of the same experts as the district court did here in the exercise of its gatekeeping role [is] an indication that the district court was not operating on the outer fringe of its discretion.'" Brief of Defendants-Appellees at 22 (quoting *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1311 (11th Cir. 1999) (breast implant litigation)).

4. On a more detailed level, SPC argues that the district court was well within its discretion in finding that the contested experts' reliance on case reports, chemical analogies and animal studies did not satisfy *Daubert*. *See* Brief of Defendants-Appellees at 23-46.

a. **Case Reports:** SPC provides several reasons supporting its contention that the district court correctly concluded that anecdotal case reports were "of doubtful validity" in this case. *See id.* at 24 (citing *Siharath*, 131 F. Supp.2d at 1361).

i. First, the Eighth Circuit in the Parlodel® litigation has found that case reports do not constitute scientifically valid proof of causation:

> Much of the evidence relied upon by Drs. Kulig and Petro has been culled from case reports in which doctors reported patient strokes following their ingestion of Parlodel. A case report is simply a doctor's account of a particular patient's reaction to a drug or other stimulus, accompanied by a description of the relevant surrounding circumstances. Case reports make little attempt to screen out alternative causes for a patient's condition. They frequently lack analysis. And they often omit relevant facts about the patient's condition. Hence, '[c]ausal attribution based on case studies must be regarded with caution.' (citation omitted). Though case reports demonstrate a temporal association between

> Parlodel and stroke, or stroke-precursors, that association is not scientifically valid proof of causation.

Id. at 25 (quoting *Glastetter*, 252 F.3d at 989-90 and citing *Brumbaugh*, 77 F. Supp.2d at 1156 (Parlodel® case reports "do not contain a testable and systematic inquiry into the mechanism of causation…")).

ii. Second, plaintiffs own experts had previously acknowledged that case reports do not establish general causation. *See* Brief of Defendants-Appellees at 26-28.

iii. Third, given that "[f]rom 1980 to 1994, millions of women took Parlodel®[,] [t]he modest number of case reports associating the drug with stroke or even postpartum hypertension is not what would be expected." Brief of Defendants-Appellees at 27 (quoting *Siharath*, 131 F. Supp.2d at 1361).

iv. Fourth, many of the case reports relied upon were not reports of patients with hemorrhagic stroke. *See* Brief of Defendants-Appellees at 29 (citing *Siharath*, 131 F. Supp.2d at 1361, 1363 (discussing heart attack and noting absence of scientific support in the record for its relationship to stroke)).

v. Fifth, contrary to Plaintiffs' assertion on appeal, the district court did not ignore plaintiffs' "dechallenge" and "rechallenge" case report data. In fact, the court specifically held that defendants "effectively discredited these additional case reports as evidence of a relationship between Parlodel® and postpartum stroke." Brief of Defendants-Appellees at 30 (quoting *Siharath*, 131 F. Supp.2d at 1361). This conclusion was not an abuse of discretion. Indeed, the Eighth Circuit also rejected the dechallenge / rechallenge reports on the grounds that they are statistically insignificant and involve artery spasms and heart attacks, as distinct from hemorrhagic strokes. *See* Brief of Defendants-Appellees at 32-33.

vi. Sixth, SPC takes issue with the plaintiffs assertion that the trial court ignored at least five published case reports of postpartum hemorrhagic strokes. SPC emphasizes that four of these five reports were authored by a former Parlodel® expert whose opinions were excluded in another case and that the fifth report did not involve a hemorrhagic stroke. *See id.* at 33-34.

vii. Seventh, the FDA advises against relying on case reports to determine causation. *See id.* at 34. Moreover, the FDA never concluded that bromocriptine causes seizure and stroke. *See id.* at 35 (citing *Siharath*, 131 F. Supp.2d at 1366). Indeed, the current FDA-approved Parlodel® package insert states that a cause-and-effect relationship between Parlodel® and stroke has not been established. *See* Brief of Defendants-Appellees at 36 (citations omitted).

viii. Lastly, SPC argues that the "strong epidemiological evidence that pregnancy itself is a strong risk factor for stroke" also justifies the district court's rejection of case reports. *See id.* at 36-37 (quoting *Siharath*, 131 F. Supp.2d at 1363).

b. **Chemical Analogies:** SPC also provides several reasons supporting the conclusion that the expert testimony "extending general conclusions about similar drugs does not meet *Daubert*'s requirements of reliability." Brief of Defendants-Appellees at 38 (quoting *Siharath*, 131 F. Supp.2d at 1363-64).

i. For instance, "bromocriptine differs physically from other ergot alkaloids," and "Plaintiffs' experts in this case cannot show that bromocriptine, the active ingredient in Parlodel®, affects the body in a manner similar to other ergot alkaloids." Brief of Defendants-Appellees at 38-39 (quoting *Siharath*, 131 F. Supp.2d at 1363-64) (other citations omitted). Even plaintiffs' experts recognize that just because bromocriptine is an ergot alkaloid does not mean that it causes vasoconstriction. *See* Brief of Defendants-Appellees at 39-40.

ii. In addition, a leading treatise on medical toxicology recognized by plaintiffs' experts indicates that the vasoconstrictive property of bromocriptine is zero. *See id.* at 40.

iii. Furthermore, in rejecting the chemical analogies, the district court followed ample post-*Daubert* precedent for the proposition that "'[s]mall differences in molecular structure often have significant consequences.'" *See id.* at. 41 (quoting *Siharath*, 131 F. Supp.2d at 1364 (*citing Schudel v. General Electric Co.*, 120 F.3d 991, 996-97 (9th Cir. 1997), *cert. denied*, 523 U.S. 1094 (1998))).

iv. In addition, plaintiffs' own expert admitted that "no epidemiology or even learned treatises link [any] ergot alkaloids to hemorrhagic strokes." Brief of Defendants-Appellees at 42 (quoting *Siharath*, 131 F. Supp.2d at 1365).

c. **Animal Studies:** SPC argues that the district court properly found that "the animal studies upon which plaintiffs' experts relied were so dissimilar to the facts of this case, and the experts' proposed extrapolations were so speculative, that the studies could not offer relevant or reliable support for their opinions." Brief of Defendants-Appellees at 43 (citing *Siharath*, 131 F. Supp.2d at 1366-69).

i. Plaintiffs' experts did not cite any studies showing that bromocriptine causes stroke, and they could not state that Parlodel® caused hypertension in animals. *See* Brief of Defendants-Appellees at 44 (citations omitted).

ii. As the Eighth Circuit has held and plaintiffs' experts admitted, it is difficult to extrapolate reliably from the results of studies on small animals to effects on humans. *See id.* at 45-46 (citing *Glastetter*, 252 F.3d at 991).

5. SPC counters the argument of Plaintiffs-Appellants that the district court should have viewed the totality of the evidence instead of dissecting each piece with quotes from one of the contested experts indicating that each element of proof must have individual validity and warning against "'lumping together several pieces of evidence which are equally hollow so

that together they hide one another's fundamental deficiencies.'" *See* Brief of Defendants-Appellants at 46-47.

6. Lastly, SPC asserts that there is no merit to the claim of Plaintiffs-Appellants that the district court imposed an absolute epidemiology requirement, a "statistics plus a checklist" requirement, or any other requirement other than reliability and relevance. *See id.* at 50. Accordingly, SPC argues, the district court did not abuse its discretion. *See id.* at 55.

a. SPC emphasizes that the plaintiff's experts did not and cannot rely on epidemiology to support their opinions and failed to cite any study showing an increase or decrease in the incidence of postpartum stroke relative to Parlodel®. While it does not contend that such evidence is a requirement to prove causation, SPC argues that the non-existence of such scientific studies is surely "a factor that a court should consider in assessing the reliability of expert opinions on causation, as *Daubert* makes clear." *Id.* at 51-52.

b. SPC also takes issue with the argument of Plaintiffs-Appellants that the district court misinterpreted the existing epidemiological evidence. It maintains that the epidemiological evidence consisted of three studies where no positive causal relationship was found and one study that tended to show a negative relationship between Parlodel® and stroke. *See id.* at 53 n.40.

c. SPC also notes that the district court explicitly held that "'[e]pidemiological evidence is *not* the only legally sufficient proof for establishing a *prima facie* case of medical causation.'" *Id.* at 53-54 (*quoting Siharath*, 131 F. Supp.2d at 1358); *see also Siharath*, 131 F. Supp.2d at 1358 (lack of epidemiological support "is not automatically fatal to Plaintiffs[']s case"). It then examined the other types of causation evidence proffered by the plaintiffs and found that none of them were sufficiently reliable or relevant to be admissible. *See* Brief of Defendants-Appellees at 54-55 (*citing Siharath*, 131 F. Supp.2d at 1370).

F. Reply Brief of Plaintiffs-Appellants

1. In their Reply Brief, Plaintiffs-Appellants first attempt to distinguish the present cases from other toxic tort cases and other Parlodel® cases relied upon by SPC. Specifically, they argue that these cases are distinguishable from *Joiner* because the contested experts did not attempt to infer causation directly from animal and epidemiological studies, but rather explained their inference of causation from a multitude of data sources. Similarly, they distinguish the breast implant litigation, in which there existed a substantial body of negative epidemiological evidence. They also highlight differences between the proffered evidence in these cases and the earlier Parlodel® cases relied upon by SPC. *See* Reply Brief of Plaintiffs-Appellants at 4-8.

2. Plaintiffs-Appellants next argue that the present cases are distinguishable "because the court was so explicit in its errors." *See id.* at 8. In particular, they maintain that the district court erred by:

a. Saying it was not requiring epidemiology and then making it clear that it was really requiring epidemiology plus chemical evidence, general acceptance, a plausible animal model and dozens of well-documented case reports;

b. Finding negative epidemiology in the absence of a valid study showing a negative relationship;

c. Ignoring the difference between dechallenge / rechallenge tests and ordinary case reports; and

d. Completely failing to mention important pieces of evidence. *See id.* at 8-9.

3. Plaintiffs-Appellants next argue that the central scientific issue is whether Parlodel® causes vasoconstriction, not whether vasoconstriction causes hemorrhagic stroke, as SPC argues. They maintain that the Eighth Circuit's opinion in *Glastetter*, 252 F.3d at 989, recognizes that vasoconstriction can cause either ischemic stroke or hemorrhagic stroke. *See* Reply Brief of Plaintiffs-Appellants at 16. Thus, according to Plaintiffs-Appellants, all they need to prove in these cases is that Parlodel® causes vasoconstriction. They maintain that this burden is satisfied because the drug does cause vasoconstriction where there is low vascular resistance, as is typical in postpartum women. *See id.* at 14.

4. Finally, Plaintiffs-Appellants contend that the district court either ignored or misinterpreted the proffered causation evidence. *See id.* at 17-33.

a. The few citations to a small part of the record are evidence that the district court failed to properly consider at least four specific pieces of dechallenge / rechallenge tests, as well as objective medical tests measuring vasoconstriction. *See id.* at 17-20

b. Plaintiffs-Appellants also contend that their experts did not cite animal studies as direct evidence of causation, as the district court thought, but rather as evidence that bromocriptine can cause either vasodilation or vasoconstriction. *See id.* at 22-23.

c. Similarly, Plaintiffs-Appellants maintain that their experts did not rely upon chemical analogies to directly infer causation, as the district court believed, but only to demonstrate that bromocriptine was suspect for vasoconstriction because it is an ergot alkaloid. They also cite a later edition of the medical toxicology treatise cited by SPC that lists bromocriptine as a hypertensive agent and notes postpartum stroke symptoms possibly associated with the drug. *See id.* at 23-24.

d. Plaintiffs-Appellants explain that the paucity of case reports is due to the relative rarity of postpartum stroke, the same reason that explains the lack of epidemiological evidence. *See id.* at 25-27.

e. Lastly, Plaintiffs-Appellants reiterate that the epidemiological evidence does not point away from causation, as SPC contends and the district court found.

They highlight the fact that the one study that found a negative relationship between Parlodel® and stroke was withdrawn from publication. Of the remaining three studies, one showed a statistically insignificant positive relationship between the drug and strokes. *See id.* at 28-30. Thus, Plaintiffs-Appellants contend, the epidemiological evidence "points weakly toward causation, not away from it." *Id.* at 30.

V. SIGNIFICANCE OF PARLODEL® LITIGATION TO PHARMACEUTICAL DEFENSE COUNSEL

A. Demonstrates That Most Lower Courts Are Taking Their Gatekeeping Responsibilities Seriously

1. In *Joiner* and *Kumho Tire*, the Court engaged in detailed analyses of the proffered expert evidence. *See Joiner*, 522 U.S. at 143-147; *Kumho Tire*, 526 U.S. at 153-58. The level of detail in *Joiner* and *Kumho Tire* illustrates the importance getting specific when assessing the reliability and relevance of shaky expert testimony. *See, e.g.*, Carr, Dabney J. *et al.*, "After *Kumho Tire*: Challenging Non-Scientific Experts," 41 *For the Defense* 12, 50-51 (Defense Research Institute 1999) (emphasizing the need to sell the importance of the gatekeeping responsibility, to identify the specific opinion proffered and to engage in a detailed *Daubert* analysis of the expert's method in arriving at the contested opinion).

2. The Parlodel® litigation demonstrates that for the most part, lower courts are taking the Supreme Court's examples in *Joiner* and *Kumho Tire* to heart and carefully examining proffered expert testimony, in keeping with their important gatekeeping responsibilities. *See supra* § III.

3. Accordingly, counsel owe it to their clients to vigilantly and proactively assess the reliability and relevance of proffered expert testimony.

B. Reveals A Determined And Organized Attempt By Plaintiffs' Bar To Minimize/Eliminate Significance Of Epidemiological Evidence In Toxic Exposure Cases

1. Undeterred by an unsuccessful appeal of the exclusion of the contested evidence in the Eighth Circuit in *Glastetter*, 252 F.3d 986, plaintiffs are pursuing appeals of two district court opinions excluding the same evidence in both the Tenth and Eleventh Circuits. *See Hollander*, 95 F. Supp.2d 1230 and *Siharath*, 131 F. Supp.2d 1347.

2. The thrust of plaintiffs' arguments on appeal is that the district court applied too stringent a standard because it emphasized the lack of epidemiological evidence, and was skeptical of the other proffered evidence of general causation in light of the lack of epidemiological evidence. *See supra* § IV; *see also, e.g.*, Reply Brief of Plaintiffs-Appellants at 8-9 (district court said it was not requiring epidemiology but really was requiring epidemiological evidence plus additional scientific evidence). In short, plaintiffs argue against any standard that emphasizes epidemiological and other objective evidence and advocate instead

a standard that allows general causation to be determined on the basis of more subjective evidence frequently relied upon within the medical community. *See supra* § IV; *see also, e.g.*, Brief of Plaintiffs-Appellants at 25-28 and n.26. Needless to say, the resolution of this issue could have far-reaching effects in toxic exposure cases.

3. The *Siharath* appeal currently pending in the Eleventh Circuit has captured the attention of distinguished legal and medical scholars, as evidenced by the three *Amicus Curiae* briefs filed in support of the Plaintiffs-Appellants. The *Amicus* briefs were filed by two law professors and a professor of medicine who have authored parts of the Federal Judicial Center's *Reference Manual on Scientific Evidence*, and three other distinguished professors of medicine, one of whom served as Editor-in-Chief of the *New England Journal of Medicine* from 1991 through 1999. *See supra* § IV.

4. Furthermore, the *Amicus Curiae* Briefs, like the Briefs of Plaintiffs-Appellants, decry the use of any formula in determining the admissibility of expert testimony and advocate instead the use of a more subjective standard. *See* Amicus Brief of Berger-Kassirer at 15-18 (advocating a standard that would admit *any* reliable data that seem to bear on a causal relationship); Amicus Brief of Green-Greenland at 6-15 (evidence required to prove causation by various toxic agents must be flexible); Amicus Brief of Kipen-Wartenberg at 6-9 (no formula for determining causation in science).

C. Includes An Invitation By Plaintiffs' Bar To Retreat From The Abuse Of Discretion Standard Established In *Joiner*

1. In the Eleventh Circuit appeal of *Siharath*, the Plaintiffs-Appellants argue that the standard of review is *de novo* because the district court misinterpreted the *Daubert* Trilogy. *See infra* § IV.A.

2. If accepted, this argument would represent a definite retreat from *Joiner*'s holding that "abuse of discretion is the proper standard by which to review a district court's decision to admit or exclude scientific evidence." *See Joiner*, 522 U.S. at 146.

3. This argument is also significant because virtually any appeal of a district court decision regarding the admissibility of expert evidence could be couched as a misinterpretation of the *Daubert* Trilogy. Thus, if accepted, this argument could result in a sea change in the degree of deference accorded trial court decisions in this area of the law.

D. Demonstrates The High-Stakes Nature Of The Expert Wars In Pharmaceutical Litigation

1. The Parlodel® litigation also provides a compelling example of the high-stakes nature of the expert wars in pharmaceutical litigation. In *Siharath*, for instance, SPC offered testimony from three of its experts in the course of a three-day *Daubert* hearing regarding the exclusion of five of plaintiffs' experts. *See Siharath*, 131 F. Supp.2d at 1348-1354. Preparations for this hearing – undoubtedly including at least written discovery, fact depositions,

expert depositions, briefs and argument – obviously required tremendous expense on the part of the litigants.

E. Exemplifies The Elements Of An Effective Defense In A Pharmaceutical Case

1. The Parlodel® litigation also serves as an example of how to effectively defend causation issues in pharmaceutical litigation.

a. Where plaintiffs lack epidemiological evidence, defense counsel should vigorously challenge the reliability and relevance of plaintiffs' other causation evidence, such as case reports, animal studies and chemical analogies. *See supra* § IV.

b. If plaintiffs present an epidemiological study in support of causation, defense counsel should: (1) analyze the strength or weakness of the association and argue that an association between an agent and a disease is not causation; (2) analyze whether the epidemiologist studied groups or populations that are not comparable; (3) examine the possibility for error, including chance or sampling error, selection and/or information bias and the presence of confounding factors; (4) assess the statistical significance and confidence interval of the study; (5) consider alternative explanations for the alleged association; and (6) determine whether the results have been replicated or disputed. *See* Green, Michael D., et al., "Reference Guide on Epidemiology", *Reference Manual on Scientific Evidence*, (2d ed. 2000) at 348-377.

c. Negative epidemiological evidence is particularly persuasive to courts. *See, e.g.*, Amicus Brief of Green-Greenland at 8-9 (negative epidemiological evidence in Benedictin and breast implant cases persuasive); *see also* Reply Brief of Plaintiffs-Appellants at 5-6 (noting significance of negative epidemiological evidence in silicone breast implant litigation). Accordingly, defense counsel should obviously locate any epidemiological evidence supporting the defendant's causation theory.

VI. APPENDIX

A. Strokes

1. Neurologists generally classify strokes as "ischemic (lack of blood to brain and tissue death) or hemorrhagic (bleeding within the brain)." Brief of Defendants-Appellees at 6. Hemorrhagic strokes are classified as subarachnoid hemorrhage ("SAH") or intracerebral hemorrhage ("ICH"). *See id.* at 2, 6.

2. Strokes may affect both sexes and all ages. *See id.* at 6 (citation omitted). "The cause is unknown in one-third or more cases." *Id.* (citing Kittner, et al., "Cerebral Infarction in Young Adults," 50 *Neurology* 890-94 (1998) (in 50.5% of cases, no probable cause of stroke could be identified by neurologists)). Postpartum women have an increased risk of hemorrhagic stroke. Brief of Defendants-Appellees at 7 (citations omitted).

B. Epidemiology

1. "Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals." Green, Michael D., et al., "Reference Guide on Epidemiology", *Reference Manual on Scientific Evidence* 335 (2d ed. 2000).

2. Among the primary objectives of epidemiology are: a) identifying factors that increase the risk of disease; b) understanding the incidence rate of a disease in a given period of time; c) determining the number of cases of a disease at a given time; d) determining how long it takes a disease to develop; e) evaluating the efficacy of new therapies, such as drugs; and f) assisting in the regulation of environmental factors affecting the rate at which a disease develops and persists. *See* Rogers, James F., "Epidemiology: The Absolute Minimum You Need to Know," *Defense Research Institute Drug & Medical Device Litigation Seminar* Tab 18, at 381 (April 1999) (*citing* Parker, Bruce R., "Understanding Epidemiology and Its Use in Drug and Medical Device Litigation," 65 *Defense Counsel Journal* 35, 35-36 (1998)); *see also* Gordis, Leon, *Epidemiology* 3 (1996).

3. In the context of litigation, "Epidemiology 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?)." Green, "Reference Guide on Epidemiology", at 336.

4. Ultimately, epidemiologists try to determine whether a causal relationship exists between a suspected toxic agent and a disease. *See id.* at 348. A preliminary step in that determination is identifying an association between exposure to an agent and a disease. An association exists when the disease and the exposure exist more frequently than one would expect by mere chance. An association, however, does not necessarily mean that a causal relationship exists between the exposure and the disease. *See id.* at 336 and n.8, 348. The strength of an association between a toxic agent and a disease is described in terms of its "relative risk," which is the ratio of the incidence of the disease in those exposed to the agent to the incidence of the disease in those not exposed to the agent. *See id.* at 348.

5. There are two primary types of studies through which epidemiologists attempt to identify either an association or a causal relationship between an agent and a disease:

a. Case control studies identify individuals with a certain disease and compare that group with an appropriate control group of people who do not have the disease and then look "backward in time to examine all possible causes of the disease." Littlepage, Zoe, "Epidemiology Requirements: A New Burden for the Plaintiffs?," 6 *Mealy's Emerging Drugs & Devices* 20, at 30 (Oct. 18, 2001). In other words, the independent variable in a case control study is whether an individual has a disease. The dependent variable is the individual's exposure to the toxic agent, which is measured in order to determine if there is an association between the agent and the disease. *See* Green, "Reference Guide on Epidemiology" at 338-39.

b. Cohort or incidence studies are prospective studies that identify groups of people and observe them "over time to see if one group is more likely to develop a specific disease." Littlepage, "Epidemiology Requirements: A New Burden for the Plaintiffs?," at 30. In other words, the independent variable in cohort studies is an individual's exposure to a toxic agent, and the dependent variable is the effect of that level of exposure on the incidence of disease. *See* Green, "Reference Guide on Epidemiology" at 338-39.

c. Case reports, i.e., doctor's reports regarding symptoms in a patient or group of patients and potential causes thereof, however, are not epidemiological studies because they do not compare the observed patient group with a control group. *See* Rogers, "Epidemiology: The Absolute Minimum You Need to Know," at 381.

d. Likewise, animal studies are not epidemiological studies because the effects of a toxic agent on animals must be extrapolated to another species, which may yield varying responses due to differences in absorption, metabolism and other factors. In addition, animal studies frequently involve extremely high doses of the toxic agent, which begs the question of whether a threshold no-effect dose exists. *See* Green, "Reference Guide on Epidemiology", at 346; *see also* Rogers, "Epidemiology: The Absolute Minimum You Need to Know," at 381 (*citing* Hayes, *Principles and Methods of Toxicology* 1 (3d ed. 1994)).