United States District Court for the Eastern District of Missouri

Tina M. GLASTETTER and Steven J. Glastetter, Plaintiffs,
v.
NOVARTIS PHARMACEUTICALS CORP., Defendant

No. 1 :97CV00131ERW

Decided Aug. 14, 2000.

Counsel:

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AMENDED MEMORANDUM AND ORDER

WEBBER, District Judge.

This matter is before the Court following a Daubert hearing upon defendant's Motion in Limine to Exclude Plaintiffs' Experts [Document # 170] and defendant's Motion for Summary Judgment [Document # 211]. In both motions, defendant challenges the qualifications of plaintiffs' experts on causation, Dr. Kenneth Kulig and Dr. Denis Petro. Defendant claims that both experts must be excluded, because they do not meet the test of scientific reliability set forth by the Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). If such experts are excluded, defendant claims, plaintiffs' case must fail, because plaintiffs will be unable to present any evidence of causation in this case. In addition, defendant argues that it is entitled to partial summary judgment on plaintiffs' failure to warn claim due to the learned intermediary doctrine. Finally, defendant claims that plaintiffs' claim for punitive damages must fail on the facts of this case. Having considered the arguments advanced by the parties at the hearing, the Court concludes that defendant is entitled to summary judgment, because plaintiffs' evidence of causation fails the test for scientific reliability set forth in Daubert.

I. STANDARDS GOVERNING MOTIONS FOR SUMMARY JUDGMENT.

While defendant styled its initial motion with respect to plaintiffs' experts as a Motion in Limine, defendant seeks summary judgment in the event that its Motion in Limine is granted. Thus, the Court will undertake its analysis in this matter under the standards governing motions for summary judgment. The standards applicable to summary judgment motions are well settled. Pursuant to Federal Rule of Civil Procedure 56(c), a court may grant a motion for summary judgment if all of the information before the court shows "there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law." See Celotex Corp. v. Catrett, 477 U.S. 317, 322, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). The United States Supreme Court has noted that "[s]ummary judgment procedure is properly regarded not as a disfavored procedural shortcut, but rather as an integral part of the federal rules as a whole, which are designed to 'secure the just, speedy and inexpensive determination of every action.' " Id. at 327, 106 S.Ct. 2548 (quoting Fed.R.Civ.P. 1).

In order to obtain summary judgment, the moving party must demonstrate "an absence of evidence to support the non-moving party's case." Celotex, 477 U.S. at 325, 106 S.Ct. 2548. Once the moving party carries this burden, the nonmoving party must "do more than simply show there is some metaphysical doubt as

to the material facts." Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). The non- moving party may not rest on allegations or denials in the pleadings, but "come forward with 'specific facts showing that there is a genuine issue for trial.' " Id. at 587, 106 S.Ct. 1348 (quoting Fed.R.Civ.P. 56(3)).

In analyzing summary judgment motions, the Court is required to view the facts in a light most favorable to the non-moving party, and must give the non- moving party the benefit of any inferences that can logically be drawn from those facts. Matsushita, 475 U.S. at 587, 106 S.Ct. 1348; Buller v. Buechler, 706 F.2d 844, 846 (8th Cir. 1983). Moreover, this Court is required to resolve all conflicts in favor of the non-moving party. Robert Johnson Grain Co. v. Chemical Interchange Co., 541 F.2d 207, 210 (8th Cir.1976). The trial court may not consider the credibility of the witnesses or weigh the evidence. White v. Pence, 961 F.2d 776, 779 (8th Cir. 1992).

II. DISCUSSION.

This case concerns the use of a drug called Parlodel, which has been utilized in the past by some women, like plaintiff Tina Glastetter (Glastetter), for the prevention of postpartum physiological lactation. The plaintiffs in this action, Glastetter and her husband, Steven Glastetter, bring this product liability action against defendant Novartis Pharmaceuticals Corporation ("NPC"), formerly known as Sandoz Pharmaceuticals Corporation, alleging that Glastetter suffered an intracerebral hemorrhage following her ingestion of Parlodel. Glastetter delivered a child on August 2, 1993. On day 13 of a 14-day course of Parlodel drug therapy, she became symptomatic and on August 17, 1993, she was taken to a hospital where she was diagnosed with

an intracerebral hemorrhage. Glastetter was 36 years old at the time of this second cesarian section delivery. Bromocriptine mesylate ("bromocriptine") is Parlodel's active ingredient. Plaintiffs will attempt to establish that Parlodel caused the injury at issue in this case through the testimony of expert witnesses.

At this time, defendant has presented the issue of these witnesses' qualifications to testify under the standards set forth by the Supreme Court in the case of Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). Defendant argues in both its motions that plaintiffs have failed to come forward with sufficient reliable evidence to demonstrate that Glastetter's intracerebral hemorrhage ("ICH") could be and was caused by defendant's drug Parlodel. Defendant claims that plaintiffs' experts admit that their hypotheses have not been tested and validated using the scientific method and that there is no epidemiological evidence supporting their theories. In addition, defendant claims that plaintiffs' experts admit that they rely upon evidence such as case reports,
temporal proximity, animal studies, and inferences based on other drugs to support their hypotheses. Defendant claims such evidence fails under the requirements of Daubert. Also, defendant argues that plaintiffs' experts have no reliable means of ruling out other possible causes of the ICH at issue in this case.

In Daubert, the United States Supreme Court confronted the issue of the proper standard for evaluation of expert testimony by trial judges in light of Federal Rule of Evidence 702. In Daubert, the Supreme Court began by noting that Rule 702 superceded the Frye test, which required courts to exclude all "expert" evidence that was not derived from generally accepted principles or theories. See Jaurequi v. Carter Manuf. Co., Inc., 173 F.3d 1076, 1081 (8th Cir.1999) (citing Frye v. United States, 293 F. 1013 (D.C.Cir.1923) and Daubert, 509 U.S. at 586, 588-89, 113 S.Ct. 2786). Rule 702 provides as follows:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.

While the Supreme Court found that Rule 702 altered the Frye test in that "general acceptance" was no longer an "absolute prerequisite to admissibility," the Court "emphasized that trial courts must still screen proffered expert testimony for relevance and reliability." Jaurequi, 173 F.3d at 1081 (citing Daubert, 509 U.S. at 588-89, 113 S.Ct. 2786). The Court noted that the adjective "scientific" in Rule 702 "implies a grounding in the methods and procedures of science" while the word "knowledge" "connotes more than subjective belief or unsupported speculation." Daubert, 509 U.S. at 589-90, 113 S.Ct. 2786.

After setting forth this interpretation of Rule 702, the Supreme Court focused much of the remainder of its opinion in Daubert to the issue of how a trial court should determine the reliability of scientific "expert" testimony. Jaurequi, 173 F.3d at 1081-82. [FN1] The Court noted that in determining whether proposed evidence is valid, trial courts should consider the following factors: (1) whether the underlying theory

or technique can or has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether the technique has a known or knowable rate of error; and (4) whether the theory or technique is generally accepted in the relevant community. Id. (citing Daubert, 509 U.S. at 593-94, 113 S.Ct. 2786). However, the Court made clear that these four factors are not exclusive, and that the trial court has flexibility in adapting its analysis to the particular facts of the case before it. Id. (citing Daubert, 509 U.S. at 594-95, 113 S.Ct. 2786). [FN2] In General Elec. Co. v. Joiner, 522 U.S. 136, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997), the Supreme Court made clear that rulings on the admissibility of evidence pursuant to Rule 702 under these principles are entrusted to the discretion of the trial court. In addition, in Kumho Tire Co., 526 U.S. at 152, 119 S.Ct. 1167, the Court emphasized the importance of the trial judge's gatekeeping role in analyzing proffered testimony of experts.

The Supreme Court decisions involving Federal Rule of Evidence 702 make clear that in evaluating testimony pursuant to Rule 702 in this case, this Court must consider the relevancy and the reliability of the proposed expert testimony. Blue Dane Simmental Corp. v. American Simmental Assoc., 178 F.3d 1035, 1040 (8th Cir. 1999) (citing Kumho Tire Co., 526 U.S. at 147, 119 S.Ct. 1167); see also Jaurequi, 173 F.3d at 1082 (quoting Daubert, 509 U.S. at 594-95, 113 S.Ct. 2786, for the proposition that the "polestar ... must always be 'scientific validity--and thus the evidentiary relevance and reliability--of the principles that underlie a proposed submission' "). In making the determination of whether the proffered expert evidence is reliable in this case, this Court is guided by the four Daubert factors set forth supra. as well as any other factors that might fit this particular case. Applying such factors in this case, the Court concludes that the opinions of plaintiffs' expert witnesses fail to meet the reliability requirements of Rule 702. In this case, it is clear that plaintiffs' proffered expert witnesses are imbued with "technical, or other specialized knowledge," but it is equally clear that any opinions they have to offer for a jury's consideration are inadmissible, since they cannot "assist the trier of fact to understand the evidence or to determine a fact in issue," because they are not qualified to testify to general causation in regards to cause and effect of Parlodel and intracerebral hemorrhage. Because such opinions are not admissible, and plaintiffs are unable to establish causation without it, defendant is entitled to summary judgment' for the reasons that follow.

The plaintiffs' experts in this case, Dr. Dennis Petro, a board- certified neurologist, and Dr. Kenneth Kulig, who is board certified in toxicology and emergency medicine, are both presented with impressive credentials. Kenneth William Kulig, M.D., is licensed to practice medicine in Colorado. A practicing physician for twenty-two years, Dr. Kulig received a B.S. Degree from Michigan State in 1972 followed by a M.D. Degree from Wayne State Medical School in Detroit in 1978. His internship was in internal medicine and his residency was in emergency medicine. He did a two-year fellowship in clinical toxicology at the University of Colorado. He was affiliated with both the Denver General and the Rocky Mountain Poison Center in Denver for ten years. In 1991, he went to Porter Hospital in Denver where he established a private practice where he remains to this date. Dr. Kulig has published at least one journal article related to Parlodel.

Dr. Petro received his M.D. degree at Penn State University. He completed his residency in neurology at the Hershey Medical Center. He was employed at the Food and Drug Administration, Washington, D.C. in 1977, where he reviewed drug applications relevant to neurologic disorders, specifically, those that pertained to analgesics and drugs of abuse. When he started with the FDA, Parlodel was an investigation drug, i.e., it had not yet been approved for Parkinson's Disease. After leaving the FDA, he continued part-time employment with the FDA as a consultant and became employed by the New York State Department of Health. He then worked in the field of development of neurologic drugs in a division of American Home Products. Thereafter, he was employed by Pfizer Pharmaceuticals. He then went to the Nassau County Medical Center on Long Island to run the Neurologic Department Research Program. From there, he want to the Fidia Pharmaceutical Company in Washington, D.C. He left that firm and became a consultant in the area of development of new drugs. Since 1980, he has been a member of The American Heart Association's Stroke Council. He has published medical articles in peer-reviewed journals.

In this case, both experts set forth what they described as their methodology for diagnosing the cause of the injury at issue in this case. Both experts referred to their methodology as "differential diagnosis." The Court believes that the court in Hall v. Baxter Healthcare Corp., has set forth the proper definition of "differential diagnosis" as used and explained by Dr. Kulig and Dr. Petro in this case:

Differential diagnosis is a patient-specific process of elimination that medical practitioners use to identify the 'most likely' cause of a set of signs and symptoms from

a list of possible causes.
947 F.Supp. 1387, 1413 (D.Or.1996).

Discussing their use of differential diagnosis, both experts explained that they analyzed Glastetter's case, including relevant medical records, looked at possible "other" causes of her ICH, such as her weight and history of smoking, and concluded, at the end of the process, that Parlodel caused such injury. According to Dr. Kulig, when Glastetter presented at the hospital 13 days after delivery of the child, she developed an "excruciating headache,". A CT scan revealed an intracerebral hemorrhage--blood in the brain tissue causing some motor paralysis and speech difficulty. He concludes that she suffered a bleeding-type stroke, as opposed to a "dry stroke" or ischemic-type stroke. Dr. Kulig notes that Glastetter took Parlodel after her first delivery in 1981 with no adverse reactions. However, it is Dr. Kulig's opinion that Glastetter's intracerebral hemorrhage was caused by the drug Parlodel. He outlines his "scientific method" that led him to this conclusion as follows:

Your Honor, this is basically what I call the scientific method for analyzing adverse drug reactions. I've talked to many people. I've heard many lectures on the subject. I've read textbooks on this. To me, this is not a mysterious approach that only a few select people can understand. This is common sense and it's what is done on a daily basis by physicians, scientists, regulatory agencies, and drug manufacturers, and I believe that this is the approach that was used by Sandoz itself in analyzing cases of possible adverse drug reactions reported to it at their Drug Monitoring Centre in Basle, Switzerland.

The approach is basically, you learn what you can about the patient, then you learn what you can about the drug in question, and then you put all that information together and ask the question, Was the drug in question the cause of ADR [Adverse Drug Reaction]?
When you, first of all, learn what you can about the patient, you review the medical records. If you have the patient in front of you, you would do a history and physical, or an H and P. And you would ask many questions about their past history, what drugs they've been on in the past, what drugs they're on now. Are there any risk factors for stroke? If it's a stroke patient, was there a family history of stroke? Do they have hypertension? Et cetera.

You may want to do some laboratory testing, do some blood work. If the patient, for example, had a hemorrhagic stroke, you may want to make sure that they don't have a bleeding disorder, so you would do some clotting studies in the patient.

In order to find out what kind of stroke they had, if it was a stroke patient, you might want to order some x-rays, including CAT scans, MRIs, angiograms, whatever is clinically warranted in that patient, and this is what's called the "patient workup" basically.

You may want to examine some specific heart tests to determine if the cause of the patient's stroke originated in the heart. If it was an embolic stroke, meaning a blood clot traveled from someplace going up into the brain, a common source of that, it would be the heart. Where a blood clot may form in the heart, a little piece of it may break off and travel to the brain causing an ischemic stroke. The way you determine that is to look at the heart itself, commonly with an echocardiogram.

Finally, you'd want to interview people who know the patient. If the patient has had a stroke, they may not be able to give you a very good history because they may be confused or even unable to speak. So you would want to interview family members or friends of the patient. I would ask them questions about prior drug use. Street drug abuse is always important. Is this person a known cocaine abuser or an amphetamine abuser? And sometimes the patient won't tell you that, but you may get that information from a friend or family member.

So basically, again, it's learn what you can about the patient. If you don't have the ability to interview the patient, you can still look at the medical records, you can read reports or depositions given by treating physicians to learn more, you can read the deposition of the patient themselves to help fill in some of the gaps that invariably occur in the medical record.

Secondly, the approach is to learn what you can about the drug in question, and that might begin with the package insert, but you can certainly also look at textbooks. Looking at the family of drugs from which the drug originated is important. That doesn't tell you automatically that the drug must act like other family members, but it gives you an idea of what the expected side effects might be.

If you know the side effect of aspirin, for example, and there's a drug that is an aspirin derivative, one might conclude that you would expect the side effects of that derivative to be like aspirin. It may or may not be true, but it's a good place to start.

Computerized searches. With the internet capability

today, it's very easy to very quickly get hundreds of articles on a given drug, and pulling that information off of the internet is often important.

Epidemiology, if it exists, is important It's unusual for there to be epidemiology involving adverse drug reactions. In this case there is some, and I will talk about that in a few moments, but clearly epidemiology is important. One must examine that scientifically to determine if it's valid epidemiology and if the conclusions are supported by the data presented.

Case reports have their place. Contrary to what's been represented, I don't have--I don't believe that case reports prove causation. On the other hand, if there are no case reports, if no one has ever see a case of a stroke from a drug where it's been alleged maybe a drug caused it, who would ever think that the drug could cause it if it's never been seen? So case reports are important.

The analysis of the case report is important as well, especially if it's published in a peer-reviewed journal and other people have the opportunity to critique the case report and even exclude it from publication if it's too far out scientifically.

Case series means more than one case report published together.

Rechallenge and dechallenge information is just critical, especially involving a very rare adverse drug reaction. If you have a given case where the patient develops an adverse drug reaction, they get better when the drug is withdrawn, and they're rechallenged with the same drug and they develop the exact same phenomenon that can be objectively measured, that's critical to the thinking that the drug was the cause of the reaction in that particular patient. It's not proof necessarily, but it's powerful evidence, and regulatory agencies, as well as manufacturers, place a very heavy emphasis on rechallenge information.

Clinical trials are important, but it's important to keep in mind that when a drug comes to market, there may have only been a few hundred or at most a few thousand patients who have received that drug in clinical trials, meaning premarket trials where the drug is being tested to see if it's effective and if it's safe. If the adverse effect in question is very rare, if it only occurs in one in 5,000 patients, it would be unusual to see it in the clinical trials. But nevertheless, that information can be important.

Animal studies are important. Again, it would be inappropriate to rely solely on animal studies, but if you do have animal studies, for example, showing a given drug is a vasoconstrictor in animals, that is evidence that it could be a vasoconstrictor in man.
Vol. I: 68-73 (Kulig) (March 20, 2000).

Dr. Kulig later continued to address the issue of causation by the differential diagnosis method as follows:

... Finally, we come to the bottom line. Was the drug in question a cause or the cause or a substantial factor in the development of the adverse drug reaction? My approach and, again, the generally accepted approach, is first of all to formulate a differential diagnosis. What else could be the cause in this patient? Did this patient have a head injury? Did this patient have an arteriovenous malformation, an anatomical defect in the brain that was the result--excuse me, that was the cause of the stroke as opposed to postulating a drug being the cause? And we'll go through a differential diagnosis in just a moment in this particular case.

Then you attribute an appropriate weight to the various components of the medical evidence. The medical evidence could include, involving the drug Parlodel, is Parlodel a vasoconstrictor? Does Parlodel cause vasospasm? Has Parlodel been associated with stroke in human beings? Is there animal evidence that Parlodel is a vasospastic agent? Do the pharmacokinetics of the drug lend themselves to saying it makes sense, that it's plausible the drug was the cause? And again, I'm not saying that any of these components individually leads one to draw that conclusion, but in compilation of all of the evidence involving all of these components, one might be able to reach a conclusion.

Many scientists and physicians end right there, Your Honor. They say, I've seen enough. I'm willing to say that in Patient X, the drug caused the adverse drug reaction. I've taken it even one step further and I use the Bradford-Hill criteria, which is outlined in detail in my affidavit. It's my representation that the Bradford-Hill criteria are generally accepted criteria for analyzing causation, both for drugs and for nondrugs such as chemicals.

The toxicologic community, my peers, use Bradford-Hill extensively. When a paper is presented at our scientific meeting, it is not uncommon for people to say, I believe causation exists because I've applied the Bradford-Hill criteria and here's what my analysis shows.

In the case of Sandoz, they used a different criteria, they

used the Karch Lasagna criteria. Many of the principles overlap; they're quite similar. But what I'm saying, Your Honor, is that it is appropriate to use an outline, a construct, a logical construct to say, I believe cause and effect exists because of all of this, but in addition, I've taken the extra step and applied a published, generally accepted criteria to the analysis. You may not agree with everything I have to say about that analysis, you may interpret the evidence differently, but at least I'm willing to lay it on the line and say, Here is my thought process, here is the evidence I've looked at and why I believe cause and effect exists. And the Bradford-Hill criteria, in my opinion, it's a generally accepted scientific methodology for the analysis of adverse drug reactions.
Vol. I: 77-79 (Kulig) (March 20, 2000).

Dr. Kulig also explained that in his differential diagnosis, he ruled out arteriovenous malformation (AVM), an aneurysm that is essentially an outpouching of an artery, as the cause of Glastetter's injury, concluding that the neurosurgeon removed a clot and surrounding tissue which was submitted for pathologic analysis. His view is that Glastetter's treating physicians would have been able to diagnose AVM by objective tests, "To the best of their capabilities...." Vol. I: 93-95 (Kulig) (March 20, 2000).

In his differential diagnosis, Dr. Kulig also ruled out hypertension as a cause of Glastetter's stroke. He notes that she was never treated for hypertension. He observes that "her first recorded blood pressure was during the elevate--evolution of her stroke, recorded during the critical period where she was becoming quite ill from her stroke and evolution and it's certainly possible that the blood in her brain was causing the blood pressure elevation." Vol. I: 99-101 (Kulig) (March 20, 2000). Similarly, Dr. Kulig also looked at coaqulopathy, i.e., consideration of whether her blood was clotting properly. Her blood-clotting tests, he concludes, were unremarkable. Vol. I: 101-102 (Kulig) (March 20, 2000). Dr. Kulig also ruled out infection as a cause of the Glastetter stroke, finding no evidence of infection in the medical records.

Likewise, he testified that he found no evidence of venous thrombosis-- excessive blood-clotting--in Glastetter. Dr. Kulig also ruled out vasculitis--inflamation of blood vessels--as a cause of Glastetter's stroke. Vol. I: 102 (Kulig) (March 20, 2000). Dr. Kulig believes that Glastetter's stroke was an arterial event rather than a venous event because a craniotomy--brain surgery to evacuate the blood clot with a suction machine--was necessary. "That is very unlikely to be a venous bleed, in my opinion," he stated. Dr. Kulig also ruled out brain tumor as a cause of the Glastetter hemorrhagic stroke, primarily on the basis of the radiographic studies and tissue samples from the surgery.

Dr. Kulig next considered the effect of other drugs as a probable cause of Glastetter's stroke. In reviewing the case, he considered drugs such as cocaine, methamphetamine, courmadin, heparin and aspirin overdose. He testified that no evidence indicates that any other drugs contributed to Glastetter's stroke. Vol. I: 103-106 (Kulig) (March 20, 2000).

Dr. Kulig also recognized that Glastetter was postpartum with a history of headaches and sinusitis. He observed a history of migraine headaches by noting that she "does have a five-year history of intermittent vertex throbbing headaches. These headaches were associated with nausea and vomiting in addition to photophobia and sonophobia, and if she were able to sleep in a dark room, she would often wake up with a complete resolution to the headache. Each attack would last about two hours and she would have no more than two monthly. The headaches were getting progressively worse since about one year ago." Vol. II: 87-88; 90-91 (Kulig) (March 20, 2000). He is not sure if the history of migraine headaches pre-dated the cesarian section birth, but concludes that migraine headaches do not cause intracerebral hemorrhage, and if she had migraine headaches, it did not cause her stroke. He testified that there is evidence that migraine headaches can cause ischemic strokes where blood vessels can clamp down so that brain tissue no longer receives blood, but that is different than hemorrhagic stroke. He stated that in general, he does not believe there is an association between migraine headaches and hemorrhagic stroke, and he does not believe there are any epidemiologic studies verifying such association. Vol. II: 87-88; 90-91 (Kulig) (March 20, 2000). He ruled out migraine headaches as a cause of Glastetter's stroke. Vol I: 106-108 (Kulig) (March 20, 2000).

In conducting his differential diagnosis, Dr. Kulig also recognizes that Glastetter smoked a pack of cigarettes each day for about six years before her stroke. He is aware of an epidemiologic study showing increased risk of hemorrhagic stroke in cigarette smokers. Also, when he was asked whether cigarette smoking causes vasospasm, he answered, "I think the nicotine in cigarette smoke can cause some element of vasoconstriction. Whether or not it actually causes the pathologic condition vasospasm, I'm not sure." In addition, when he was asked about Berger's

disease in heavy smokers, he stated, "That's generally where you see it, yes." He also stated that "only in a very rare, very susceptible individual who is a heavy smoker," one might find that "cigarette smoking causes Berger's disease through the mechanism of vasospasm." In the same line of questions, he acknowledged that vasospasm can be so severe that it causes gangrene and digit amputation. He confirmed that a physiological mechanism for vasospasm could be responsible for some cases of otherwise itcopathic intracerebral hemorrhage. Vol. II: 99-101 (Kulig) (March 20, 2000).

Regarding such medical or scientific evidence as to the relationship between smoking and hemorrhagic stroke, Dr. Kulig testified that there "is some evidence that that occurs.... Her short smoking history, although a pack a day is a pretty heavy habit, I think did not cause her stroke because there was no evidence for atherosclerosis on her angiogram, which is one of the reasons smoking may be associated with stroke to begin with. Her blood vessels were clean." Vol. I: 108-110 (Kulig) (March 20, 2000).

While Dr. Kulig did not concur that Glastetter was "clinically obese" when she became pregnant and at the time of her stroke, he confessed that she was "heavy"--"overweight." He says he's seen some evidence that suggests obesity is a risk factor for stroke. Vol. II: 92-94 (Kulig) (March 20, 2000). [FN3] While he observed that Glastetter was overweight with a cholesterol of 201 which is "minimally elevated," he said this did not cause her stroke. Vol. I: 111 (Kulig) (March 20, 2000).

The last factor Dr. Kulig considered in his differential diagnosis was the postpartum status of Glastetter. He recognizes the existence of multiple studies performed on strokes in the postpartum period, and that some have concluded that there is an increased risk of stroke. He questions the results of the studies, because the larger studies have not examined whether women were eclampsic or whether they were on Parlodel. He testified that if eclampsia is ruled out, or if medication use is ruled out in the postpartum period, "it is not at all clear that there'sthis greatly elevated risk of stroke in the postpartum period specifically." However, he states that he recognizes that eclampsia is a disease occurring only in the immediate postpartum period, and that it is characterized by severe elevations of blood pressure as well as significant edema or swelling of the body, with protein being found in the urine in excessive concentration. He stated that it "can result in stroke if the blood pressure elevations are excessive." However, Dr. Kulig is not convinced that cesarian section represents an increased risk for stroke. He stated that it "just seems to me to be totally unscientific to say that an epidemiologic study shows that the postpartum period by itself is a risk factor and Parlodel therefore, is not when the study did not examine whether or not the women were on Parlodel." However, he is not specific in his exclusion of surgical delivery as a cause in this case, and he recognizes some risk of stroke from general anesthesia. Vol. I: 97-99 (Kulig) (March 20, 2000).

However, notwithstanding his apparent disagreement with respect to the conclusion that women in the postpartum period, especially women who had cesarian sections, [FN4] are at risk of stroke, Dr. Kulig indicated that he considered such risk in his differential diagnosis. He stated that "[w]hether or not I believe that to be true, I did consider cesarian section in her and ruled that out as a cause of her stroke." Glastetter's 1993 delivery was by cesarian section, but Dr. Kulig concluded that she was not preeclamptic during her 1993 pregnancy. While he did note that in Glastetter's 1981 pregnancy, she had "some blood pressure elevations," and that her physician found "toxemia," which he says is another word for "eclampsia or preeclampsia," he stated that Glastetter reported no significant elevations in blood pressure in her 1993 pregnancy. Vol. I: 95-96 (Kulig) (March 20, 2000).

After discussing his consideration of all these factors, Dr. Kulig concluded his differential diagnosis exercise by saying that it was his "opinion that the intracerebral hemorrhage in Mrs. Glastetter was caused by the drug Parlodel." Vol. I: 111-116 (Kulig) (March 20, 2000).

Following Dr. Kulig's testimony on direct examination, defendant inquired in regards to his conclusions on cross-examination. Cross-examination of experts is very important in determining whether their testimony is reliable or relevant. Cross-examination of plaintiffs' expert witnesses in this case is particularly instructive. Dr. Kulig demonstrated frequent episodes of poor or selective memory, and his answers, when challenged, demonstrate the unreliability of his conclusions. [FN5] Dr. Kulig had much trouble remembering the testimony he has given in many prior cases which involve Parlodel. When reminded of answers he previously gave under oath, which confirm in most cases the responses sought from counsel in cross- examination, Dr. Kulig frequently responds that the testimony occurred a long time ago. Dr. Kulig's opinions are not based upon scientific studies but are, in the final analysis, reposed in the realm of "may cause" or

"possibly could cause."

With respect to his conclusions about the postpartum period in his differential diagnosis, Dr. Kulig was asked on cross-examination if he agreed that the postpartum period is a period of increased risk for stroke in the general female population, and he at first responded, "I'm not sure the period itself is the cause as opposed to things that can happen during that period being the cause, such as drug use or eclampsia." He was asked if he had given another answer in a deposition in a prior case against Sandoz to this question, "You're not aware that there is an increase of stroke in postpartum women as opposed to women who are not prepartum?" His reported answer was, "I am willing to say that pregnancy and delivery are risk factors for the development of stroke." Vol. I: 120-123 (Kulig) (March 20, 2000).

Dr. Kulig acknowledged familiarity with the Kittner Study published in the New England Journal of Medicine in 1996, a peer-reviewed article reporting the relative risk of intracerebral hemorrhage at a point during the six-week period after delivery, with an increased risk of more than 28 times the risk for a woman not in the postpartum period. The relative risks were adjusted for age and race. The paper reports an increased risk of intracerebral hemorrhage postpartum statistically significant at the 95% confidence interval. After shown the Kittner paper with its conclusion that "A causal role for a preeclampsia and eclampsia does not fully explain the much stronger associations with stroke found for the postpartum state than for pregnancy itself," and when asked if it was his opinion that preeclampsia and eclampsia account for a significant percentage of postpartum stroke, Dr. Kulig said he did not think he ever made such a statement, but that preeclampsia and eclampsia account for some percentage of stroke postpartum, and that Parlodel does not cause preeclampsia or eclampsia or eclampsic stroke or eclampsic seizure. He admitted that blood volume decreases from the time of delivery to the end of the postpartum recovery. He was unwilling to agree on a specific percentage of blood volume decrease but testified, "And there is probably some range that may include 50 percent, but I would be reluctant to accept that figure as being true." Vol. I: 124-130 (Kulig) (March 20, 2000).

In addition, Dr. Kulig admitted that he was not familiar with any study which shows Parlodel affects the coagulating factors of blood. He admitted that he was familiar with a postpartum epidemiology study published by Dr. Lanska in 1998, which looked at postpartum stroke and showed an increased risk of stroke postpartum. The report was reviewed in a journal called Neurology.

Like Dr. Kulig, Dr. Petro also relied upon differential diagnosis in reaching his conclusions in this case:

Q: Doctor, what methodology have you used in reaching your opinions with regard to the itiology of Glastetter's intracerebral hemorrhage?
A: Well, in general issues, you use certainly the scientific method, but as part of the practice of medicine, the practice is to use--the classic technique is to use the technique of differential diagnosis.
"You begin with horses and you end up with zebras." Vol. I: 61 (Petro) (March 21, 2000).

Like Dr. Kulig, Dr. Petro excluded possible risk factors of stroke in his differential diagnosis. He concluded that Glastetter did not have chronic hypertension. Her hypertension in the emergency room, he concludes, is complicated to evaluate "because obviously she's evolving an event that can either cause the transient rise in hypertension, just because of the stress of having a brain hemorrhage. That's clearly obvious."

He also mentions other factors relevant to autoregulation in the brain which may impart in terms of a presser effect, and he says there are cases where patients on Parlodel in the postpartum period develop hypertension. Vol. I: 64 (Petro) (March 21, 2000). Dr. Petro also ruled out AVM as a cause of Glastetter's stroke. After first noting that he recognizes that they are of varying sizes, he noted that a large or medium AVM would appear on tests and "would be seen at the time of the craniotomy." He recognizes that cryptogenic AVM, which Barnett references as invisible AVM which bleeds, leaves no residual to be seen, meaning there would not be 100% exclusion of something that is both invisible and leaves no remnants. As he stated, "[t]here's no way to essentially rule out an invisible vascular malformation." Also, he notes that Glastetter's multiple radiological studies showed no evidence of AVM. The neurosurgeon who performed the craniotomy evacuated the material in the area. The pathology showed no finding of arteriovenous malformation. Vol. I: 64- 68 (Petro) (March 21, 2000).

In his differential diagnosis, Dr. Petro also ruled out all other drugs as a cause of the intracerebral hemorrhage other than Parlodel. He acknowledges that she had taken analgesics, but he noted that there

is no indication she had taken other prescription medication. He concluded there was no evidence of infection, tumors, inflammation or vasculitis to explain the hemorrhage. Vol. I: 70 (Petro) (March 21, 2000).

In conducting his differential diagnosis, Dr. Petro also recognizes the difference between a risk factor and a cause. As he observed, "there's really a distraction between factors which may or have some connection that is distant to the event versus the actual precipitation of the event by some causal agent." Dr. Petro also recognizes other risk factors, noting that "some of them include things such as use of other drugs, use of--certainly other things such as tobacco use, certainly nowadays it's caffeine use, and many, many other factors. Also, race, issues of race, and also obesity, cholesterol levels, et cetera, et cetera."

When asked whether Glastetter's smoking history was the cause of her hemorrhage, he responded, "my opinion is it was not a factor. It was not a causative factor in her hemorrhage." In expanding his answer, he said there were "a whole series of factors associated with chronic smoking over long periods of time. So that's to be considered more likely in older patients." He testified that there is a relationship between smoking and atherosclerosis, but from laboratory tests, he concluded that no evidence indicated she had atherosclerosis. Vol. I: 70-73 (Petro) (March 21, 2000).

Dr. Petro also ruled out caffeine as a causative factor, because he believes that there has not been a consensus in terms of neurologic findings that it plays a role in stroke. He also believes that obesity was not a factor in Glastetter's stroke. Because she was 36-years old, he contrasts her with women in the sixty-year range, explaining that obesity in combination with diabetes and hypertension work together to "perhaps have an influence." In a 35-year old, premenopausal female, "that's not a significant factor." Vol. I: 73 (Petro) (March 21, 2000). Dr. Petro also ruled out cholesterol measurements as a causative factor for Glastetter's hemorrhage. He noted that he thinks low levels of cholesterol may be a risk factor. Vol. I: 75 (Petro) (March 21, 2000) (emphasis added).

In addition to the foregoing, it did not appear that Dr. Petro believed that Glastetter's postpartum period was a causative factor for her intracerebral hemorrhage. He testified, "Yeah, I think just in a sentence these kind of questions is to look at what are recorded in neurologic treatises, and when I look at the standard treatises that are in neurology and I look at the postpartum period, I don't see that as any particular factor, certainly as presented in the standard treatises that I use." Vol. I: 75 (Petro) (March 21, 2000).

Thus, plaintiffs' experts indicated that their conclusions with respect to the likely cause of Glastetter's ICH, to the exclusion of other causes, were reached through a scientific process known as differential diagnosis.

As plaintiffs note, other courts have embraced differential diagnosis as a sound scientific methodology. See Westberry v. Gummi, 178 F.3d 257, 262 (4th Cir.1999) (noting that "[d]ifferential diagnosis, or differential etiology, is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated" and that such technique "has widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results.") (citations and internal quotations omitted); Heller v. Shaw Industries, Inc., 167 F.3d 146, 155-56 (3d Cir.1999); Hose v. Chicago Northwestern Trans. Co., 70 F.3d 968, 973 (8th Cir. 1995) (noting that "ruling out alternative explanations for injuries is a valid medical method") (citation omitted). In addition, defendant does not contest plaintiffs' use of a differential diagnosis.

Concluding that differential diagnosis is a sound scientific methodology, however, does not end the Court's inquiry. As the court in Hall noted, "differential diagnosis does not by itself prove the cause, even for the particular patient." 947 F.Supp. at 1413. The Hall court emphasized that while differential diagnosis is important and an accepted methodology with respect to issues of "specific causation," such diagnosis may not be helpful with respect to "general causation:"

> The process of differential diagnosis is undoubtedly important to the question of "specific causation." If other possible causes of an injury cannot be ruled out, or at least the possibility of their contribution to causation minimized, then the "more likely than not" threshold for proving causation may not be met. But, it is also important to recognize that a fundamental assumption underlying this method is that the final, suspected "cause" remaining after this process of elimination must actually be capable of causing the injury. That is, the expert must "rule in" the suspected cause as well as "rule out" other possible causes. And, of course, expert opinion on the issue of "general causation" must be derived from scientifically valid methodology.

Id. at 1413 (citations and internal quotations omitted).

Plaintiffs' experts also indicate that the differential diagnosis is not helpful in assessing general

causation. When asked if differential diagnosis as applied to a specific patient cannot establish general causation, between the exposure and the disease end point generally, Dr. Kulig said differential diagnosis in a specific patient "has nothing to do with general causation except for the items in the differential diagnosis are probably accepted by the physician as being shown to be general causes of the condition in question. We just have to find out now in a given patient if that's the operative process." When asked if he testified in a prior case in 1997 to the question, "can differential diagnosis as applied to a specific patient establish general causation between the exposure and the disease end pont generally?," he answered, "No." Dr. Kulig also testified that a differential diagnosis is designed to answer questions in a specific patient "and that's all it really can do." Vol. II: 77-78 (Kulig) (March 20, 2000).

When asked whether general causation between "a drug and a disease cannot be established by a process of differential diagnosis, is that correct?," Dr. Kulig said, "Well, it's not--it's not designed to do that. It--it--a differential diagnosis is designed to be used for a specific patient which is not what general causation concerns, as you know." Vol. II: 80 (Kulig) (March 20, 2000).

Similarly, Dr. Petro was asked if he understood the difference between general causation and specific causation. He agreed that general causation means whether substance A can cause Effect B. He also agreed that before it can be concluded that bromocriptine did cause intracerebral hemorrhage in Glastetter, it must first be known that bromocriptine can cause intracerebral hemorrhage, generally. Vol. I: 101-102 (Petro) (March 21, 2000).

Thus, while plaintiffs' experts testified that in performing differential diagnosis in this case, they ruled out other possible causes of Glastetter's ICH, the experts and plaintiffs must also come forward with evidence "ruling in" Parlodel as a possible cause of ICH. If no evidence suggests that Parlodel can cause ICH in humans generally, then the Court does not believe that plaintiffs' experts conclusions that Parlodel caused ICH in Glastetter, as evidenced by their use of differential diagnosis, passes the reliability standards under Daubert and its progeny. [FN6] See National Bank of Commerce v. Dow Chemical Co., 133 F.3d 1132 (8th Cir.1998) (affirming exclusion of evidence under Daubert when plaintiffs failed to demonstrate that proffered expert testimony had a valid scientific foundation, "because it was not based on accepted scientific methodology for determining whether a chemical agent can cause birth defects in humans"); Brumbaugh v. Sandoz Pharmaceutical Corp., 77 F.Supp.2d 1153, 1155, n. 1 (D.Mont. 1999) (noting that specific causation is only material "if plaintiff can demonstrate general causation between Parlodel and her injury").

In their papers and at the hearing, plaintiffs came forward with the following evidence supporting their claim that Parlodel can cause ICH: (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" in their Memorandum in Opposition; (4) determinations by the FDA that Parlodel is unsafe because of stroke and other vasopastic risks; and (5) allegedly hidden internal company admissions by Sandoz concluding that Parlodel can cause such conditions, including information related to animal studies. Having reviewed this evidence, heard the testimony from plaintiffs' experts, and considered plaintiffs' arguments in their papers and at the hearing, the Court does not believe that this evidence is sufficient to establish the reliability of plaintiffs' proffered expert testimony.

A. CASE REPORTS ARE NOT RELIABLE IN ESTABLISHING CAUSATION.

At the outset, the Court notes that plaintiffs' experts' reliance on case reports is not sufficient to make their causation opinions reliable under Daubert. Plaintiffs' experts indicated at the hearing that they have reached their conclusions based, at least in part, upon numerous case reports or individual case studies. Much of Dr. Kulig's support for his causation conclusions comes from case reports, which he describes as "important." More specifically, Dr. Kulig refers to two cases where women were taking Parlodel, and, in his opinion, had adverse drug interactions. He claims such cases prompted the writing of his report. The first woman he saw was a postpartum patient taking Parlodel for lactation suppression who developed "a very bad headache while taking the drug ... and was given Midrin, which is a common headache medication." She was released, then returned in "critical condition ... in ventricular tachycardia.... She apparently did not suffer a myocardial infarction, however, but she was in preinfarction condition." The neurologist who was involved in treating this patient related to Dr. Kulig a case history of a woman taking Parlodel for lactation suppression who developed a headache and was given a drug before she had a stroke, while on both medications. The day after her stroke, she had an angiogram which showed "widespread diffuse vasospasm on the

angiogram." A repeat angiogram performed several months later was normal. "It was my belief that the condition was that she was on one or both drugs that I had mentioned, Parlodel with or without the [other drug], that was clearly causing spasm and the subsequent stroke. So the analogies between this--that case and Mr. Glastetter were clear to me. Be that as it may, I published both cases together." That publication, Bromocriptine--Associated Headache, Possible Life-Threatening Sympathomimetic Interaction, was received as plaintiffs' exhibit 1400. Thereafter, these patients contacted attorneys who contacted Dr. Kulig. He then associated himself with these patients as an expert witness in litigation involving Parlodel. Vol. I: 57-59 (Kulig) (March 20, 2000).

Like Dr. Kulig, Dr. Petro relied, in part, on case reports to reach his conclusions. At the hearing, he indicated that he has reviewed clinical trials for Parlodel in the course of litigation where he has served as an expert witness. He testified concerning a particular patient's case report under controlled conditions where the patient was under consistent observations of a treating physician and was monitored for new signs and symptoms and for regulation of medication. Soon after initiation into the study, she developed profound hypertension. Dr. Petro testified that hypertensive encephalopathy is a potential precursor to an intracerebral hemorrhage; however, the patient was dropped from the program, and the reports of these clinical trials were summarized to the FDA, but this patient's encephalopathy was not referenced in the summaries. Vol. I: 30-35 (Petro) (March 21, 2000).

In addition, while Dr. Petro worked with the FDA, he made a report concerning adverse drug reactions with Parlodel and the Parkinson's indication in 1979. He noted three deaths in the Parlodel group, two attributed to myocardial infarction and one from intestinal obstruction and gangrene. [FN7] Caution was suggested in use of bromocriptine in patients at risk for cardiovascular disease. He commented that the literature and sponsor study demonstrate neuropsychiatric complications (hallucinations, confusion, psychosis) and cardiovascular effects (vasospasm, arrhythmia, myocardial ischemia, etc.), which limit the usefulness of bromocriptine in elderly patients with Parkinson's disease. He suggested continued surveillance for adverse toxic reactions, with particular attention to patients with vascular disease, hepatic impairment or hematologic disorder. He concluded that the three deaths suggest "some ergotism in the study population." He recommended approval of the Parlodel indication, subject to appropriate surveillance, at a time when he was a consultant with the FDA. Sandoz was then required to list ergotism and symptoms of ergotism in the package insert for the Parkinson's indication for Parlodel. Vol. I: 19-24 (Petro) (March 21, 2000).

In addition, he observed that Dr. Davoisin reported a Parkinson's Disease patient developing pallor and painful sensations in the fingers which disappears when the drug was withdrawn and resurfaced after a period of time when Parlodel was re-introduced to the patient. Vol. I: 19-24 (Petro) (March 21, 2000). Dr. Petro also relied on other published case studies that he expressly mentioned at the hearing, including some discussed by the Court infra. [FN8]

The Court does not find that the case reports support the reliability of plaintiffs' experts' testimony. As defendant notes, a number of courts have concluded that case reports are not a scientifically reliable basis for a causation opinion. See generally Allison v. McGhan Med. Corp., 184 F.3d 1300, 1316 (11th Cir.1999) (noting that "case studies pale in comparison" in the face of "population-based epidemiological studies" and that district court did not abuse its discretion by discounting expert's "reliance on case reports in the face of the overwhelming contrary epidemiological evidence presented"); Hollander v. Sandoz Pharmaceuticals Corp., 95 F.Supp.2d 1230, 1235-38 (W.D.Okla.2000) (noting that "case reports have been repeatedly rejected as a scientific basis for a conclusion regarding causation") (citing In re Breast Implant Litigation, 11 F.Supp.2d 1217, 1228 (D.Colo.1998); Willert v. Ortho Pharmaceutical Corp., 995 F.Supp. 979, 981 (D.Minn.1998)); Pick v. American Med. Sys., 958 F.Supp. 1151, 1161-62 (E.D.La.1997) (noting that "courts have frequently rejected case studies as an insufficient basis to decide causation when they lack control groups" and that "the individual reports cited must be shown to be independently reliable under Daubert before they can be admitted"); Haggerty v. Upjohn Co., 950 F.Supp. 1160, 1164 (S.D.Fla.1996) (citing Casey v. Ohio Medical Products, 877 F.Supp. 1380, 1385 (N.D.Cal.1995), for the proposition that "while case reports may provide anecdotal support, they are no substitute for a scientifically designed and conducted inquiry"). Such case reports are not reliable, because normally, such reports "record nothing more than a temporal association between an exposure and a particular occurrence," and are therefore less reliable than epidemiological studies, because "[e]pidemiologists use their population studies to eliminate the chance associations and confounding factors, which inherently

infect anecdotal reports, to determine whether a statistically significant positive association exists." Wade-Greaux v. Whitehall Labs., 874 F.Supp. 1441, 1453 (D.Vi.1994); see also Hollander, 95 F.Supp.2d at 1237-38 (noting that the problem with case reports and adverse drug experience reports is that "they are not controlled studies and do not eliminate confounding variables," which means that "the reported effect or injury could be due to some other cause than Parlodel").

Dr. Kulig apparently has recognized these flaws with case reports, as he testified at the hearing in this matter that case reports "do not establish causation" and that he did not believe "that case reports prove causation." Vol. I:71, 138. He admitted that "case reports by themselves do not prove causation and I would never attempt to do so." In his prior testimony in a case in New York, Dr. Kulig gave testimony in response to the question, "Doctor, on a more general level, can a cause-and-effect relationship be established with a disease as common as breast cancer in humans without just showing an association through a controlled study?" His answer there was "no." When asked, "Can it be shown with case reports?", he said, "no." Vol. I: 134-139 (Kulig) (March 20, 2000).

He also admits that clinical trials would be a very small component of the entire list of evidence that he would consider, and he would not say that clinical trials in isolation prove anything. He stated that he believes that case reports are traditionally viewed as the least vigorous form of proof of a hypothesis or validation of a theory, and he testified at an earlier hearing that he would put case reports as his least important evidence of causation. Moreover, Dr. Kulig testified in an earlier case that a single case report is uncontrolled, and he confesses that relative risk factors cannot be derived from case reports. He acknowledges that he is not giving the Court an estimate of Parlodel's risk based on case reports. He agrees that case reports and temporal associations taken together are unlikely to give proof of causation. In a prior hearing, Dr. Kulig was asked the following question, "Sir, do you agree with FDA's caveat number one that for any given case report there is no certainty that the suspect drug caused the reaction?" He answered by stating, "I would agree with that." Dr. Kulig testified he is not saying that vetro evidence proves that Parlodel causes stroke. Vol. II: 26; 28- 38; 41; 72 (Kulig) (March 20, 2000).

In addition, while plaintiffs in this case, like the plaintiffs in Hollander, emphasize that a number of the case reports include dechallenge/rechallenge [FN9] information, [FN10] Dr. Kulig testified that while such evidence is "powerful," he also stated that "it's not proof necessarily," Vol. 1:72, and that such dechallenge/ rechallenge reports are not controlled except in "a very loose sense." Vol. II:44. [FN1 1] Thus, in light of the case law discussing case reports and the testimony of plaintiffs' experts, this Court, like the Hollander court, does not believe that the case studies in this case are sufficient alone to "establish the requisite causation, as they fail to take into account the postpartum incidence of stroke and other factors." 95 F.Supp.2d at 1237-38. Therefore, the case reports, including the re-challenge/ de-challenge studies, are not sufficient to establish the reliability of plaintiffs' experts' causation opinions.

B. PLAINTIFFS' MAY NOT SHOW CAUSATION MERELY BY PRESENTING TESTIMONY AND OTHERWISE DEMONSTRATING THAT OTHER ERGOT ALKALOIDS CAUSE HYPERTENSION OR BY PRESENTING PUBLISHED WORK BASED UPON CASE STUDIES IN THE ABSENCE OF EVIDENCE ESTABLISHING THAT PARLODEL CAN CAUSE INTRACEREBRAL HEMORRHAGE

Plaintiffs and their experts have come forward with evidence they claim indicates an "association" between bromocriptine and vasoconstriction in some parts of the body and under certain conditions. Dr. Kulig says that bromocriptine is a vasoconstrictor, that bromocriptine and pergolide share some common properties with the parent family of ergot compounds, including digital vasospasm, and that bromocriptine is on the differential diagnosis for myocardial infarction. Vol. I: 83-85 (Kulig) (March 20, 2000). He concludes that vasospasm is ergotism and ergotism is vasospasm; however, he testified that just because bromocriptine is an ergot does not mean it causes vasoconstriction. [FN12] Notwithstanding such testimony, he believes, apparently for other reasons, that there is clear and convincing evidence that broncocriptive causes myocardial infarction and that such evidence can be used, "that, therefore, it appears that bromocriptine possibly [FN13] could cause stroke as well because the physiologic mechanism is identified. You would have to have some evidence, as well, but again, you're looking at a toxicologic syndrome of ergotism where these things happen together from the same drug." Vol. II: 72-73 (Kulig) (March 20, 2000).

However, Kulig does not know the mechanism by which bromocriptine causes seizure. He believes it to be a vasoconstrictive phenomenon. However, his conclusion lacks scientific support. He relies upon his conclusion, which is about to be published in a textbook, that bromocriptine is not generally thought to

lack vasoconstrictive properties. Dr. Kulig's opinion on whether bromocriptine is a vasoconstrictor is a moving target. In 1991, after reviewing published literature, he concluded that bromocriptine is generally thought to lack vasoconstrictive properties; however, he claims he has changed his opinion based on review of published literature. Vol. I: 144-147 (Kulig) (March 20, 2000).

Overall, Dr. Kulig's testimony as to causation of vasospasm by Parlodel in humans is inconclusive. When he was asked whether he had an opinion "as to the specific biological or pathological mechanism by which Parlodel causes the vasoconstriction in humans," he answered as follows:

Well, I've been cross-examined for many hours on that very subject by members of your law firm and I've given multiple possibilities as to what the cellular pharmacologic receptor mechanism could be for that vasoconstriction. It is true that I was not able to say that there is one that is more likely than not the mechanism. Vol. I: 152-153 (Kulig) (March 20, 2000).

Dr. Kulig has also previously testified that he recognizes that Dr. Ellenhorn has published a learned treatise which reported that the vasoconstrictive property for bromocriptine on Parlodel is zero. Dr. Kulig disagrees with that conclusion. Id.

In addition, plaintiffs cite Martindale, The Extra Pharmacopoeia, (3rd Ed., 1993), which states under "Adverse Effects" that "Bromocriptine is a vasoconstrictor." Similarly, plaintiff's cite Goodman & Gillman, 9th Ed., for the proposition that bromocriptine "shares some properties with the parent family of ergot compounds including the ability to induce ... digital vasospasm." Plaintiffs also cite to the American Hospital Formulatory Service (AHFS) Drug Information, 1999 for the following:

Seizures and stroke have been associated rarely with bromocriptine therapy for suppression of postpartum lactation (See Cautions: Cardiovascular Effects); however, the drug no longer is labeled for such use in the US.... Hypertension (sometimes developing with initiation of therapy but often during the second week); seizures (mean onset about 7 days postpartum but up to 2 weeks in some patients), with or without hypertension, occasionally presenting as status epilepticus; potentially fatal cerebrovascular accident (stroke) (mean onset about 13 days postpartum), principally in postpartum women whose prenatal and obstetric courses were uncomplicated; and acute myocardial infarction have occurred rarely in women receiving the drug for postpartum lactation.

Also, at the hearing in this matter, Dr. Petro testified that the relationship between ergot and stroke is recognized in neurology tests and treatises. He recognized that a text of Neurology by Boqousslavsky and Fisher, and notes that a table on page 352 refers to a differential diagnosis of ischemic stroke and in parenthesis, "(ergotism toxic vasculitis and serotonin antagonists)." He states that there is a relationship between ergot and stroke recognized in a treatise on stroke by Barnett. He recited from the text, "The physiopathology and cause of reversible angiopathy is focal arterial vasoconstriction which may be due to sympathomimetic drugs such as ergot derivatives, crack cocaine, methylamphetamine, and phenylpropanolamine...." Vol. I: 3 8-40 (Petro) (March 21, 2000). [FN14]

In addition, plaintiffs refer the Court, in their papers, to an article entitled Bromocriptine and Postpartum Cerebral Angiopathy: A Causal relationship? from the June, 1996 issue of the journal Neurology, which involved a postpartum woman on Parlodel who developed stroke like symptoms, for the following:

Bromocriptine was perceived initially as an innocuous compound with mild vasodilator properties, but it may also display vasoconstrictor effects consistent with its ergot alkaloid properties ... In our patient, hemorrhages and cerebral vasospasm may have been the result of hypertension, but direct vasoconstrictive activity could not be ruled out due to the fact that hypertension had not been demonstrated in other reported cases of PCA ... in most PCA cases ergots (mainly ergonovine) or sympathomimetic drugs, or both, were given during delivery or in the first days of puerperium. [FN1 5]

Plaintiffs also direct the Court's attention to several other published case reports, plaintiffs' Ex. 25 17-2530. Understanding plaintiffs' purpose for citing to these sources, the Court does not find that such sources establish the reliability of plaintiffs' experts' testimony on the issue of whether Parlodel could cause the ICH at issue in this case. As the Court noted supra. in Section II.A., case reports are not reliable in establishing causation. Many of plaintiffs' exhibits, including the article in the French publication by C. Lucas and the article by Janssens, are simply case reports. Thus, the Court does not find that these case reports make plaintiffs' experts' conclusions with respect to causation reliable.

In addition, the Court does not find that the

other texts cited by plaintiffs in their memorandum in opposition establish the reliability of plaintiffs' experts' conclusions with respect to causation. First, some of the evidence submitted by plaintiffs concerns the tendency of other ergot alkaloids, which are in the same class as bromocriptine, to cause hypertension, vasospasm, and stroke. Goodman & Gillman, a text cited by plaintiffs, notes simply that bromocriptine "shares some properties with the parent family of ergot compounds including the ability to induce ... digital vasospasm." Dr. Petro states in his affidavit that he reached his conclusion that Parlodel causes hypertension, stroke, myocardial infarction and seizure due, in part, to the fact that "Parlodel is in the family of compounds known as ergot, which have been recognized for centuries to cause toxic vasoconstrictive effects." Like the Court in Hollander, this Court does not find, based on all the evidence, that plaintiffs' experts, and plaintiffs' evidence, establishes that "bromocriptine and the other ergots have sufficiently similar physiological effects to warrant comparison." 95 F.Supp.2d at 1238.

Second, other evidence submitted by plaintiffs identifies bromocriptine as a possible cause of "digital vasospasm." As noted supra, Goodman & Gillman states that bromocriptine, like its parent family of ergot compounds, may induce "digital vasospasm." In addition, in Martindale, plaintiffs cite the portion of the text stating that "Bromocriptine is a vasoconstrictor;" however, the text continues immediately thereafter to state that "digital vasospasm" and another side effect, "have been reported." [FN16] To the extent that plaintiffs' experts based their opinions on evidence of vasoconstriction in other parts of the body, the Court does not believe that such evidence is sufficient to establish that bromocriptine could have also caused an ICH in view of the absence of supporting evidence.

Third, other texts cited by plaintiffs claim that Parlodel causes coronary vasospasm and heart attack. However, the Court does not find these resources helpful with respect to the ICH involved in this case, because an ICH is a different injury than coronary vasospasm and heart attack. [FN17] Thus, the Court does not find such evidence helpful in determining whether plaintiffs' experts theories with respect to general causation are reliable.

Fourth, the other texts which do not fit into the categories noted supra. [FN1 8] merely state that case reports, as well as articles based upon such case reports, indicate that bromocriptine might cause effects such as stroke, hypertension, and vasoconstriction. For instance, in Martindale, it is noted that some cases of hypertension have been reported, and that some have been associated with seizures and "occasionally with stroke." In addition, the text refers to a case report involving one woman. The text also cites articles chronicling case reports to support its statements. As noted supra, case reports are not sufficiently reliable in the context of causation. Similarly, while plaintiffs cite to the AHFS Drug Information, 1999 for the proposition that bromocriptine can cause seizure and stroke in rare situations, and that such incidents have been documented, the same text states that "the absolute incidence and relative risk (the ratio of the incidence of these bromocriptine-associated effects to the background of such effects occurring in the postpartum period in women not receiving the drugs) remain to be clearly defined." Thus, the text does not appear based upon controlled studies, recounts case reports involving bromocriptine, and indicates that further "definition" is needed before further conclusions can be made. The Court does not believe that such texts are sufficient to reliably support defendant's experts' conclusions that Parlodel can cause an ICH.

C. THE ACTIONS OF THE FDA DO NOT ESTABLISH THAT PARLODEL CAUSED MRS. GLASTETTER'S ICH.

Plaintiffs argue that the FDA's regulatory findings and conclusions with respect to Parlodel and stroke are evidence supporting the causation opinions of their experts. Plaintiffs note that on August 24, 1994, the FDA published its findings on the history of Parlodel and its conclusions as follows:

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 [FN19]) 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. Moreover, bromocriptine may be an additional risk factor in patients who are already at risk for seizures and stroke.

In addition, a possible mode of action exists for these adverse events. In the general population, a risk factor for hypertensive crises and spasms is exposure to ergot

alkaloids. Bromocriptine is a semi-synthetic ergot alkaloid.

FDA now has new information suggesting that therapeutic use of bromocriptine for the prevention of physiological lactation may lead to serious adverse experiences, including death and paralysis, in a small but significant number of patients. Patients at high risk of experiencing these serious adverse experiences cannot be adequately predetermined. In light of the limited benefit of using bromocriptine for the prevention of lactation, and the effectiveness and lack of serious adverse effects of conservative treatments such as breast binding with or without mild analgesics, the risk that bromocriptine may cause a serious adverse effect in a postpartum woman is unacceptable.

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.

Plaintiffs argue that this action by the FDA, in combination with their other evidence, indicates that their experts' testimony is reliable. To support this argument, plaintiffs cite Tyler v. Sterling Drug, Inc., for the proposition that "studies relied upon by governmental agencies like those the FDA used in formulating a rule regarding aspirin have been recognized as reliable and admissible." 19 F.Supp.2d 1239 (N.D.Okla.1998).

Understanding plaintiffs' arguments that the FDA's explanation for the withdrawal of approval of bromocriptine for use in preventing lactation appears to support their claim of causation, this Court, like the court in Hollander, believes that plaintiffs' reliance on the FDA's treatment of bromocriptine is misplaced. 95 F.Supp.2d at 1234, n. 9. This case is unlike Tyler, in where a party sought to demonstrate the reliability of certain studies by noting that the FDA found such studies reliable enough to base findings upon them. 19 F.Supp.2d at 1243. Instead, the plaintiffs in this case are seeking to introduce the FDA's own findings and conclusions as support for their experts' conclusions. However, as the Hollander court noted, the methodology utilized by a government agency "results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances" and "agencies' threshold of proof is reasonably lower than that appropriate in tort law, which traditionally makes more particularized inquiries into cause and effect and requires a plaintiff to prove that it is more likely than not that another individual has caused him or her harm." 95 F.Supp.2d at 1234, n. 9 (quoting Mitchell v. Gencorp Inc., 165 F.3d 778, 783, n. 3 (10th Cir.1999) (quoting Allen v. Pennsylvania Engineering Corp., 102 F.3d 194, 198 (5th Cir. 1996)) (internal quotations omitted)). As the Hollander court noted, this different standard is evident in the FDA's statement, because it emphasized not only the concerns about bromocriptine upon people's health, but also noted the "limited benefit" of bromocriptine for prevention of lactation. Thus, the FDA's decision was motivated, at least in part, by the availability of other means for controlling lactation. [FN20]

Moreover, the statement fails to affirmatively state that a connection exists between bromocriptine and the type of injury in this case. Instead, it states that the evidence received by the FDA "calls into question bromocriptine's safety," that bromocriptine "may be an additional risk factor in patients who are already at risk for seizures and stroke," and that the FDA had new evidence "suggesting that therapeutic use of bromocriptine for the prevention of physiological lactation may lead to serious adverse experiences." (emphasis added). Such language does not establish that the FDA had concluded that bromocriptine can cause an ICH; instead, it indicates that in light of the limited social utility of bromocriptine in treating lactation and the reports of possible adverse effects, the drug should no longer be used for that purpose. For these reasons, the Court does not believe that the FDA statement alone establishes the reliability of plaintiffs' experts' causation testimony.

D. THE ALLEGEDLY HIDDEN SANDOZ DOCUMENTS, INCLUDING THOSE RELATED TO ANIMAL STUDIES, FAIL TO ESTABLISH THE RELIABILITY OF PLAINTIFFS' EXPERTS' CONCLUSIONS.

Plaintiffs also argue that internal causation evaluations by Sandoz reveal defendant's knowledge of thevasoconstrictive properties of Parlodel in certain patients. Plaintiffs note that in 1982, Dr. Robert Griffith, a Sandoz toxicologist, stated, "From our side, we felt that these cases were probably related to episodes of hypertension, which we know can occur under Parlodel in such patients." In addition, plaintiffs claim that in 1984, Dr. Pierre Krupp admitted that "a causal relationship has to be considered as the adverse effects [migraine-type headache with partial hemiparesis and paresthesia] occurred during Parlodel medication, subsided upon discontinuation of medication and reappeared after reexposure in one case." [FN21]

Plaintiffs also claim that Sandoz admitted the following in an internal document from Dr. Marion Finkel to Timothy Rothwell: "there are rare clinical reports in the literature of vasospasm secondary to bromocriptine which are described as paradoxical since bromocriptine does not produce vasospasm under ordinary circumstances. Vasospasm may result in stroke or myocardial infarction." [FN22]

While the Court understands plaintiffs' arguments based upon this evidence, the Court does not find that they establish the reliability of plaintiffs' experts' conclusions. First, the Griffith statement relating Parlodel to hypertension occurred in the context of a discussion in regards to "seizures." Pl.Ex. 49. Griffith does not mention or refer to the possibility that Parlodel could cause an ICH. In addition, while stating that hypertension has been known "to occur under Parlodel in such patients," Griffith also states, later in the communication, that he, and others, "shall look through our NDA material to see if we can find any cases of hypertension in our postpartum patients," and that he desired the opinion of Dr. Saameli, to whom the communication was addressed, as to his "views on this possibility [of hypertension in postpartum patients], and also whether the occurrence of 'seizures' has been a problem in other countries." [FN23] Thus, this communication does not appear to approach the level of an admission by a Sandoz employee that Parlodel causes hypertension, seizures, or ICH.

Similarly, in plaintiffs' exhibit 47, Dr. Westlin does state that he is "beginning to think that there is some association between seizures, hypertension, and Parlodel therapy in the postpartum period;" however, such statement again falls short of an admission that Parlodel actually causes these effects, because he indicates that he is "beginning" to have these thoughts, and that he believes they should "take a look at the blood pressure data from our studies to look for any evidence of hypertension." Such statements indicate concern, but his suggestion for further testing and his use of the words "beginning to think" indicate that he had not, at that time, concluded that Parlodel caused seizures or hypertension. Moreover, he makes no reference in his letter to ICH or vasospasm.

The other letter cited by plaintiffs, the letter from Dr. Finkel to Timothy Rothwell, does state that "vasospasm may result in stroke or myocardial infarction," (emphasis added), however she never states in the letter that it has been determined by anyone that bromocriptine actually causes vasospasm, stroke, or hypertension. In addition, her use of the word "may" is not conclusive as to whether vasospasm does cause stroke or myocardial infarction. Instead, she merely indicates, apparently in preparation for a hearing before the FDA, that clinical reports exist of vasospasm secondary to bromocriptine. She also indicates, consistent with the FDA's decision as noted supra, that the FDA might conclude that the benefit of keeping the drug's indication for prevention of lactation might no longer outweigh "any increase in risk, even though there is no real proof of such a risk." (emphasis added).

For these reasons, the Court does not find that any of the Sandoz documents support the reliability of plaintiffs' experts' conclusions with respect to causation. The documents merely reflect that case reports exist that may support an association between Parlodel and vasoconstriction, stroke, or other side effects. As noted supra, case reports and conclusions based upon them are not sufficient to establish causation with the reliability required under Daubert. Moreover, at the hearing in this matter, Dr. Petro was asked, "Sir, you are not relying on or citing to this Court today a single DMC [FN24] causality assessment of intracerebral hemorrhage in which the investigator or some personnel at Sandoz stated there was probably a relation to bromocriptine, are you?" He answered, "No." Vol. I: 112-113 (Petro) (March 21, 2000.)

Dr. Petro also testified with respect to other reports and evaluations performed or related to Sandoz. In his testimony, he indicated that such evidence did not support his conclusions in this case. He first described a case of stroke in a 62-year old woman that the Sandoz' physicians at the Drug Monitoring Centre in Basle determined, according to Petro, was probably due to Parlodel. He admitted the woman was an acromegaly patient with a hypertensive history with a diagnosis of cerebrovascular ischemia. The author had posited hypotension as the mechanism for the stroke. Dr. Petro was asked, "Let me ask you this. If you accept the reporter's statement that this cerebrovascular ischemia was probably due to hypotension, that it is not consistent with what you say is the mechanism involved in Mrs. Glastetter's stroke, is it?" His answer was, "No." He admits that the event box on the completed form for this patient due to drug administration is checked under "possible." He recognizes that the report does not state that this 62-year old acromegaly patient had intracerebral hemorrhage due to vasoconstriction. The authors of the report conclude, that, with respect to this woman, the relationship to the treatment using bromocriptine in this 62-year old woman is "more dubius." He admits that the woman had a pituitary

tumor, had transsphenoidal surgery to remove part of the tumor which was impinging on the circle of Willis of her brain, that she had radiotherapy and that she was hypertensive. He admits that none of those factors or conditions apply in relation to Glastetter. Vol. I: 114-123 (Petro) (March 21, 2000).

In his affidavit, Dr. Petro stated that, "My fears about the vascular toxicity were realized as Parlodel came into wider use and reports of its toxic effects on blood vessels began to accumulate," and "Among the adverse side effects reported during bromocriptine use were patient experiences involving gangrene, limb cyamopsis and amputation." He was asked if gangrene, limb cyamopsis and amputation were conditions from the list of things he said demonstrated ergotism. He responded, " Well, they are signs of these forme fruste of ergotism." One patient upon which Dr. Petro relied to form this conclusion was a 78-year old male Parkinson's disease patient with "gangrene of toes." This patient had polycythemia vera or PCV where bone marrow is making high levels of platelets, red blood cells and white blood cells so the vessels became engorged with blood cells. He admits symptomatic polycythemia vera includes a condition such as peripheral venous thrombosis phlebitis and the arterial vessels of a PCV patient may become diffusely thickened, predisposing to coronary thrombosis, claudication, acroparesthesias, Renaud's syndrome and thromboangiitis obliterans. When asked if Sandoz concluded that it was more likely that the disease polycythemia vera contributed to the development of this patient's gangrene, Dr. Petro said, "It could have contributed to the gangrene, yes." He admits that the patient also had a history of arterial fibrillation, a condition that generates embolisms, but notes that he was on coumadin, which should prevent embolism. Dr. Petro admits that Sandoz could not rule out polycythemia vera as a contributing cause of the gangrene. Vol. I: 124-133 (Petro) (March 21, 2000).

Dr. Petro also refers in his affidavit to a 29-year old Italian woman with amenorrhea/galactorrhea being treated with a drug called clordiazepine (the same as librium). She was on 5 milligrams bromocriptine for two days. Dr. Petro was asked if according to the clordiazepine label, strokes have been reported in patient's using librium. When asked if there was a way to rule out her transitory stroke as caused by clordiazepine, he said the reporter suggested that it was drug-related, "my assumption is that it was felt that the ergot property caused the transient hemiparesis." He admits there is no indication that she had intracerebral hemorrhage, and there is no indication she had a bleed in her brain. Dr. Petro recognizes that Sandoz concludes that they consider any relationship with Parlodel in this 29-year old woman's transitory hemiparesis as highly unlikely. Dr. Petro was asked, "You sir, are unable to state to a reasonable degree of medical certainty that Parlodel caused this 29-year old Italian woman's hemiparesis; isn't that true?" He answered, "Yes." Vol. I: 141-149 (Petro) (March 21, 2000).

In his affidavit, Dr. Petro refers to a 34-year old male with a cerebrovascular accident, hemiparesis, with acromegaly who was receiving 20 milligrams of bromocriptine for 192 days. The patient also had Brown-Sequard Syndrome which is caused by spinal cord lesions. He admits that vasospasm is the most likely cause of Brown-Sequard Syndrome. Dr. Petro also testified that he would not say to a reasonable degree of medical certainty that the cause of Brown-Sequard Syndrome was Parlodel. He agrees that Sandoz concluded that any relationship with Parlodel was highly unlikely. Vol. I: 144-153 (Petro) (March 21, 2000).

Dr. Petro refers to a Canadian patient with acromegaly who reported to have a 1977 hemiparesis. Little information was reported to Sandoz about this patient. Dr. Petro agrees that the information supplied to Sandoz is inadequate to determine to a reasonable degree of medical certainty that Parlodel was the cause. Vol. I: 154-156 (Petro) (March 21, 2000).

In his affidavit, Dr. Petro refers to a 1978 case of a 29-year old woman from Great Britain with unilateral paresthesia and numbness, possibly due to spinal cord demyelination. Dr. Petro, referring to patient no. 7 in paragraph 3 of his affidavit, concluded the patient had numbness and tingling of the left arm and leg which suggested a focal cerebral vascular toxicity. The original investigators concluded, however, "Examination by a neurologist revealed no neurological or drug-related cause for these symptoms." Regarding this patient he was asked, "And sir, you weren't suggesting this morning in your direct testimony that Sandoz buried this or didn't submit this to the FDA, did you? Were you?" He answered, "No, I'm sorry if that was misinterpreted. The issue is when--when study information generated from the study was presented, I thought you were referring to a document that would have highlighted this serious adverse event that occurred in the study. That's really what I was referring to. I apologize if I misinterpreted."

The subject of this report was a woman who had galactorrhea for 168 months before she entered the study. She also had alopecia totalis (baldness) which,

Dr. Petro admits, could be associated with autoimmune disease which is sometimes associated with high blood pressure. He also noted that in this patient, he could not rule out vasospasm or vasoconstriction as a cause of her baldness. Dr. Petro admits that Dr. Stark, who did the study, reported that he was uncertain whether headache and dizziness were caused by Parlodel. Vol. I: 156-157; Vol. II: 4-21 (Petro) (March 21, 2000).

Dr. Petro was also asked about his earlier testimony concerning three deaths from the Parlodel clinical trials in Parkinson's patients. In his summary report, Dr. Petro said the three deaths may or may not have been related to the drug therapy when he testified before the advisory committee of the FDA considering whether to approve Parlodel for the Parkinson's indication in 1980. He admits he had reviewed case reports of investigators, whom he had earlier described as highly qualified to perform the studies as peer neurologists, who were listing Parlodel. When asked if it were true that each of the investigators on the Parkinson's disease trials "did not believe

that those three deaths which you described in your testimony were caused by Parlodel?," Dr. Petro answered, "I didn't say they were. I said they may or may not be related so--." The next question was, "And none of the original investigators in those clinical trials believed that those deaths were caused by Parlodel; isn't that right?" Dr. Petro's answer was, "I don't specifically recall, but I have no reason to question your statement now...." Dr. Petro admits that one of the patients was elderly and suffered an acute myocardial infarction while pushing his car in the snow, and that he had the case report before him when he made his review. He admits that the second of the three deaths was reported by the investigator to have had torsion around the mesentry in the artery, due possibly to an earlier surgical adhesion and that gangrene was due to the vascular occlusion

of the mesentric artery subsequent to torsion, and that it was not due to Parlodel. The third death was of an elderly gentleman who died in his sleep of an unexplained cardiac event. Vol. II: 22-30 (Petro) (March 21, 2000).

In redirect examination, Dr. Petro was asked about a Sandoz' report in acromegoly and the occurrence of stroke from reports received by Sandoz' monitoring center as of 1987, wherein it was noted, "Sandoz Drug Monitoring Center received a total of 25 reports of cerebral vascular accidents in patients who received Parlodel," nine of which reported as occurring in the postpartum period which were most likely due to intracranial bleeding. On re- cross-examination, however, regarding reports to Sandoz of adverse drug experiences, Dr. Petro was asked, "You didn't mean to suggest that in fulfilling its regulatory studies in reporting those cases that Sandoz believed there was a causal relationship between Parlodel and those ADEs including strokes, did you?" He answered, "No."
Dr. Petro was asked, "The only causality assessment that you have and that you've testified about involving Parlodel and stroke states that the mechanism was vasodilation or hypotension; isn't that right?" He answered, "Yes." Next, Dr. Petro was asked, "And that's the opposite of the mechanism that you believe was in play in Mrs. Glastetter's case which you testified was vasoconstriction or vasospasm, true?" He answered, "Yes." Next, he was asked, "And even the one reported case in which Sandoz said was a probably hypotensive mechanism did not involve an intracerebral hemorrhage, correct?" He answered, "Correct." Vol. II: 73; 85-87 (Petro) (March 21, 2000).

For these reasons, the Court must conclude that the allegedly hidden Sandoz documents do not establish the reliability of the conclusions drawn by plaintiffs' experts. Therefore, in the absence of other evidence, the Sandoz internal documents fail to establish the reliability of plaintiffs' experts' opinions.

In addition, the Court does not find that the evidence of animal studies establishes the reliability of plaintiffs' experts' conclusions. First, the plaintiffs make note of the "hindlimb study." Second, the plaintiffs claim that other animal studies included studies on rats, mice, and cats. Plaintiffs claim that these animal studies support their experts' testimony that Parlodel can cause vasoconstriction and hypertension. However, while plaintiffs mention the animal studies in their papers, plaintiffs' experts admit that the animal studies do not show that Parlodel causes stroke. Dr. Petro testified as follows:

Q: Mr. Hollingsworth asked you about animal models and you've done some literature search [sic] with regard to animal models?
A: Yes. And also at the recent Stroke Council of the American Heart annual meeting, a lecture was given by Dr. Grotta about animal models and stroke.
Q: And what was the short answer to what his lecture was?
A: In one sentence, animal models are unproductive in terms of elucidating issues relative to stroke.
Q: Now, you were asked--
A: Stroke in humans.
Q: You were asked whether any of the studies on animal models showed a relationship with bromocriptine causing stroke, do you recall that?

A: Yes.
Q: Were any of--any studies ever designed to do so?
A: No.
Vol. II:47-48 (Petro) (March 21, 2000).

In addition, Dr. Petro said he had read hundreds of studies on bromocriptine relating to humans and animals, and he has never found a study in which researchers have concluded in any animal that intracerebral hemorrhage was associated with bromocriptine. Vol. II: 41; 43-44 (Petro) (March 21, 2000).

Dr. Kulig's testimony was similar to the testimony given by Dr. Petro. When Kulig was asked, "[i]f you considered only studies in intact animals, intact animals, Dr. Kulig--you would not be able to tell Judge Webber that you have a controlled study showing that Parlodel causes stroke, would you?," he answered as follows:

That's probably true. However, I think we would be able to say that the animal study shows Parlodel is a vasoconstrictor.

However, Kulig also testified that he knew of no preferred animal model to rely upon to study potential effects of the blood pressure system in man or whether humans metabolize bromocriptine differently from primates. He testified that he believed that most primates metabolize drugs similarly, but in earlier testimony, he answered, "I'm not sure that's known." He did agree that "what happens in animal studies generally with regard to what happens to animals would not necessarily happen to humans." Vol. II: 64-66 (Kulig) (March 20, 2000).

In addition, plaintiffs experts have indicated that they are not aware of any studies involving intact animals showing that bromocriptine causes high blood pressure or any other injury purportedly secondary to cerebral vasospasm. Def.Ex. 19 at 207-08 (Kulig testifying in Brasher v. Sandoz that the "vast majority of the animal studies never attempted to measure blood pressure," and that he couldn't recall "if there were increases (in blood pressure)); Ex. 21 at 172 (similar testimony by Dr. Petro with bromocriptine"). Thus, in the absence of evidence indicating that the animal studies involved an injury like the cerebral injury at issue in this case, [FN25] the Court must conclude that the animal studies are unreliable, because they are not similar to the facts involved in this case.

E. PLAINTIFFS' EXPERTS DO NOT RELY ON EPIDEMIOLOGICAL STUDIES TO SUPPORT THEIR POSITION THAT PARLODEL CAUSES STROKE.

Plaintiffs' experts admitted that epidemiological evidence is the best evidence supporting a connection between a drug and an adverse effect. When asked if such studies are the strongest evidence of cause and effect, Dr. Kulig said it depends on how well they are done, but then, when asked whether he agreed "that well-done, consistent epidemiologic studies are likely to be the strongest evidence of cause and effect, true?," he answered, "True." Vol. II: 4-5 (Kulig) (March 20, 2000). [FN26] In addition, as the Court noted supra, in his prior testimony in a case in New York, Dr. Kulig gave testimony in response to the question, "Doctor, on a more general level, can a cause-and- effect relationship be established with a disease as common as breast cancer in humans without just showing an association through a controlled study?" His answer there was "no." Notwithstanding their admission to the importance of such studies, plaintiffs' experts do not rely on such evidence in reaching their conclusions. Kulig acknowledges, when asked if he knows of any statistical significant study demonstrating an association between ergot and stroke, that he didn't "recall any off the top of [his] head where there--there were enough patients in the study to do a statistical analysis."

Dr. Kulig was also asked about the ERI case controlled study, which considered over 200,000 deliveries from three big health care data collection companies. The investigators found ten cases of stroke. One of the ten women had taken Parlodel, and the authors concluded that the data on stroke was not informative. Dr. Kulig recognizes Dr. Rothman, the lead author of the study, as having a reputation of being a very knowledgeable epidemiologist. Dr. Kulig believes the study has some problems, however. He previously testified that the study was inherently unreliable. In an earlier hearing, he testified that he was not claiming that the study shows that Parlodel causes stroke, and when asked about his opinion in this case, the following is reported:

"And you're not telling Judge Webber that the ERI study is a controlled study which reliably proves a causal association between Parlodel and stroke, are you, sir?"
"No, I wouldn't say that."

Also, when asked whether he was "claiming that the ERI study establishes an association even strong, weak, medium or otherwise between Parlodel and hemorrhagic stroke specifically," he answered, "Well, it certainly doesn't establish that, but despite its methodolic flaws, it did show a relative risk of 8.4 for the development of stroke in women taking this drug versus women not taking the drug...." He reported that Sandoz

had written to him saying the ERI study reinforced the safety of Parlodel, which he believes is untrue. Vol. II: 7-11 (Kulig) (March 20, 2000).

Dr. Kulig was also referred to the HCIA study and was asked if it did not find any statistical significant association between bromocriptine and stroke. He answered, "I do recall that, but the study was also really incapable of finding such an association even if one existed." Vol. II: 19-20 (Kulig) (March 20, 2000).

In addition, Dr. Kulig testified that he was not sure if he would characterize the Herings and Stricher study as epidemiologic, but that he was familiar with it. He admits that he is not an epidemiologist. Dr. Kulig does not disagree that it was a study where investigations compared hospital admissions and pharmaceutical prescriptions to identify women who had had stroke, hypertension or heart attacks both during and after use of Parlodel for the prevention of physiologic lactation. He does not disagree that the study shows that among 2,130 women, none were hospitalized for ischemic heart disease, hypertension or cerebral vascular events during the index period or two-month period after discontinuance of bromocriptine use, and that adverse reactions or events may therefore be wrongly associated with bromocriptine use. Vol. II: 20-23 (Kulig) (March 20, 2000).

Dr. Kulig also refers to a non-epidemiologic study by Dr. Watson who formed an opinion that women who took Parlodel for postpartum lactation suppression who did not have pregnancy induced hypertension did not seem to have an increased incidence of postpartum hypertension if they were taking Parlodel. He acknowledges that Glastetter did not have pregnancy-induced hypertension in 1993. Vol. II: 24-25 (Kulig) (March 20, 2000).

Petro also indicated that no epidemiological evidence supported his conclusions. He describes the Rothman study of 200,000 as inadequate to make definite determinations. With respect to the Herings and Stricher study, he testified that the incidents of stroke in postpartum are rare, and there would never be an expectation to ascertain a case of Parlodel induced stroke. Vol. I: 92-93 (Petro) (March 21, 2000).

Plaintiffs' experts admit that the absence of such evidence severely limits their ability to reach a conclusion as to general causation. Dr. Petro agrees that to determine whether substance A can cause Effect B, the scientific method must be applied and that the scientific method consists of the formulation and testing of hypothesis. He agrees that, "Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified." He also agreed that the hypothesis in this case is whether Parlodel can cause intracerebral hemorrhage in postpartum women. Vol. I: 105 (Petro) (March 21, 2000).

When asked if prospective double-blind randomized placebo controlled studies are the way to use the scientific method to determine whether A causes B, he testified, "That is one element as far as the evaluation, as far as whether A causes B, yes". When asked the exact question at a Daubert hearing in a former case, however, he had answered, "[t]hat is correct." He also admitted there was no such study to show that Parlodel can cause intracerebral hemorrhage in postpartum women. He also testified that there is no such study where the original authors state that Parlodel probably caused intracerebral hemorrhage in postpartum women. Vol. I: 105-107 (Petro) (March 21, 2000).

Dr. Petro also agreed, when asked on cross-examination, that a fundamental concept, when a scientific study is conducted, is to have a recorded methodology, and to have exclusion--inclusion criteria and to have definitions. He was asked, "Now, sir, you cannot point to a study with a written methodology and a protocol and with exclusion--inclusion criteria and with definitions and with guidelines in which the authors state that Parlodel can cause intracerebral hemorrhages in postpartum women, can you?" He answered, "No." The next question was, "And you cannot point to a study with a written methodology and a protocol and with exclusion--inclusion criteria and with definitions and guidelines in which the authors state that Parlodel probably caused intracerebral hemorrhage in postpartum women, can you." He answered, "No."

Dr. Petro is unaware of any single report from a clinical trial where the investigator stated that Parlodel can cause intracerebral hemorrhage. He also can not cite to a single report from a clinical trial in which the original investigator stated that Parlodel probably caused an intracerebral hemorrhage. He admits there is no study showing the risk of postpartum stroke increased during the period of 1980 to 1994, when Parlodel was indicated for the prevention of physiologic lactation in the United States. When asked, "Sir, there is no clinical trial that states that Parlodel is a cause of stroke in postpartum women, is there?," he answered, "No, I'm sorry, there is no-- there is no study, yes. I'm sorry, I, you know, went negative, but I answered your question." Vol. I: 109-111 (Petro) (March 21, 2000).

The absence of any epidemiological evidence

amplifies statements made by plaintiffs' experts indicating the lack of foundation for their opinions. For instance, Dr. Petro was asked on cross-examination about Glastetter's medical records. He admits that an angiogram had been performed on Glastetter and a pathologic examination of her tissues and blood vessels taken from her brain were reported, and that there was no indication from all of the medical records that any of her treating physicians thought there was a scintilla of evidence that Glastetter had vasospasm at the time of her admission. Vol. II: 31 (Petro) (March 21, 2000).

In addition, Dr. Kulig was asked, "sir, you are of the opinion that drugs-- drugs that cause vasospasm or vasoconstriction are also drugs that cause stroke; is that right?" He responded by saying that he did not want to be that specific. When asked, "can you state to a reasonable degree of medical probability, sir, that drugs that cause vasospasm are drugs that cause stroke?" he stated, "I try not to be that general. That's language I would not want to use."

In the absence of their own epidemiological evidence supporting the conclusions of their experts that Parlodel can cause an ICH, the best plaintiffs can do is attack defendant's studies. However, as the court noted in Brumbaugh, 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." 77 F.Supp.2d at 1156; see also National Bank of Commerce v. Dow Chemical Co., 965 F.Supp. 1490, 1519 (E.D.Ark.1996), aff'd, 133 F.3d 1132 (8th Cir.1998) (noting that "plaintiffs have no epidemiology study supporting their theory of causation, and it is the plaintiffs who have the burden of proof on the Daubert issues"). For all these reasons, the Court finds that plaintiffs' experts' opinions are not based upon any epidemiological studies. In the absence of any such studies, as well as the absence of any other reliable evidence supporting the plaintiffs' experts' opinions with respect to causation, [FN27] the Court is unable to find that plaintiffs' experts' opinions are grounded on reliable scientific evidence.

F. CONSIDERING THE ABSENCE OF EVIDENCE INDICATING THAT PARLODEL CAN CAUSE AN ICH, PLAINTIFFS' EXPERTS ARE NOT SUFFICIENTLY RELIABLE UNDER DAUBERT.

In summary, this Court concludes that (1) in the absence of supportive epidemiological evidence, (2) the lack of similarity between the animal studies and the facts of this case, (3) the fact that bromocriptine is a member of the family of ergot alkaloids is not sufficient along to establish that it causes vasoconstriction, (4) the lack of reliability of the case reports and other evidence based upon them, (5) the lack of conclusiveness or reliability of clinical trials, and (6) the lack of reliable support for plaintiffs' experts' conclusions in the FDA findings and the internal Sandoz documents, the data and methods of plaintiffs' experts are not scientifically valid bases for the conclusion that Parlodel can cause an ICH in a human. [FN28] See Hollander, at 1238-39 (concluding 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 the 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 stroke"). [FN29] In the absence of reliable scientific evidence supporting their causation testimony, plaintiffs' experts must be excluded. See Daubert, 509 U.S. at 590, 113 S.Ct. 2786 (expert testimony must be based on "more than subjective belief or unsupported speculation"); Concord Boat Corp. v. Brunswick Corp., 207 F.3d 1039, 1057 (8th Cir.2000) (noting that an "expert opinion cannot sustain a jury's verdict when it is not supported by sufficient facts to validate it in the eyes of the law, or when indisputable record facts contradict or otherwise render the opinion unreasonable" and that "[e]xpert testimony that is speculative is not competent proof and contributes nothing to a legally sufficient evidentiary basis.") (internal quotations and citation omitted); see also Wright v. Willamette Indus., Inc., 91 F.3d 1105, 1108 (8th Cir. 1996) (holding that motion for judgment should be granted where an expert opinion on causation is speculative in nature). Thus, defendant's Motion in Limine shall be granted. In addition, in the absence of any scientifically valid evidence supporting plaintiffs' theory of causation, defendant is entitled to summary judgment as well. [FN30]

IT IS HEREBY ORDERED that defendant's Motion in Limine to Exclude Plaintiffs' Experts [Document # 170] is GRANTED; and

IT IS FURTHER ORDERED that defendant's Motion for Summary Judgment [Document # 211] is GRANTED.

Opinion Footnotes:

FN1. The Court also discussed the trial court's duty to ensure that the proffered expert testimony is relevant or helpful to the trier of fact. If the evidence is not

applicable to the facts of the case or not sufficiently tied to the facts of the case, then it may not be helpful to the trier of fact. See Daubert, 509 U.S. at 593, 113 S.Ct. 2786.

FN2. In Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 147, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999), the Supreme Court held that Daubert and the Daubert factors apply to all expert testimony.

FN3. Kulig also noted that advanced maternal age may be a risk factor for stroke. He first did not agree that advanced maternal age is a risk factor for intracerebral hemorrhage, but the then said, "I--I don't know," when confronted with his earlier testimony where he said, "barely, but it is."

FN4. In earlier testimony, Dr. Kulig stated that he would like to see more than one well-conducted study before becoming comfortable in opining on whether c-section presented an increased incidence of stroke to an individual.

FN5. As is the case of Dr. Kulig, Dr. Petro's conclusions come apart under cross-examination. They believe there is substantive evidence that Parlodel did cause the reaction in Glastetter's case. However, as noted in more detail infra, they are unable to support that conclusion by reliable scientific evidence.

FN6. In Westberry, the Fourth Circuit indicated that only a "reliable differential diagnosis provides a valid basis for an expert opinion on causation." 178 F.3d at 266 (emphasis added).

FN7. In addition, as noted infra, the results of this study are not particularly persuasive in any event, because such study does not concern the injury at issue in this case in a postpartum woman taking Parlodel for lactation.

FN8. Dr. Petro also referred to a case report by Jansens in the journal Stroke titled Postpartum Cerebral Angiopathy Possibly Due to Bromocriptine Therapy. Petro also discussed a report in a French journal referencing a 37-year old postpartum patient summarized under the title of Postpartum Cerebral Angiopathy and Bromocriptine. Vol. I: 45 (Petro) (March 21, 2000). He also made reference to an article in the journal, Neurology in 1996, by Coma Bella titled Bromocriptine and Postpartum Cerebral Angiopathy, a Causal Relationship?, which featured a 30-year old woman who developed headaches, hypertension and speech disturbances after ingesting bromocriptine to suppress lactation. Vol. I: 46-48 (Petro) (March 21, 2000). He also referred to a case report of a 37-year old patient with a clinical diagnosis of migraine who, during an episode, took a series of anti-migraine drugs and developed multiple intracerebral hemorrhages. An angiogram revealed severe vasospasm of both anterior cerebral arteries. Vol. I: 50-54 (Petro) (March 21, 2000).

FN9. As plaintiffs note, dechallenge is removing the drug exposure to determine if an adverse event abates while rechallenge involves re-exposing a patient to the drug in order to ascertain whether the adverse event reappears. Like the Hollander court, this Court notes that plaintiffs have come forward with very few rechallenge results supporting their claims. 2000 WL 430174 at *2, n. 10. Three of the human studies referred to by plaintiffs in their memorandum in opposition involved evidence of coronary artery spasm and myocardial infarction. However, this case involves Mrs. Glastetter's ICH, not coronary artery spasm or myocardial infarction.

FN10. On redirect examination, Dr. Kulig referred to a case report described as Lazarret, in which a Sandoz' evaluation form shows a causality assessment for myocardial infarction, total occlusion and severe chest pain. Parlodel was given to the patient for postpartum lactation inhibition. A pharmacalogic reaction was noted. There was a rechallenge in that case, "and they felt that the myocardial infarction was probably caused by their drug, bromocriptine." Following this statement by Kulig, the following exchange occurred: Q: "[A]nd there's a handwritten comment which says vasoconstrictive properties of ergot derivatives, does it not?" A: "Yes, it does." Q: "That Parlodel possesses vasoconstrictive processes of ergot derivatives, is that in accordance with your testimony as well?" A: "Absolutely." Vol. II: 109-111 (Kulig) (March 20, 2000).

FN1 1. In direct response to defendant's question that "in the strict sense of the word, [rechallenges and dechallenges] are not controlled experiments?" Dr. Kulig stated, "True." Vol. II:44.

FN 12. When asked if he could state which scientific reliability that the mechanism by which one ergot may cause vasoconstriction is the sameas the mechanism at work in the case of bromocriptine, he testified, "I can't say that with--with medical certainty, that's true. But if one ergot alkaloid can be proven to a reasonable degree of medical certainty to cause a vasoconstriction, for example, by one mechanism, I think that is likely to be the mechanism of the others as well, but that is

not necessarily the case." When he was then asked, following this statement whether he was offering that testimony to a reasonable degree of medical probability, he answered, "I am not, no." Vol. II 74-75 (Kulig) (March 20, 2000).

FN13. As the Court noted supra, Dr. Kulig's opinions are not based upon scientific studies but are, in the final analysis, reposed in the realm of "may cause" or "possibly could cause."

FN 14. As noted infra, the Court does not find that the plaintiffs' experts' opinions are reliable to prove a causative link between Parlodel and stroke simply because they conclude that bromocriptine is a member of the family of ergot alkaloids.

FN1 5. Plaintiffs also referred the Court to a similar article in a French publication by C. Lucas in Rev.Med. Interne 1996, Elsevier, Paris.

FN16. The Court again notes that a "report" of a certain event appears, under the authority noted supra. in Section II.A., to be insufficient to establish causation.

FN17. The Court believes this same reasoning applies to the evidence presented by plaintiffs related to bromocriptine and ischemic stroke. The injury at issue in this case is an ICH, which differs from an ischemic stroke. Plaintiffs experts agree that the injury in this case was an ICH, not an ischemic stroke. An ischemic stroke (dry stroke) occurs when blood supply is cut off as vessels constrict. Intracerebral hemorrhage (wet stroke) occurs when vessels rupture and bleeding occurs outside the arteries and into the brain tissue.

FN1 8. Indeed, as defendant notes, all the texts, treatises, and journals cited by plaintiffs appear based upon the accumulated case reports or individual case reports. The Court does not believe that texts and treatises that draw an "association" between Parlodel and vasoconstriction based upon case reports make such texts and treatises any more reliable than the case reports on which they rely. As noted supra, case reports are not sufficiently valid to establish the reliability of plaintiffs' experts' opinions with respect to causation.

FN19. Cardiovascular accidents.

FN20. The Court notes that the fact that the FDA did not withdraw its support for all uses of bromocriptine emphasizes the balance between risk and social utility. Dr. Petro testified that Parlodel remains approved by the FDA for Parkinson's therapy, for acromegaly, amenorrhea, galactacrasia, for treatment of pralactinomas and for some cases of female infertility. Vol. I: 99-101 (Petro) (March 21, 2000).

FN21. This evidence submitted by plaintiffs in exhibit 83 consists of an evaluation of an adverse drug reaction like a case report. As noted supra, case reports are not reliable in establishing causation. Moreover, like case reports, such a causality assessment involves only one individual, and, in any event, is not sufficient to establish causation. As defendant notes, M.N.G. Dukes, RESPONSIBILITY FOR DRUG-INDUCED INJURY: A REFERENCE BOOK FOR LAWYERS, THE HEALTH PROFESSIONS AND MANUFACTURERS 46 (2d ed. Dec.1998) provides as follows with respect to such assessments:

An outcome grading employing such terms as "not possible," "unlikely," "possible," and "probable" is currently used by some adverse reaction monitoring agencies, primarily to determine which reports of suspected reactions contribute to the total evidence, which do not, and which deserve further consideration. However, these useful scales have no objective reliability which would render them useful in a wider environment. At the very least, a court considering evidence based on the use of formalized causality assessment should require evidence that its dependability in the type of case under consideration has previously been demonstrated, and where an alogorithm provides results which do not concord with conclusions based on common sense and clinical judgment the latter may prove dependable. For these reasons, the Court does not find that plaintiffs' exhibit 83 establishes the reliability of plaintiffs' experts' opinions with respect to causation.

FN22. At the hearing, Kulig indicated that he had reviewed the Sandoz documents. Kulig was shown the memorandum from Dr. Griffith. In addition, the Court notes that evidence at the hearing indicated that Dr. Krupp testified that "vasoconstriction, if they are occurring in special regions of the brain, may cause, depending on the severity and where they are located, may cause seizures." Vol. II: 137-138 (Kulig) (March 20, 2000).

FN23. In addition, the Court notes that the "RE:" portion of the communication indicates that the communication involves "potential side effects." (emphasis added).

FN24. Drug Monitoring Center.

FN25. In addition, the Court does not find that plaintiffs' reliance upon the "hindlimb study" establishes the

reliability of their experts' conclusions with respect to causation, especially in light of the experts' testimony with respect to the ineffectiveness of animal studies in forming conclusions with respect to the effects of a drug in humans as noted supra. As Dr. Petro noted with respect to the "hindlimb study" in his deposition in the Brasher case in March, 1999, "comparing a mongrel ten kilogram dog to a pregnant woman I would say is a stretch." Def.Ex. 21 at 213. (Kulig discusses hindlimb?)

FN26. Dr. Petro also described epidemiology as helpful, but noted that because stroke in the postpartum period is not a common event, the sample size of the study must be large.

FN27. The plaintiffs cite cases that they claim stand for the proposition that epidemiological evidence is not required when a party has direct evidence of causation. However, to the extent that courts have come to such conclusion, such cases are of no assistance to plaintiffs in light of the fact that plaintiffs have come forward with no reliable or direct evidence of causation as noted supra.

FN28. In short, the factors set forth under Daubert have not been satisfied in this case. To the extent that the underlying theory or technique can or has been scientifically tested in this matter, no tests conclude that Parlodel can cause an ICH. In addition, the theory that Parlodel can cause ICH has been subjected to peer review and publication, but, so far as the Court can determine, only in the form of unreliable case reports. The Court finds no peer reviewed epidemiological study or publication concluding that Parlodel causes ICH. Thus, the Court has no data available to ascertain whether the theory has a known rate of error. Therefore, it does not appear that the theory that Parlodel causes ICH in humans generally is accepted in the relevant scientific community.

FN29. Because the Court finds that plaintiffs' experts are unreliable with respect to general causation, the Court need not address defendant's arguments with respect to specific causation. However, like the court in Hollander, this Court also believes that because the plaintiffs' general causation evidence is unreliable, the plaintiffs' experts' conclusions with respect to specific causation are also inadequate, because in the absence of general causation, the experts are unable to demonstrate that Parlodel, as opposed to other risk factors such as the increased risk of stroke in the postpartum period, caused the injury to Mrs. Glastetter in this case. 2000 WL 430174 at *5, n. 27. Thus, plaintiffs' experts' conclusion that Parlodel caused Mrs. Glastetter's ICH based upon differential diagnosis in the absence of evidence indicating that Parlodel can cause an ICH represents improper use of differential diagnosis. As defendant notes, improper use of an otherwise proper methodology will not satisfy Daubert. See Blue Dane Simmental Corp., 178 F.3d at 1040-41 (noting that even though an expert "utilized a method of analysis typical within his field," he did not use it in the manner it is "typically used").

FN30. Like the court in Brumbaugh, this Court wishes to state that its conclusion in this case is only that plaintiffs have not met the Daubert standard. See 77 F. Supp.2d at 1157, n. 2. The Court is not, by this opinion, concluding that plaintiffs' experts are simply wrong or that Parlodel is safe for use in postpartum women. Id.

FN3 1. In light of the fact that plaintiffs are unable to establish that the product at issue in this case caused the injury in question in the absence of expert witnesses, the Court has not included a discussion of defendant's claims for partial summary judgment based upon the learned intermediary theory and on plaintiffs' claim for punitive damages. The Court has considered such arguments, but no discussion is indicated in light of the fact that plaintiffs are unable to establish causation in this case.